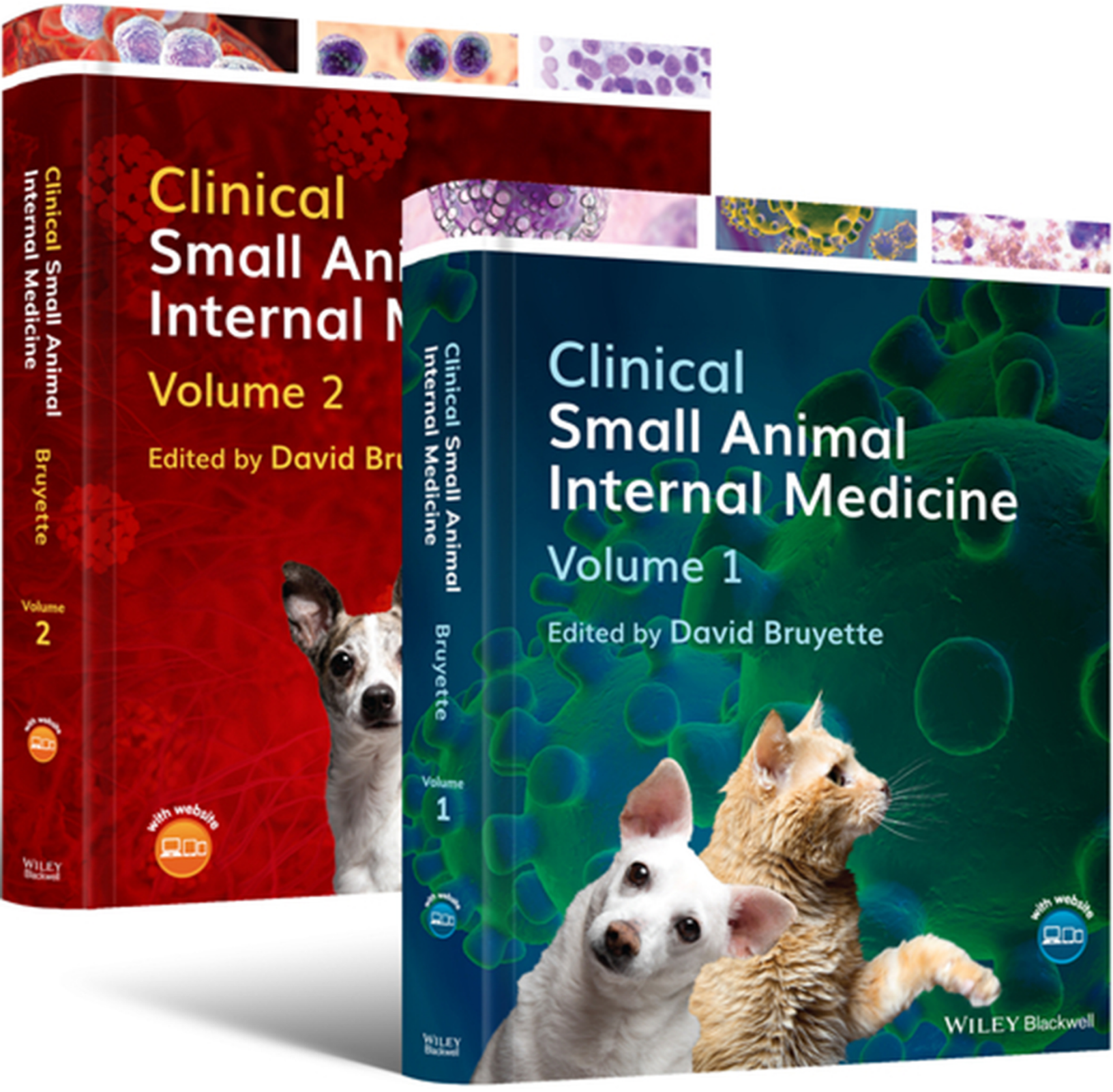

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Clinical Small Animal Internal Medicine

Clinical Small Animal Internal Medicine

Volume 1

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Dedication

To CB Chastain, Dick Nelson and Ed Feldman for trying their best to make me a better clinician. For someone interested in internal medicine and endocrinology I could not have had better mentors.

To all of my former students, interns and residents, thanks so much for always keeping me honest and forcing me to try to stay ahead of those I was supposed to be teaching.

To all the wonderful folks at Wiley (Erica Judisch, Gillian Whitley, Purvi Patel, Holly Regan-Jones, and Katrina Maceda) that made this book possible and tried their best to keep me on track. You turned the idea into reality and improved the book at every step in the process.

To my amazing children McKenna, Taylor, Ivy and Cole, thanks for letting me be a part of your lives. Being your Dad is the best job in the world.

To my amazing wife and best friend Maya. You make my life complete and I look forward to sharing every day with you.

Contents

Preface *xix*
List of Contributors *xxi*
About the Companion Website *xxix*

VOLUME I

Section 1 Evaluation and Management of the Patient *1*

1 **The Concept of One Medicine** *3*
Lonnie J. King

2 **Statistical Interpretation for Practitioners** *7*
Philip H. Kass

3 **Using Data for Clinical Decision Making** *17*
Philip H. Kass

Section 2 Endocrine Disease *27*

4 **Principles of Endocrinology** *29*
Robert Kemppainen

5 **Neuroendocrinology** *35*
Maya Lottati

6 **Feline Acromegaly** *43*
David S. Bruyette

7 **Pituitary-Dependent Hyperadrenocorticism in Dogs and Cats** *49*
David S. Bruyette

8 **Polyuria and Polydipsia** *65*
Jennifer L. Garcia

9 **Canine Hypothyroidism** *71*
David S. Bruyette

10 **Feline Hyperthyroidism** *75*
David S. Bruyette

11 Hypoadrenocorticism in Dogs and Cats 81
Patty Lathan

12 Diabetes Mellitus in Dogs and Cats 93
Jacquie S. Rand

13 Hypoglycemia in Patients without Diabetes Mellitus: Evaluation and Management 103
Rhett Nichols

14 Canine Autoimmune Polyglandular Syndromes 113
Deborah Greco

Section 3 Cardiovascular Disease 117

15 Approach to the Patient with Suspected Cardiovascular Disease 119
Ingrid Ljungvall and Jens Häggström

16 Imaging in Cardiovascular Disease 127
Valérie Chetboul

17 Electrocardiography 165
Anna R.M. Gelzer and Marc S. Kraus

18 Pathophysiology of Heart Failure 175
Barret J. Bulmer

19 Management of Heart Failure 185
Steven Rosenthal and Mark A. Oyama

20 Ventricular Arrhythmias 199
Amara H. Estrada and Romain Pariaut

21 Supraventricular Arrhythmias 205
Romain Pariaut and Amara H. Estrada

22 Systemic Hypertension 219
Rebecca L. Stepien

23 Pulmonary Hypertension 225
Heidi B. Kellihan

24 Congenital Heart Disease 231
Brian A. Scansen

25 Valvular Heart Disease 245
Michele Borgarelli

26 Canine Myocardial Disease 253
M. Lynne O'Sullivan

27 Feline Myocardial Disease 267
Virginia Luis Fuentes

28 Pericardial Disease 275
Ashley B. Saunders and Sonya G. Gordon

Section 4 Respiratory Disease 287

29 A Respiratory Pattern-Based Approach to Dyspnea 289
Christopher G. Byers

30 Feline Bronchial Asthma 297
Christine M. Serafin

31 Canine Chronic Bronchitis 305
Kevin Kumrow

32 Pulmonary Thromboembolism 313
Robert Goggs

33 Surgical Approaches to Thoracic Disease 325
Raegan Wells

34 Pleural Effusion 333
Ashley Allen and Gareth Buckley

Section 5 Critical Care Medicine 345

35 Approach to the Patient in the Critical Care Setting 347
Sarah Allen

36 Fluid Therapy 355
Teresa Rieser

37 Cardiopulmonary Resuscitation 365
Nathan Peterson

38 Respiratory Monitoring in Critical Care 373
Mathew Mellema

39 Acute Respiratory Failure 381
Matthew Mellema

40 Mechanical Ventilation 393
Kate Hopper and Mathew Mellema

41 Approach to the Patient with Shock 403
James W. Barr

42 Cardiogenic Shock 413
Nathan Peterson and James W. Barr

43 Septic Shock 421
James W. Barr

44 Disorders of Heat and Cold 431
Sarah Allen

45 Acute Poisoning 437
Ben O'Kelley

46 Medical Management of Trauma and Burns 445
Nathan Peterson

47 Venomous Snake Bites 459
Nathan Peterson

Section 6 Gastrointestinal Disease 467

48 Gastrointestinal Imaging 469
Susanne M. Stieger-Vanegas

49 Gastrointestinal Endoscopy 507
Craig Ruaux

50 Diseases of the Oral Cavity and Salivary Glands 533
Maria M. Soltero-Rivera and Alexander M. Reiter

51 Gastritis and Gastric Ulceration in Dogs and Cats 547
Katie Tolbert and Emily Gould

52 Disorders of the Esophagus 557
Silvia Funes and Craig Ruaux

53 Motility Disorders of the Alimentary Tract 563
Reto Neiger and Silke Salavati

54 Exocrine Pancreatic Insufficiency in Dogs and Cats 583
Panagiotis G. Xenoulis

55 Pancreatitis in the Dog 591
Caroline Mansfield

56 Pancreatitis in the Cat 601
Craig Ruaux

57 Rectoanal Diseases – Medical and Surgical Management 609
Craig Ruaux and Milan Milovancev

58 Dysbiosis and the Use of Pre-, Pro- and Synbiotics 621
Jan S. Suchodolski

59 Diagnosis and Management of Chronic Enteropathies 627
Karin Allenspach

Section 7 Diseases of the Liver, Gallbladder, and Bile Ducts 639

60 Approach to the Patient with Liver Disease 641
Emma O'Neill

61 Imaging in Hepatobiliary Disease 659
Esther Barrett

62 Metabolic, Toxic, and Neoplastic Diseases of the Liver 677
Jan Rothuizen

63 Feline Inflammatory Liver Disease 687
Nicki Reed

64 Canine Inflammatory Liver Disease 695
Nick Bexfield

65 Cirrhosis and its Consequences 705
Katherine Scott

66 Portosystemic Shunts and Microvascular Dysplasia 713
Geraldine Hunt

67 Diseases of the Gallbladder and Extrahepatic Biliary Ducts 721
Ben Harris

Section 8 Neurologic Disease 727

68 The Neurologic Examination 729
Alexander de Lahunta

69 Central Nervous System Trauma 741
Simon R. Platt

70 Seizures and Movement Disorders 759
Michael Podell

71 Disorders of the Forebrain 773
Sam N. Long

72 Vestibular Disease 789
Tammy Stevenson

73 Meningoencephalitis and Meningomyelitis 795
Christopher L. Mariani

74 Diseases of the Neuromuscular Junction 803
David Lipsitz

75 Myopathies 811
Marguerite F. Knipe

76 Myelopathy 815
Joan R. Coates

77 Neuroophthalmology 823
Bradford J. Holmberg

VOLUME II

Section 9 Infectious Disease 829

Part 1 Diagnostic Considerations 831

78 Epidemiology of Infectious Disease 833
Peggy L. Schmidt and Helen T. Engelke

79 Laboratory Diagnosis of Infectious Diseases 839
Laia Solano-Gallego and Gad Baneth

Part 2 Select Infectious Diseases and Disease Agents 849

80 Canine Distemper 851
David S. Bruyette

81 Canine Herpesvirus 855
Yvonne Drechsler

82 Canine Viral Enteritis 857
Margaret C. Barr

83 Viral Papillomatosis 861
Margaret C. Barr

84 Canine Influenza Virus 865
Ellen Collisson

85 Feline Parvovirus 869
Margaret C. Barr

86 Feline Coronavirus 873
Yvonne Drechsler

87 Feline Leukemia Virus 877
David S. Bruyette

88 Feline Immunodeficiency Virus 883
Tom Phillips

89 Feline Viral Upper Respiratory Tract Disease 887
Yvonne Drechsler

90 Rabies in Dogs and Cats 891
Emily Beeler and Karen Ehnert

91 West Nile Virus 899
Tracey McNamara

92 Ebola Virus 901
Linda Kidd

93 **Ehrlichiosis and Anaplasmosis** *903*
Pedro P. Vissotto de Paiva Diniz

94 **Salmon Poisoning Disease** *913*
Pedro P. Vissotto de Paiva Diniz

95 ***Wolbachia pipientis* Infection** *917*
Pedro P. Vissotto de Paiva Diniz

96 **Bartonellosis** *919*
Pedro P. Vissotto de Paiva Diniz

97 **Hemotropic *Mycoplasma*** *927*
Séverine Tasker

98 **Nonhemotropic *Mycoplasma*, *Ureaplasma*, and L-Form Bacteria** *931*
Joachim Spergser

99 **Spotted Fever and Typhus Group Rickettsia** *937*
Linda Kidd

100 **Lyme Borreliosis** *941*
Meryl P. Littman

101 **Leptospirosis** *945*
Katharine F. Lunn

102 **Yersiniosis** *951*
Maria Grazia Pennisi

103 **Tularemia** *955*
Linda Kidd

104 **Q Fever** *959*
Linda Kidd

105 **Brucellosis** *963*
Erin E. Runcan and Marco A. Coutinho da Silva

106 **Tetanus and Botulism** *967*
Andrea Fischer

107 **Anthrax** *971*
Wayne E. Wingfield and Jerry J. Upp

108 **Actinomycosis, Nocardiosis, and Mycobacterial Infections** *977*
Joanna Whitney and Vanessa R. Barrs

109 **Fungal Infections** *985*
Jane E. Sykes

110 **Protozoal and Protozoa-Like Infections** *1003*
Gad Baneth and Laia Solano-Gallego

111 Coccidia 1023
Chris Adolph

112 Surgical, Traumatic, and Bite Wound Infections 1029
Laura L. Nelson

113 Canine Infectious Respiratory Disease Complex 1035
Jonathan Dear

Part 3 Therapeutic Considerations 1039

114 Antimicrobial Therapy in Dogs and Cats 1041
Katrina R. Viviano

115 Antifungal Therapy 1049
Daniel S. Foy

Part 4 Special Topics 1055

116 Nosocomial and Multidrug-Resistant Infections 1057
Jason W. Stull and J. Scott Weese

117 Management of Infectious Disease in Kennels and Multicat Environments: Creating a Culture of Compliance 1063
Frank Bossong

Section 10 Renal and Genitourinary Disease 1067

118 Disorders of Sodium and Water Homeostasis 1069
Julien Guillaumin and Stephen DiBartola

119 Disorders of Phosphorus and Magnesium 1079
Rosanne Jepson

120 Acute Kidney Injury 1089
Adam E. Eatroff

121 Glomerular Disease 1101
Shelly L. Vaden

122 Obstructive Uropathy 1109
Edward Cooper and Brian A. Scansen

123 Urolithiasis in Small Animals 1123
Alice Defarges, Michelle Evason, Marilyn Dunn, and Allyson Berent

124 Prostatic Diseases 1157
Serge Chalhoub

125 Management of Chronic Kidney Disease 1165
Jessica Quimby

126 The Role of Dialysis 1175
Adam E. Eatroff

127 Micturition and Associated Disorders 1181
Julie K. Byron

128 Urinary Tract Infections 1189
Nicole Smee

Section 11 Oncologic Disease 1197

129 Approach to the Cancer Patient 1199
Lisa DiBernardi

130 Biology of Cancer and Cancer Genetics 1205
Mary-Keara Boss

131 Endocrine Manifestations of Cancer: Ectopic Hormone Production 1213
Cory Brown

132 Paraneoplastic Syndromes 1217
Cory Brown

133 Lymphoid Leukemias, Myeloid Neoplasia, and Myelodysplastic Syndrome 1223
Angela R. Kozicki

134 Lymphomas 1231
Kristine Elaine Burgess

135 Plasma Cell Disorders 1241
Orna Kristal

136 Central Nervous System Tumors in Dogs and Cats 1247
David Ruslander

137 Cancer of the Nose and Mouth 1253
Lauren Askin Quarterman

138 Tumors of the Eye and Ocular Adnexa 1261
Erin M. Scott and Paul E. Miller

139 Cancer of the Heart 1271
Nick A. Schroeder and Lisa DiBernardi

140 Cancer of the Airway and Lung 1277
Joanne L. Intile

141 Cancer of the Esophagus and Stomach 1283
Avenelle I. Turner

142 Cancer of the Small and Large Intestine 1287
Edwin Brodsky

143 Exocrine Pancreatic Cancer 1293
Avenelle I. Turner

144 Pancreatic Endocrine Tumors 1297
Karen Eiler

145 Liver and Biliary Tract Tumors 1303
Amanda K. Elpiner

146 Tumors of the Urinary Tract 1307
Pedro A. Boria

147 Tumors of the Male Reproductive System 1311
Trina Hazzah

148 Gynecologic Cancers 1317
Trina Hazzah

149 Mammary Cancer 1321
Julie Bulman-Fleming

150 Tumors of Bone and Joint 1327
Stephanie L. Shaver, William T.N. Culp, and Robert B. Rebhun

151 Soft Tissue Sarcomas 1333
Lauren Askin Quarterman

152 Hemangiosarcoma 1339
Christine B. Oakley and John D. Chretin

153 Melanoma 1347
Philip J. Bergman

154 Nonmelanoma Skin Cancers 1353
Barbara E. Kitchell

155 Mast Cell Neoplasia 1359
Zachary M. Wright

156 Apheresis in Companion Animals 1369
Steven Suter

Section 12 Skin and Ear Diseases 1373

157 Approach to the Patient with Dermatologic Disease 1375
Lisa V. Reiter

158 Principles of Therapy of Dermatologic Diseases 1397
Sandra N. Koch

159 Atopic Dermatitis 1403
Alison Diesel

160 Allergic Skin Diseases 1413
Patrick Hensel

161 Cutaneous Adverse Food Reactions 1419
Ralf S. Mueller

162 Autoimmune and Immune-Mediated Skin Diseases 1423
Nicole A. Heinrich

163 Approach to Alopecia 1433
Linda A. Frank

164 Canine Sterile Papular and Nodular Skin Diseases 1441
Sandra Diaz

165 Parasitic Skin Diseases 1449
Elizabeth E. Toops

166 Bacterial Pyodermas 1461
Jennifer R. Schissler

167 Otitis 1471
Sue Paterson

168 Cutaneous Manifestations of Systemic Disease 1481
Kinga Gortel

169 Superficial Necrolytic Dermatitis 1491
Mitchell D. Song

170 Miscellaneous Skin Diseases 1495
Lisa V. Reiter and Sheila M.F. Torres

Section 13 Diseases of Bone and Joint 1507

171 Skeletal Development and Homeostasis 1509
Matthew J. Allen and Gert J. Breur

172 Metabolic Bone Diseases 1521
Keren E. Dittmer

173 Osteoarthritis in Small Animals 1529
Steven A. Martinez

174 Developmental Orthopedic Diseases 1537
Gert J. Breur, Nicolaas E. Lambrechts, and Heather A. Towle Millard

Section 14 Social and Ethical Issues in Veterinary Medicine 1553

175 Canine and Feline End of Life Care 1555
Robin Downing

Section 15 Preventive Care *1565*

176 Role of Immunization *1567*
Melissa Kennedy

177 Behavior Triage for Internists and the General Practitioner *1571*
Karen Lynn C. Sueda

Section 16 Laboratory Support *1581*

Index *1583*

Preface

Internal medicine is hard. Progress in science and technology makes it almost impossible to keep abreast of recent advances and on top of that, all of us want to balance our life both at work and home. Is there enough time in the day for everything?

There are a variety of ways in which we learn and the path is not the same for everyone. For those of us with an interest in internal medicine, and I'm assuming that includes the reader of this book, we rely on a number of resources. Our colleagues, continuing education seminars, the literature, professional educational networks, and reference textbooks. A concern of mine over the past few years has been the increasing reliance on technology to arrive at a clinical diagnosis rather than emphasizing the need to understand physiology and the value of a complete history and a thorough physical examination. We feel increasing pressure to arrive at a specific and definitive diagnosis and, more importantly, to arrive at that diagnosis almost immediately.

Your goal in internal medicine is not to arrive at a diagnosis. I would much prefer to see a pet respond to my treatment and recover without a definitive diagnosis than to arrive at a definitive diagnosis at necropsy. If you are successful in achieving a diagnosis, that can be very rewarding. However, your goal should be to accurately identify problems and address those problems in a logical, timely, and cost-effective manner, always weighing the risk/benefit of running myriad diagnostics versus improving the quality of life of your patient and the pet owner. While not every pet owner will be able to afford or desire to follow each and every one of our recommendations, it is our job to make sure that whatever decision the owner makes is based on being fully informed.

Illness is really physiology gone awry. If you have an understanding of what is normal, it makes your job of identifying the abnormal much easier. The body has a limited repertoire of responses to an insult so often many diseases will have very similar clinical presentations. While we all like to make lists of the 20 differential diagnoses for a given patient's abnormalities, it's important to recognize that in clinical practice, common things occur commonly and those differentials should be at the top of your rule-out list.

There are numerous excellent textbooks on the market and I use many of them on a daily/weekly basis. Some serve as definitive reference works for the topic under discussion. Some are brief, bullet point, clinically oriented texts that one can use to find something quickly. What I thought was currently lacking was a text that would be continually updated, provide enough background physiology to help the reader understand normal versus abnormal, and provide useful and, more importantly, clinically relevant material to help you with your patients.

The goal of this text was to first identify section editors who were recognized experts in their field both academically and clinically. The section editors then identified topics they felt were of greatest clinical importance and selected authors who could translate this information into a text that would be used every day. I hope we have achieved that goal. We will be updating the text online with new information and updated references on a quarterly basis, adding additional sections and chapters with future editions, and uploading podcasts consisting of interviews with the authors to highlight and emphasize the material in the text and any recent advances in the field.

We hope that you will find the text helpful and all credit for that success goes to the authors. Any omissions or errors lie with me so please let me know both the good and the bad so we can improve things going forward.

As my favorite philosopher once said "It's a magical world, Hobbes, ol' buddy, let's go exploring."

All the best and enjoy exploring the mysteries of medicine.

Dave

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Section 1

Evaluation and Management of the Patient

1

The Concept of One Medicine

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Today's world is rapidly changing, complex, and progressively more interconnected. The convergence of people, animals, and our environment has created a new dynamic characterized by a profound and unprecedented interdependence in which the health of all three domains is now inextricably linked and elaborately connected. Over the last three decades, approximately 75% of new emerging human diseases have been zoonotic. The human–animal interface is expanding, accelerating, and becoming increasingly more consequential. At the same time, we have permanently altered a significant portion of our environment, ecosystems, and habitats and have created a new ecological milieu that is changing both the conditions of our human–animal interface and the conditions for microbial adaptation and the emergence and reemergence of infectious diseases worldwide.

Our new interdependence includes social, economic, political, and biological conditions that are creating new threats to the health of people, animals, and our environment. We can no longer focus on these threats separately from each other. Our contemporary challenge is to create and implement a new mindset and strategies to address our threats to health based on a holistic and integrated approach with a special emphasis on prevention and attacking problems closer to their origin that is often within the animal and environmental domains. This approach is the essence of the concept of One Health.

One Health can be defined as the collaborative effort of multiple disciplines – working locally, nationally, and globally to attain optimal health for people, animals, and our environment. The scope of One Health is impressive, broad, and growing. Much of the recent focus on One Health has been limited to emerging infectious diseases yet the concept clearly embraces environmental and ecosystem health, social sciences, biodiversity, ecology, noninfectious diseases and chronic diseases and much more.

While the concept of One Health is not new, it has enjoyed a new recognition based on today's complex challenges to our health. The veterinary profession is especially well equipped through our broad training in herd health, comparative medicine, epidemiology, problem solving, and disease ecology to play an important role in implementing new One Health strategies.

Factors Driving One Health

In a publication entitled *Microbial Threats to Health: Emergence, Detection, and Response*, authors from the Institute of Medicine suggested that a group of factors have simultaneously converged to create a "perfect microbial storm" [1]. The most important of these factors include:

- adaptation of microbes
- global travel and transportation
- host susceptibility
- intent to do harm
- climate change
- economic development and land use
- human demographics and behavior
- a breakdown of both public and animal health infrastructures.

The Human Domain

The world population has a growth rate of 1.2% per year and the next century will represent a period of exponential growth. We add approximately 10 000 people per hour to our global population every day. Approximately 90% of the world's population growth is occurring in the developing countries where we are most concerned about a lack of adequate public and animal health infrastructure. In addition, almost 1 billion people live in

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periurban or slum settings in the developing world's largest cities and these sites are where the most rapid growth in our human populations will continue. Concurrently, there is unprecedented immigration, translocation, and movement of people worldwide. Unique diasporas have emerged and there are large numbers of immunocompromised individuals dispersed throughout the US and global populations who are especially susceptible to infections involving food- and water-borne illnesses.

The Animal Domain

While there is also legitimate concern about the approximately 800 million people who are undernourished, we are concurrently observing a relative increase in wealth in the developing world and as per capita incomes rise, people eat more calories and consume different products, including a demand for meat and protein from animal sources. Thus, a new agricultural phenomenon is emerging – the Livestock Revolution; we will need to increase protein from animal sources by 50% over the next several decades. We will also need to increase food-animal production with minimal impacts on the environment and our ecosystems. Veterinarians will be engaged with ecologists to help ensure the sustainability of our lands.

At the same time, companion animals and pets are also rapidly increasing globally and there are untold numbers of wildlife that are increasingly involved at the human–animal interface and responsible for carrying and transmitting more and more zoonotic diseases. West Nile virus, Lyme disease, Nipah, Hendra, and hantaviruses are some important examples.

With a new appreciation of the need for detecting and identifying human infectious disease threats at animal and ecosystem level, our scope of disease surveillance must also be expanded to include these domains. Currently, 80% of select agents are zoonotic which further emphasizes the need for integrating animal disease surveillance into human disease surveillance programs. In addition to the benefits of earlier detection and warning, surveillance within these domains will give us new insights and analyses on disease prediction and new possibilities to prevent future disease occurrences and exposures. Thus, animal disease surveillance has taken on a new importance and relevance.

Until we address the underlying factors that lead to disease emergence and reemergence, we will continue to address infectious disease problems one at a time and based on reactive responses. A new commitment is necessary to refocus our efforts to prevent and control diseases in ways that also address these underlying conditions and the animals, animal products, and their vectors.

For example, human exposure to *Borrelia burgdorferi*, the etiologic agent of Lyme disease, is maintained and spread based on the complex relationships among wildlife populations, tick life cycles, host preferences, habitat, ecosystem, and landscape design and other dynamics of this disease ecology. Effective prevention and control may need to focus on ecologic interventions rather than treating the human illness after exposure and infection. Thus, rather than a narrow focus on humans and their interactions with pathogens, we need to focus on the dynamic interplay among humans, animals, and animal products, and our changing environment – in other words, a One Health approach.

Role for Companion Animal Experts

The purpose of including this introduction on One Health for a text on internal medicine is to help create a new awareness of the concept across the veterinary profession and to suggest that companion animal practitioners also have new opportunities, as well as obligations, to support public health in the future.

Practitioners can be extremely helpful and contribute in the following ways:

- enhance surveillance for emerging and zoonotic diseases
- identify cases of zoonoses that will then prevent human illnesses
- educate clients regarding One Health and zoonotic diseases
- be involved in a potential surge capacity in case a significant epidemic or natural disaster calls for your support
- promote the human–animal bond but with knowledge of both the benefits and potential negative impacts of the human–animal interface, including wildlife.

Conclusion

Our global interdependence and growing convergence of animals, animal products, and people ensure that diseases will continue to be a significant threat to health. There is nothing on the horizon suggesting that the era of the perfect microbial storm will lessen or be abated. The factors creating this reality are well entrenched and emerging and reemerging zoonoses are growing and expanding in scope, scale, and impact. These diseases now have a much greater impact and influence beyond health. Global outbreaks of SARS and influenza have demonstrated how such diseases create immense economic losses in goods, services,

travel, and trade in addition to their profound health costs and consequences.

Contemporary societal issues such as global trade and commerce, movements and migrations of populations, changes and insults to our ecosystems, population growth in developing countries, the Livestock Revolution, and disruptions of the environment are helping to create a complex, nonlinear and disruptive world that is riskier and impacts health in the domains of people, animals, and our environment. The ability to improve and optimize health in the future will depend on working in these three domains concurrently, holistically, and synergistically. A One Health mindset and accompanying actions are now a necessity and no longer just a concept. In order to reconcile our significant contemporary challenges and threats with our habitual, narrow and traditional thinking in medicine, new levels of thinking across disciplines and professions will become the new normal. Veterinarians are becoming essential leaders in this movement and a new concept of community health, including veterinary medicine, is emerging.

Public health and animal health are no longer the domain of any single discipline, profession or boundary; rather, they require the work of epidemiologists, clinicians, ecologists, veterinarians, entomologists, engineers, and many more experts coming together to provide new insights and perspectives using new scientific and technological tools. Addressing, predicting, and preventing diseases certainly demand the richness of new scientific and medical teams.

For veterinary medicine, our horizon has never been richer nor our possibilities more promising. Our profession's challenge is to be relevant and meet the changing needs of society regarding public health, global food systems, ecosystem management, and biomedical research. One Health is the framework, mindset, and new collective purpose to help define our expanding responsibilities, including, and beyond, traditional clinical medicine.

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2

Statistical Interpretation for Practitioners

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The need for an understanding of how to conduct statistical analyses and, more importantly, how to interpret them derives from a natural tension between aspiration and reality: the desire to make encompassing statements concerning the characteristics and causal properties about populations of animals, juxtaposed with the inability to study more than a small sample of them. Statistical inference therefore provides the necessary linkage between using samples to make inferences about populations.

External Validity

It is often taken as a matter of faith that studies conducted in relatively circumscribed subpopulations (such as a cohort of patients seen at an individual hospital in a defined period of time) can have relatively generalizable findings. For example, a hospital-based study examining the relative clinical efficacy of two or more chemotherapeutic regimens to treat newly diagnosed canine lymphoma by inducing remission may motivate the authors to make recommendations for adoption well beyond the hospital's patient catchment area. When are such generalizations justified?

Sampling of populations is required to scientifically justify extrapolating results from sample-based studies to target populations. Thus, to make scientific inferences about a population, it is necessary to study a representative sample. In many cases, the sample size need not be particularly large, and can be obtained through random (or more complex) sampling schemes. The process of random sampling ensures representative selection, and that in turn provides the key link between a study sample and a target population.

Because few studies are actually conducted using true sampling of a target population, the ability to generalize study findings (that is, having "external validity") typically depends on prior medical belief and knowledge, as well as key assumptions. For example, the initial epidemiological research into the association between tobacco smoking and lung cancer was performed in the 1950s in a cohort of male British doctors [1]. Technically, the findings of this research strictly applied to the entire population of male British doctors who were contemporaries of the study subjects. The choice to generalize these findings – namely, that the incidence of lung cancer was many-fold higher among smokers than nonsmokers – to other populations rested on key assumptions motivated by scientific reasons independent of the actual research. These assumptions included that the effect of tobacco smoking on lung cancer incidence should not meaningfully vary by gender, occupation, country of origin, ethnic identity, and birth cohort. Nothing in the original research could have provided evidence to support these assumptions; nevertheless, they helped create the basis for the landmark 1964 report in the US officially affirming a causal link between tobacco smoking and lung cancer [2].

A more recent example of the dangers of extrapolating study results to nonstudy populations can be found in an article on the association between mitotic index (MI) and survival in dogs diagnosed with mast cell tumors [3]. The authors found a substantially lower survival in dogs seen at a California veterinary medical teaching hospital whose MI was 5 or fewer versus those whose MI was 6 or greater. In contrast, Elston *et al.* performed similar analyses on dogs from Brazil and recommended somewhat different MI cut-off values [4]. The original authors responded by underscoring the difficulty of externally validating studies:

> This underscores the fallibility of classification schemes in clinical veterinary medicine: they may work well in a study population and its corresponding reference population but may not perform nearly as well in a target population of inherently different animals or where measurement standards may not necessarily be completely

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> concordant. The latter can be influenced by how different pathologists measure, count, and ultimately determine MI, and whether such determinations are so precise as to be perfectly replicable by others. Such studies are then relegated to determining average effects across potentially heterogeneous patient populations even within a community, much less between countries. Thus, patient characteristics such as age, breed, sex, and owner propensity for diagnosis (including biopsy) would be expected to vary, perhaps substantially, between institutions such as ours and Elston et al.'s. [5]

These illustrations should presumably compel veterinarians to be circumspect about relying too heavily on any single study, particularly one conducted in a geographically restricted region, and for authors to exercise restraint in advocating wider than justified implications for a single study. Although the heterogeneity existing across populations may have a negligible impact on the universality of study findings, a cautious approach to generalizability is often warranted.

Internal Validity

Unlike external validity, which relies on information not usually obtained in a study to make inferences beyond the bounds of a study population, internal validity depends on the relative presence or absence of two sources of error pervasive to all clinical studies: imprecision (random error) and invalidity (systematic error).

Imprecision has multiple formal statistical definitions and interpretations, but can best be understood as how variable the results are expected to be from multiple studies measuring the same quantity. As an example, if a veterinarian were to repeatedly weigh a patient using a scale, precision would imply obtaining similar weights each time; conversely, imprecision implies considerable disagreement in weights with each attempt. Standard deviations, standard errors, variances, and ranges are all statistical measures for quantifying imprecision. We can make two broad qualitative statements about variability without resorting to mathematical formulas: (1) the further apart observations are from each other, the more imprecise any summary statistic based on them will be; and (2) the larger a study is, the more precise any statistic derived from it will be. This has an intuitive appeal: the findings from a large study are more likely to be accepted as more precise than those from a small study. Provided there are no biases, the source of statistical variability in a study is typically ascribed to random error.

It would be a grievous error, however, to accept a study's outcomes solely on the basis of high precision. Invalidity, another source of error in studies and equivalently called *bias*, is a distinctly different statistical measure, and represents the disparity between what one empirically measures in a study and what one strives to measure (namely, factual truth). Returning to the previous example, if a hospital scale is miscalibrated, then regardless of how precise or imprecise the replicate measurements are, the average weight will invariably be incorrect (biased), with the degree of the bias proportional to the degree of miscalibration.

All medical research is potentially susceptible to imprecision and bias, and it is only through circumspect study design that these errors can be prevented or controlled. Such errors exist on a quantitative continuum (parenthetically often reduced to crude descriptors, such as "very" imprecise or "small" bias), so it becomes important to recognize that all studies must be judged by both error criteria and not just one (or neither). Such lack of circumspection is pervasive, even in academic settings, and helps explain the often contradictory results one so often reads about in the popular media [6]. It also underscores the often unappreciated theme that even very large-sample studies are susceptible to bias, and despite their exceedingly high precision can conceivably be as misleading as a much smaller study.

Hypothesis Testing

Perhaps the most obvious manifestation of the use of statistical analysis in clinical research is through much misunderstood hypothesis testing. Although investigators and clinicians typically want to know if the differences between study groups are real, or if the association between risk factors and health outcomes is real, hypothesis tests are unable to answer these questions. Moreover, the *P*-values so ubiquitously reported in clinical articles fail to inform readers about the probabilities that measured differences or associations are real. In reality, their interpretation is surprisingly counterintuitive.

Consider the example of comparing the average (mean) alanine aminotransferase (ALT) levels between young dogs and geriatric dogs. The average in young dogs is 40 μ/L, and in geriatric dogs is 80 μ/L. The null hypothesis is that the averages in the two groups are equal; the two-sided (meaning that either group could have a higher/lower average than the other) alternative hypothesis is that they are unequal. A two-group Student's t-test is performed, and a *P*-value of 0.10 is calculated. If the level of significance (α) is 0.05, then the difference is not statistically significant. What can one conclude from this?

First, it would be an error to state that there was "no difference" between the groups. Clearly, there was a difference (of 40 μ/L). It would, however, be correct to state that because the null hypothesis of no group difference was not rejected, there was no significant difference between the groups, assuming the assumptions of the statistical model are correct (because (P = 0.10) > (α = 0.05)).

Second, the P-value does not provide a quantitative assay of the probabilities that the null or alternative hypotheses are correct. Conventional (superiority) hypothesis testing is predicated on the veracity of the null hypothesis, and so does not provide any assessment of its truth. Instead, the P-value addresses an entirely different question: how likely (probabilistically speaking) is it that one would observe differences at least as large as the one found in the study (40 μ/L) when the null hypothesis is true? In other words, instead of the P-value equaling the probability that the null hypothesis is true given the data observed in the study, it provides the probability of observing the difference in the data observed (or more extreme) given the null hypothesis is true. It follows that "large" P-values indicate substantial concordance with the null hypothesis, while "small" P-values indicate poor concordance with the null hypothesis (presumably motivating its rejection in favor of its alternative).

Third, a P-value is only numerically correct under a particular statistical model. With the Student's t-test example, the underlying model assumes that the ALT values in each group are approximately normally distributed. If the assumption of normality is violated, however, the P-value will no longer be correct; the greater the departure of the data distribution from normality, the more incorrect the P-value will be.

Fourth, another assumption is that the study data are independent, meaning that knowing one individual's ALT value does not allow the ability to predict another individual's ALT value. In this example, such an assumption is reasonable when each individual contributes only one ALT value. However, when replicates from a single individual are included, it is plausible to assume that knowing an individual's value at one time can better predict the same individual's value at another time than the value from a different individual. Such a violation of the data independence assumption leads to the estimation of an incorrect P-value; typically, the use of correlated (nonindependent or dependent) data underestimates P-values, and hence more type I statistical errors (improperly rejecting the null hypothesis) arise.

Fifth, it is important to recognize that statistical analysis is more than the analysis of single numbers (i.e., point estimates, as in averages) in groups; instead, it is more correctly described as the analysis of variability. For this reason, the presence or absence of statistical significance is more than just reflective of the magnitude of differences or associations and the chosen level of significance; it is also a function of the variance of the point estimates. Because such variances are inversely proportional to sample sizes, two studies with identical differences or associations can have completely different P-values: the smaller study's differences could be nonsignificant, while the larger study's differences may be significant.

Sixth, it directly follows that any group differences or associations can eventually be made statistically significant if the study size becomes sufficiently large. To illustrate this, two random samples of 25 individuals each were created, one assuming blood hemoglobin was normally distributed with a mean of 15 g/dL and standard deviation of 2 g/dL, and the other with a mean and standard deviation of 15.1 and 2 g/dL, respectively. No one would seriously argue that a hemoglobin difference of 0.1 g/dL is clinically important, and indeed it is not significant at α = 0.05 (P = 0.79). However, if the two groups were constructed to have 2500 individuals each, with the same means and standard deviations, this same clinically unimportant difference (0.1 g/dL) becomes statistically significant (P = 0.023). This underscores an important distinguishing principle of statistical analysis: statistical significance is distinctly different from and does not imply medical importance. In a large enough study, even trivial and unimportant differences can become statistically significant; in a small study, differences that appear to be worthy of medical pursuit may be statistically insignificant. In recognition of this principle, alternative methods of hypothesis testing have been developed that instead of examining superiority of one group over another, evaluate whether groups are noninferior or equivalent based on a determination of what constitutes an acceptably important difference or association [7].

Finally, each decision to reject or not reject a null hypothesis following hypothesis testing is prone to error. What is often unappreciated is that the more tests that are performed, the greater the probability that at least one decision will be incorrect. In a clinical setting, this is perhaps most manifest when performing clinical laboratory testing panels to screen for hematologic or chemical abnormalities in blood. Reference ranges for blood parameters are typically constructed to encompass approximately 95% of normal animals, implying that 5% of normal animals will have values falling outside the ranges.

When a reference range is appropriate for a patient's age, sex, and any other factors that can influence a particular blood parameter, it is reassuring that a normal animal's value will fall within the reference range 95% of the time. However, a universally accepted practice is to run laboratory panels simultaneously evaluating many parameters. Suppose, for example, that a blood chemistry

panel contains 30 different parameters to evaluate. Although each separate parameter has a 5% probability of being incorrect in a normal animal, when considering all parameters the probability of at least one error rises to 78.5%. In other words, a veterinarian should be surprised if at least one parameter does not fall outside the reference range even in a healthy patient.

Another related problem arises when using screening tests with imperfect properties (false-positive and -negative results) in populations with low prevalences of illnesses. Even when the test properties are excellent, with error rates less than 5%, if a disease is rare enough in a population of patients being screened, there can paradoxically be more false-positive results than true-positive results. This should be discomforting to veterinarians whose clinical decisionmaking depends on the veracity of diagnostic testing.

One approach to resolving this issue (apart from running the test again to see if the result was aberrant) is to use screening tests judiciously, reserving them for patients with a heightened suspicion of actual illness. In other words, clinical judgment and experience are as integral to the use and interpretation of diagnostic tests as contrasting the actual test results to reference ranges. Such circumspection serves to elevate the likelihood of illness in the patient being tested, or analogously the prevalence of the illness in the population being screened. This will contribute to making fewer unjustified conclusions about abnormal results in otherwise healthy patients.

Parametric versus Nonparametric Tests

All statistical tests have assumptions underlying their use. Those that assume that data follow a particular probability distribution function (also known as the sampling model) are called parametric tests (by virtue of the fact that the functions have one or more parameters in them). Probably the most common distribution function used in parametric statistical analyses is the normal distribution (with two parameters: the mean and standard deviation). As noted earlier, Student's two-group t-test assumes that the data in each group are approximately normally distributed. Other well-known parametric tests also rely on normality: the paired t-test assumes the differences are approximately normally distributed; analysis of variance and least-squares linear regression assume the model residuals (the difference between observed and predicted values) are approximately normally distributed.

How can a clinician know if data are normally distributed? Various approaches exist, including distributional tests (for example, Shapiro–Wilk, Shapiro–Francia, Kolmogorov–Smirnov tests) and plots (for example, normal probability plots). Such tests assume data are normally distributed; rejection of the null hypothesis indicates incompatibility with the null hypothesis of normality.

The problem with such tests is that they are notoriously inadequate to detect departures from normality when sample sizes are small. For example, consider the following six data points: 100, 100, 80, 70, 50, 50. This is a U-shaped distribution and so is clearly not normally distributed. Nevertheless, a Shapiro–Wilk test fails to reject the null hypothesis that the data are normally distributed when $\alpha = 0.05$ ($P = 0.22$), so if we relied on this test result we would erroneously conclude that the sample data derived from a population with a normal distribution. Interestingly, if this dataset is doubled in size (n = 12), then the Shapiro–Wilk test would become significant ($P = 0.019$) and the null hypothesis of normality would be rejected.

When sample sizes are small or when normality is an untenable assumption, then alternative statistical tests are sometimes available. These tests are called nonparametric tests, because they do not assume that data follow a particular distribution, and hence are also known as distribution-free tests. Table 2.1 contains a list of the most commonly used nonparametric tests, as well as their equivalent parametric test (if one exists).

These tests have more statistical power (for example, the ability to reject the null hypothesis when it is false) than parametric tests when data do not conform to a parametric distribution (such as normality), and are almost as powerful as parametric tests when the data do conform to a parametric distribution. When the assumption of normality is questionable based on statistical tests or the sample size is too small for reliable testing, nonparametric tests are preferable whenever possible.

Describing Data Distributions

For data that are approximately normally distributed, it is customary to describe the center of the distribution with the sample average (i.e., mean), and to describe the dispersion around the mean with either the standard deviation or the standard error of the mean (i.e., the standard deviation divided by the square root of the sample size). When data are not normally distributed, however, it is generally advisable to describe the data with statistics that do not assume a symmetric distribution around the mean. Preferable measures to use include medians, ranges, and percentiles of the data (for example, the 2.5th and 97.5th percentiles provide a 95% percentile-based interval).

Table 2.1 Commonly used parametric and equivalent nonparametric statistical tests in biomedical research.

Types of data	Type of statistical problem	Parametric test	Nonparametric test
Continuous	Two independent samples	Student's t	Wilcoxon-Mann-Whitney
	Two dependent samples	Paired t	Wilcoxon signed rank
	Three or more independent samples	Analysis of variance (one-way)	Kruskal-Wallis
	Three or more ordered independent samples		Jonckheere-Terpstra
Categorical	Unordered 2 × 2 table		Fisher's exact
	Unordered R × C table[a]		Pearson's Chi-square
	Single ordered R × C table[a]		Kruskal-Wallis
	Doubly ordered R × C table[a]		Jonckheere-Terpstra
	Two dependent samples		McNemar's (two levels) Marginal homogeneity (three or more levels)
	K independent ordered proportions[b]		Cochran-Armitage trend
	K dependent samples	Repeated measures analysis of variance (one-way)	Friedman
Ordinal	Association of two samples	Pearson correlation	Spearman correlation

[a] R = number of rows, C = number of columns.
[b] K = number of proportions or samples, K > 2.

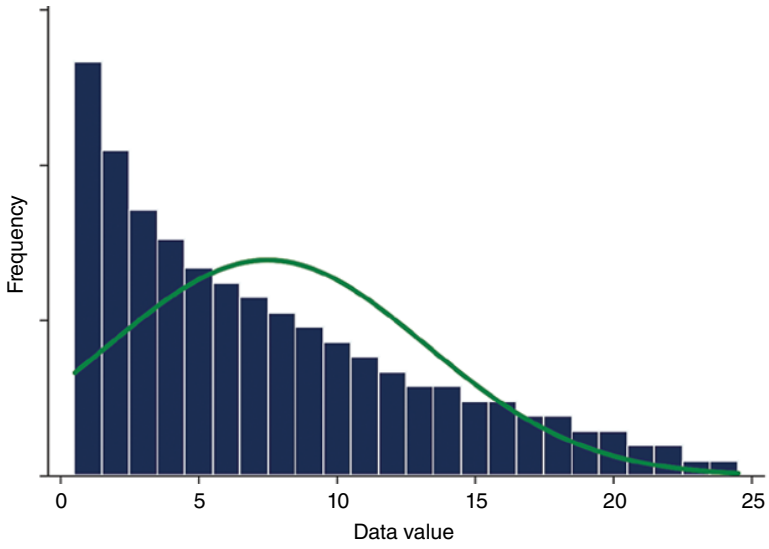


Figure 2.1 Histogram showing a hypothetical asymmetric data distribution. The green line illustrates the poor fit of a normal (Gaussian) distribution to the data.

To illustrate this point, Figure 2.1 shows a histogram of a data distribution that is clearly not normally distributed. Superimposed over the histogram is a curve of a normal distribution whose shape is completely determined by the mean and standard deviation of the actual data. Because the curve fails to closely approximate the histogram, the mean and standard deviation used to create the curve similarly fail to describe the center and dispersion of the data. For example, the mean = 7.5 while the median (i.e., the 50th percentile) is only 6.0. Similarly, the range of the data extends from 1 to 24, but a 95% confidence interval of the data distribution based on the mean and standard deviation would have a lower bound less than 0, which is less than the smallest possible

observed value. This underscores the point that when data do not conform to a particular parametric distribution, it is preferable to use a method of describing the data that does not depend on specifying a particular distribution.

Graphically representing such data is likewise inappropriate when using bar charts based on means and error bars using standard deviations or standard errors. One indispensable way of graphically portraying such data is through the use of a box and whiskers plot, as shown for the data above in Figure 2.2.

The advantage of such graphs is that they are constructed based only the data, and not on any distributional assumptions (such as normality). The lower and upper ends of the box correspond to the 25th and 75th percentiles respectively; the horizontal line within the box corresponds to the 50th percentile (i.e., the median), the bars (i.e., the "whiskers") above and below the box contain all data above and below 1.5 times the vertical width of the box (i.e., the interquartile range), and the individual points beyond the whiskers represent extreme (outlying) values. Figure 2.2 reinforces the observation from the histogram that the data are skewed towards higher values, which causes the mean to be larger than the median. This type of plot is also valuable in assessing symmetry of a data distribution (asymmetric distributions should not be described with means and standard deviations) and for identifying outliers that may represent data errors.

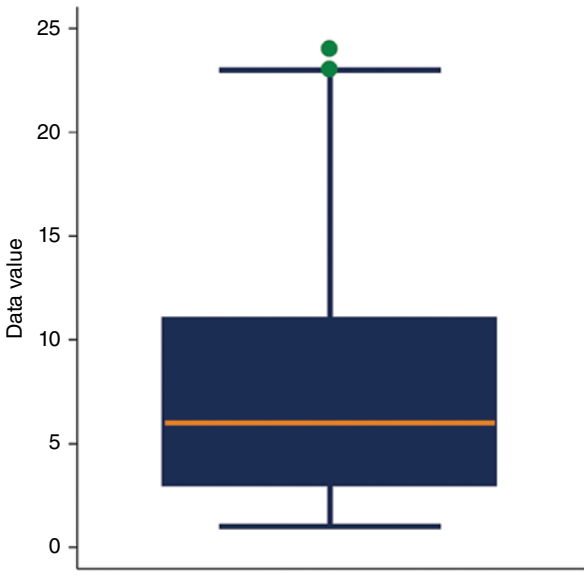


Figure 2.2 Box and whiskers plot for data shown in Figure 2.1. Lower and upper ends of the box represent the 25th and 75th percentiles, respectively; the orange line within the box equals the 50th percentile (median), the bars ("whiskers") above and below the box contain all data above and below 1.5 times the interquartile range, and individual points beyond the whiskers represent outliers.

Another common error arises when replicate measurements are taken from the same patient over time. This arises, for example, when two or more treatments are successively tested in patients with before/after comparisons, or when monitoring blood values over time. As mentioned earlier, *n* replicate measurements taken from a single individual cannot be treated as equivalent to single measurements coming from *n* different individuals.

Figure 2.3 illustrates this principle by examining before/after measurements taken on five patients at different times. Both panel 1 (left) and panel 2 (right) contain the identical 10 points but panel 1 ignores the pairing within individuals, and a regression line fitted to the 10 points suggests a negative correlation between the measurements over time. Panel 2, in contrast, links the before/after pairs within individuals and an entirely different picture emerges: every individual's values actually increased over time. Ignoring such pairing not only obscures actual effects but also in cases such as this suggests a paradoxical reversal of effects. Therefore, in studies where two or more measurements are taken from the same patients over time, it is important to not combine the patients' values at individual time points through the use of histograms, boxplots, or other graphical representations. Panel B is often called a "spaghetti plot" because it can, with larger numbers of individuals, take on an appearance of many intertwined lines across two or more times.

Measures of Association and Effect

As noted earlier, the construct and interpretation of the *P*-value is unsatisfying, if not bewildering to consumers of statistical analyses who are not well versed in their subtleties. The preoccupation with statistical testing in the medical literature should presumably be subordinate to and supplanted by a more favorable inclination towards estimation: the mathematical calculation of statistics that measure the magnitude of differences and associations in data. The imperative for this is no more evident than in the often seen but erroneous exposition that "no differences were found from a set of analyses because none were statistically significant."

Among the most common intuitively appealing measures of association are those conjoined from descriptive measures of prevalence and incidence.

Prevalence

Prevalence represents the proportion of individuals in a population who, at a single point or restricted period of time, possess a health characteristic of interest, as in

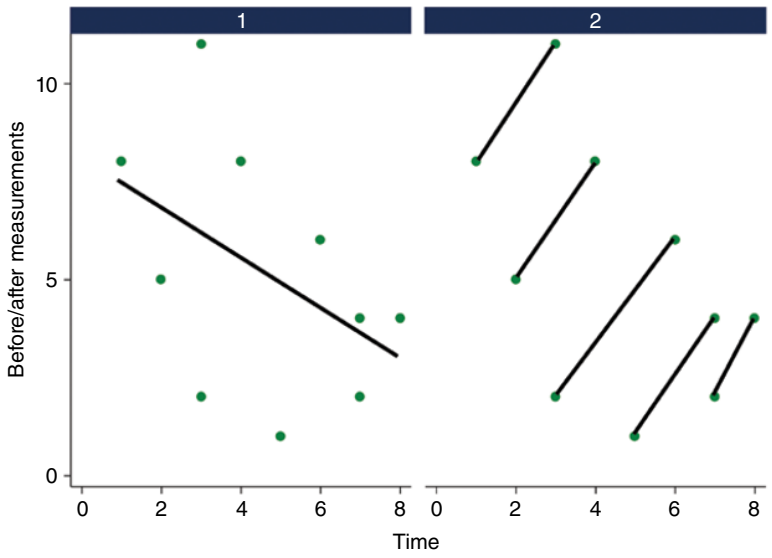


Figure 2.3 Scatterplots showing before and after measurements taken on five individuals. Panel 1 (*left*) contains a regression line with a negative slope estimated ignoring the pairing within individuals. Panel 2 (*right*) shows the paired observations, demonstrating that all measurements within individuals increased over time, in contrast to the incorrect impression conveyed in panel 1.

having a disease (or conversely being disease free). The factors that constitute why an individual possesses such a health outcome are intertwined, reflecting contributions from the risk of developing the outcome, the probabilities of recovering, succumbing, or remaining with it over a short or long time (i.e., its duration), and the probability of remaining in the population. Because the contribution of the risk of developing the outcome, also known as incidence, cannot be isolated from the effects of the other respective factors influencing prevalence, prevalence measures cannot serve as surrogates for measures of risk, incidence, or effects.

To illustrate this, suppose 100 dogs are born in January 2015 and all become chronically infected with a virus in their first three months of life so that their three-month risk of infection is 100%. Also suppose that infection only begins to be cleared after 18 months of age and is eliminated at 24 months of age. Then consider another 100 dogs born in January 2016, which all become infected in their first three months as well. Therefore, the three-month risk of infection in both groups is 100%. Unlike the other dogs, these dogs begin to clear their infection almost immediately (perhaps due to vaccination or postinfection treatment), and by six months are disease free.

However, suppose this incidence information was unknown, and a cross-sectional study of both sets of dogs (n = 200) is performed on June 30, 2016 (i.e., there is no attrition from the combined population). On this date, the prevalence in all 200 dogs will precisely be 50% because the prevalence will be 0% in the 6-month-old dogs (n = 100) and 100% in the 18-month-old dogs (n = 100). It would be an error, however, to use these prevalence figures to claim that older age is a risk factor for infection because, unknown to the study investigator, 100% of the dogs under three months of age developed the infection; if we assume recovery from infection confers immunity, it is impossible to even address the issue of age above 3 months as a risk factor. This underscores the fallacy of using prevalence to infer risk when factors that affect risk also affect recovery or mortality or leaving a population.

Prevalence nevertheless has value in quantifying the relative burden or presence of a health outcome in a population at a particular point in time. Clinicians may, for example, use disease prevalence to guide their pharmaceutical inventories or preventive medicine programs. Measures of relative prevalence can also be informative in hypothesis generation. To understand this, suppose the prevalence of antibodies to a particular organism is found more frequently in dogs with immune-mediated polyarthritis than in dogs without arthritis. This is no guarantee that the antibody response associated with infection of the organism causally leads to cross-reactivity with synovial membranes or joint surfaces, because there is no way by measuring only prevalence to distinguish infection occurring prior to onset of polyarthritis from infection occurring afterwards. Such a finding could, however, lead to experimental confirmation (or refutation) of the hypothesis that infection leads to polyarthritis. Serologic surveys are frequently used for this hypothesis-generating purpose.

Cumulative Incidence

In contrast, incidence is more appropriate for inferring risk (which can be defined as the average probability of developing a health outcome of interest in a specified time interval). Incidence, by definition, is predicated on the initial absence of the outcome among the members

of a population at risk of experiencing the outcome. The population is then followed forward in time, and within a specific time period cumulative incidence is defined as the proportion of the individuals initially at risk that newly develop the outcome (assuming no individuals have been lost to follow-up), and can only strictly fall between 0 and 1. If 300 Yorkshire terriers were followed from birth for five years without any dental interventions, and at the end of this time the presence of tooth resorption was found in 100 dogs, then the five-year cumulative incidence of tooth resorption would be 0.33 (assuming that there were no dogs that spontaneously recovered from it).

Cumulative incidence alone is not a measure of association. However, comparing two or more cumulative incidences under different conditions allows such associations to be quantified. Suppose that in addition to the finding in Yorkshire terriers above, the five-year cumulative incidence of tooth resorption in border collies was also measured as 0.10. Two important statements can now be made about these two figures. First, that over the five-year follow-up period the difference in cumulative incidences between Yorkshire terriers and border collies is 0.20 (0.30 – 0.10). Second, that over the five-year follow-up period there is a three-fold increase (0.30/0.10) in the cumulative incidence in Yorkshire terriers compared to border collies. These two measures of association are known as the *cumulative incidence difference* and the *cumulative incidence ratio*, respectively. Other terms that remain in use include risk difference and attributable risk for the former, and risk ratio and relative risk for the latter (these terms should be used with caution, however, because risk implies causation, and statistical measures are distinct from causal measures without corresponding strong causal assumptions that must be invoked).

Nevertheless, the cumulative incidence ratio is particularly well suited to effectively communicating relative impacts of factors on health in clinical practice because of its intuitive understandability. Statistical novices can appreciate, for example, a statement such as: "The incidence of parvovirus in unvaccinated puppies under 6 months of age is 10-fold greater than in vaccinated puppies."

Our understanding of how vaccines, the immune system, and viral infections work could also reasonably allow us to modify this statement by substituting the word "risk" for "incidence." Such strong biologic knowledge is not always apparent, however, which should motivate caution when using words with causal interpretations like "risk" or "likelihood." Physicians would have no hesitancy in making the correspondence between the association of tobacco smoke with lung cancer and heart disease with the statement that the risk of lung cancer and heart disease is greater among smokers than nonsmokers. However, no one would seriously entertain making such a correspondence between the association of carrying matches with lung cancer and heart disease and any causal effect. Therefore, statements about "risk" differences and ratios are best reserved for situations where the justification for alleging a causal relation is supported by knowledge other than purely statistical.

Incidence Rates

When patients are not all followed for the same amount of time, the cumulative incidence should not be utilized because the reasons for loss to follow-up (known as *right censoring*) could be related to the risk of the outcome developing. Instead, another, less intuitive measure of incidence that allows for different follow-up in each individual is the *incidence rate* (also sometimes called the hazard rate). In contrast to cumulative incidence, a proportion that has an interpretation always linked to a defined period of time, the incidence rate in a population is a joint function of the number of new (incident) outcome occurrences divided by the sum of the individual times at risk of an outcome among the members of the population, and is expressed as the number of outcomes per unit of time (for example, days, months, years, etc.). Incidence rates are analogous to speeds; across populations, they estimate the average number of outcomes expected to occur per quantity of time.

Incidence rates have particular utility in studies measuring the time from onset of follow-up to when an event occurs. Such events can be recovery, death, remission, or other outcomes. One of the most common applications for incidence rates is in survival studies of comparative treatment efficacy, where particular interest is in the rate of death (or, conversely, survival).

Suppose that in Yorkshire terriers the incidence rate of tooth resorption = 0.3 case/dog-year (or, equivalently, 30 cases/100 dog-years). This can be interpreted to mean that if 100 dogs were each followed for one year, that 30 cases would be expected; it can also be interpreted to mean that if 50 dogs were each followed for two years, 30 cases would be expected, and so on. The independence of the incidence rate from the number of individuals is perhaps best understood through the analogy of measuring the average speed of automobiles: whether 60 cars each travel one mile in one minute or one car travels 60 miles in 60 minutes, under both scenarios the total distance traveled is 60 miles, the total amount of time traveled is 60 minutes, and the speed is 60 miles per hour.

As with cumulative incidence, it is frequent to see incidence rates compared on a ratio scale to measure relative associations; these are called *incidence rate ratios* or *hazard ratios*. An incidence rate ratio greater than 1 implies

that the rate of the outcome occurring under the numerator condition (such as treatment A) is faster than the rate under the denominator condition (such as treatment B); conversely, an incidence rate ratio between 0 and 1 indicates that the rate of the outcome occurring under the numerator condition is slower than the rate under the denominator condition.

Returning to the above example, if the rate of resorption in Yorkshire terriers is 30 cases/100 dog-years, and the rate of resorption in border collies is 10 cases/100 dog-years, then the incidence rate ratio is 3.0. Not only does this indicate that the rate of developing tooth resorption is three times faster in Yorkshire terriers compared to border collies, but it also means that the time to developing tooth resorption is less in Yorkshire terriers, and that the proportion of dogs remaining free of tooth resorption (i.e., "surviving") is greater in border collies at all times.

Incidence Odds and Incidence Odds Ratios

Perhaps the least understood yet ubiquitously found measure of association in the veterinary medical literature is the *odds ratio*. Although odds ratios arise under different study designs (both experimental and nonexperimental), and their interpretations can vary, these differences are less critical than the properties they share as measures of association and potential impact of factors on the incidence of health outcomes. In order to understand odds ratios, it is necessary to first understand the statistical meaning of an *odds*.

Probabilities are measures of the likelihood of an event occurring, and are only strictly between (and including) 0 and 1; a probability of 0 implies impossibility and a probability of 1 implies inevitability. The odds is another measure of likelihood, and is calculated as the probability of an event occurring divided by the probability of an event not occurring (note that the sum of these two probabilities must equal 1). When the probability of an event occurring equals 0, the odds equals 0. However, when the probability of an event occurring equals 1, then the probability of an event not occurring equals 0, and the odds (which would equal 1 divided by 0) is undefined but infinitely large.

The restricted range for probabilities versus the infinitely large range for odds necessarily makes the former more understandable and desirable when communicating biostatistical findings. For example, if the probability of a 14-year-old cat developing hyperthyroidism in the ensuing years of its life is 0.60 (which can equivalently be expressed as 60%), then the odds of developing hyperthyroidism is 1.5 (but there is no percentage equivalent). This leads to two related but important findings. First, as the probability approaches 1, the odds becomes unintelligibly large (for example, a probability of 0.95 corresponds to an odds of 19, while a probability of 0.999 corresponds to an odds of 999). Second, when the probability is small (between 0 and 0.05), such as with the incidence of a rare disease, the odds is similarly small (between 0 and 0.053, respectively). This implies that *for rare events*, probabilities and odds are nearly equal, and for interpretive purposes are essentially interchangeable.

While odds, just like probabilities, can be expressed as unconditional (not depending on the values of other factors) estimates, it is more common to see them expressed as conditional odds; for example, the odds of developing tooth resorption among Yorkshire terriers is a conditional statement because it only applies to Yorkshire terriers and not other dog breeds. Just as ratios of two different cumulative incidences and two different incidence rates can be calculated to measure proportionate changes in incidence between two levels of a variable, so can ratios of odds. Returning to the earlier example of the cumulative incidence of tooth resorption, if the five-year cumulative incidence in Yorkshire terriers is 0.3 and the five-year cumulative incidence in border collies is 0.1, then the five-year incidence odds in the two breeds are 0.43 and 0.11, respectively. Therefore, the odds ratio relating five-year incidence of tooth resorption in Yorkshire terriers compared to border collies is 0.43/0.11 = 3.86. This can be contrasted with the cumulative incidence ratio of 3.00, and the disparity between the two measures primarily arises because the odds in (0.43) does not closely approximate the cumulative incidence (0.3) in Yorkshire terriers because the latter is not rare.

Just as cumulative incidence, as a probability, is much more comprehensible than an incidence odds, so the cumulative incidence ratio is more comprehensible than an *incidence odds ratio*. Knowing in the above example that the cumulative incidence ratio = 3.0 makes the interpretation straightforward: the five-year cumulative incidence in Yorkshire Terriers is three times the incidence in border collies. In the absence of any biases, we could attach a causal interpretation to this and claim that the average five-year risk of dental resorption in Yorkshire terriers is three times the corresponding risk in border collies.

In contrast, no such interpretation can be attributed to the odds ratio of 3.86 above, because it is not in general interpretable either as a relative measure of either risks or incidence rates. While it is legitimate to interpret it literally as a relative odds, other interpretations that include "risk," "likelihood," "probability," and "cumulative incidence" are incorrect and should not be used. This begs

the question: of what value is the incidence odds ratio if it is interpretatively inferior to other ratio measures?

The answer is that in case–control studies, where study groups are selected based on whether or not they possess (cases) or do not yet possess (controls) the outcome of interest, it is not possible to directly calculate measures of incidence because the ratio of cases to controls is determined by the study investigator. Without the ability to calculate individual conditional incidence measures in subgroups, investigators are therefore similarly unable to calculate cumulative incidence or incidence rate ratio measures of association that depend on knowing individual ones. Fortunately, case–control studies are often reserved for studying rare diseases, even conditional on the levels of other variables such as potential risk factors, so using the aforementioned rarity condition that interpretatively equilibrates the cumulative incidence and the incidence odds, the incidence odds ratio can essentially be understood as the cumulative incidence ratio. Subtle modifications in case–control study designs can also sometimes provide more interpretative latitude in extending such equivalence to incidence rate ratios [8].

Conclusion

This chapter addresses many, but certainly not all, of the most common statistical interpretive issues that face readers of the veterinary medical literature. Appreciating these issues is an important avenue to understanding the basis for evaluating clinical research articles. But statistical analyses only represent one component of medical research; not addressed here are the myriad issues that arise in the course of designing and implementing experimental and nonexperimental studies. Because study design is also inextricably linked to precision and validity issues, statistical inference complements and cannot be divorced from causal inference in evidence-based veterinary medicine. Topics involving the design of studies to generate data for clinical decision making are the subject of the following chapter.

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3

Using Data for Clinical Decision Making

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The advent of the electronic medical record was accompanied by a new-found feasibility for veterinary medical practitioners, either at individual hospitals or through multiinstitutional collaborations, to gather, analyze, interpret, and publish their clinical data. While it is still common to read individual case or case series reports in medical journals, electronic data and searchable databases extend the ability of veterinarians to design more sophisticated studies that go beyond the bounds of being purely descriptive. Such design enhancements allow the measurement of differences and associations between two or more factors of interest, and in some cases lead to estimation of measures of effect that under assumptions of unbiasedness can lead to causal inferences.

Using clinically derived data to make informed medical decisions is a central tenet underlying the practice of evidence-based medicine, an evolving form of scientific scholarship that seeks to bring objectivity and elucidation to the implementation of medical investigation, and that exists at the confluence of medicine, basic sciences, applied mathematics/biostatistics, epidemiology, and causal inference. Using data analytically is only one component of evidence-based medicine, and cannot be dissociated from equally important others. While collaboration is all but essential in ensuring that these respective component specialties are well represented, of most proximate importance to veterinarians seeking to advance beyond the hypothesis phase of their clinical research is a fundamental understanding of hospital-based epidemiologic study design, for this is the study type that determines the data collected, and in turn how it should be analyzed and interpreted [1].

The most common study designs employed in clinical veterinary research will be considered in subsequent sections of this chapter. These will be broadly partitioned into two temporal types. The first involves data measurements taken on an assemblage of patients all present at a point in time, or on a succession of patients enrolled over a typically brief period of time to obtain an adequate total sample size, which are called "cross-sectional studies." The second involves those with data on groups of patients with some defining inclusion criteria collected over a specified period of time, allowing measurement of a temporal change in patient characteristics and health status, which are called "longitudinal" studies. The latter can be further subdivided into those that are interventional (the clinical analog of experimental), where the investigators have control over the treatment(s) of primary interest the patients receive, and observational (nonexperimental), where the investigators can passively or actively record, but not manipulate, the treatment(s) of primary interest. The focus here on treatments arises from the nature of clinical research: any treatment in a clinical setting should be pursuant to the best interests of the patient and owner, and should not be any lesser quality of treatment than the accepted standard of care in veterinary medical practice.

As noted, analyses of treatments are not restricted to interventional longitudinal studies, although it will be shown that observational longitudinal studies of treatment effects are prone to potentially severe biases. Longitudinal studies also need not be restricted to studying treatment effects: intrinsic characteristics of patients, and how those may be associated with clinical sequelae, may instead be a primary objective of a researcher.

Hospital-Based Cross-sectional Studies

Cross-sectional studies are conducted when a clinician wants to establish an inventory of disease burden, patient characteristics, and exposure to factors in a population. A shelter veterinarian, for example, may be interested in knowing the crude proportion of a shelter population at any defined time point that has clinical signs of upper respiratory disease. This proportion is

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called the "prevalence" (see Chapter 2 for examples), and is contextually tied to a specific point in time. Knowing such information may be valuable in planning preventive initiatives and having an appropriate inventory of pharmaceuticals available. Hospitals, however, may not have an adequate number of patients at a single time to estimate prevalence, so instead patients fitting inclusion criteria may be captured over a period of time, and the frequency of the factor of interest is then obtained as patients are enrolled. This special type of prevalence is called "period prevalence" and is contextually defined by the beginning and end dates of patient accrual (e.g., the proportion of patients entering a hospital over one month present with clinical signs of upper respiratory disease). It is important to note that no assumptions need be made about when individuals with the outcome actually developed it; it is sufficient to note that at the time of measurement, they either had it or did not (the latter from either never having developed it or from recovering from it).

Prevalences measured from cross-sectional studies are not restricted to being crude (unconditional) measures. Factor-specific (conditional) prevalences are also estimable, as in sex-specific or age-specific prevalences. Moreover, such specific measures can be jointly used for comparative purposes, as in relative prevalences (prevalence ratios). For example, it may be of interest to estimate the proportionate change in the prevalence of feline leukemia virus (FeLV) infections in intact outdoor males compared to sterilized outdoor males.

Sampling in cross-sectional studies can be accomplished in several ways. The most straightforward is to either study an entire population of individuals or take a random sample from one. With either approach, individuals can be cross-classified by their health outcome status as well as other factors to assess joint associations. Using the previous example, the prevalence of FeLV can be measured in intact and sterilized outdoor male cats, or conversely the prevalence of male sexual status can be measured in cats with and without FeLV. Prevalence ratios provide an objective measure of how relatively common or rare an outcome of interest is between groups, but should not be used for causal inference (such as making statements about likelihood, risk, or probability of a health outcome) because when measured simultaneously, it is often not possible to know if prevalence factors, as putative risk factors, occurred prior to or after the health outcome occurrence. In addition, such factors may not potentially alter only disease incidence but also disease duration and recovery, all of which affect prevalence. Prevalence ratios, as measures of association, therefore have utility for hypothesis generation but lack a foundation for making inferences about causal associations.

An alternative approach to obtaining prevalence ratios when there is a health outcome is to sample subsets of a population defined by certain characteristics. For example, an investigator may choose to deliberately sample a fixed number of sexually intact and sexually altered male outdoor cats, and subsequently ascertain the prevalence of FeLV in these two groups. A prevalence ratio relating the prevalence of FeLV in one sexual status group versus the other is estimable, but not the converse due to the sampling being based on sexual status.

Another sampling variant of cross-sectional studies is the two-stage prevalence case–control study. This approach is indicated when a relatively rare disease in a clinical population is studied, and the goal is to estimate not the prevalence of the disease but instead factors that may be associated with it but cannot be readily measured without additional data gathering and consideration of cost/time expenditures. Initially, a cross-sectional study is undertaken in a clinical population to ascertain disease status. When the cost and effort of obtaining prevalence factor information prohibit procurement of it for every individual in the population, those with the rare disease (prevalent cases) can have it measured, along with only a sample of the remaining nondiseased individuals (nonprevalent controls). Thus, prevalence factor information is efficiently obtained only on a subset of the entire population – either all or some of the diseased individuals and a sample of the nondiseased individuals. The ratio of individuals in the two groups is at the discretion of the investigator, although a 1:1 ratio is statistically the most efficient for a fixed study size. The prevalence case–control study is the cross-sectional counterpart of the (longitudinal) incidence case–control study discussed later.

Longitudinal Observational Studies

The distinguishing feature of longitudinal medical studies, compared to cross-sectional studies, is that individuals are monitored over time, typically being followed from a state absent a particular health outcome to a later state that may or may not have experienced a change in outcome status. The two principal types of such studies are cohort studies and case–control studies, which differ in how individuals in them are sampled for study inclusion. Longitudinal studies may also be characterized by their temporality; relative to the study onset, they can be retrospective, with historical data being used during the follow-up period, or prospective, with future data being collected following study onset. Less commonly, studies can be ambispective, with both retrospective and prospective components.

Cohort Studies

Assemblages of patients that share one or more defining conditions, typically diseases or syndromes, are often referred to as a "case series" but can be more expansively thought of as a patient cohort. In a hospital setting, such patients present over a period of time; if the condition is common then the period of time for sufficient patient accrual may be brief, but if the condition is rare, it may take many years for an adequate number of patients to be enrolled unless a decision is made to extend patient enrollment to multiple hospitals. While population-based (epidemiologic) cohort studies typically study risk factors for disease incidence, the goal of hospital-based cohort studies is different: to study the outcomes of patients already diagnosed with diseases. Such outcomes are contextual to the specific diseases, but often include the occurrence of or time to remission, relapse, development of another disease condition, recovery, or death. By subdividing cohort members into groups defined by factors thought to influence the respective outcomes, it becomes possible to quantify and compare their effects.

There are two main types of outcomes of interest in the study of factors affecting cohorts of patients that share a disease in common. In this example, death will be the illustrative outcome, and sex will be the hypothesized determinant of death. The duality of outcomes is:

- whether or not death from the disease occurs following its occurrence in patients
- how long it takes death from the disease to occur (if it does) following its occurrence in patients.

The first outcome is not as straightforward to evaluate as might initially appear, because it depends on two related factors: how long a patient is diseased, and how long a patient is followed up.

To illustrate these points, consider a patient diagnosed with immune-mediated hemolytic anemia (IMHA) on January 1, 2013, and that succumbed to the disease on January 1, 2019. From the perspective of the investigator, did death occur? The answer is no if the follow-up time is less than six years (although death occurred after six years, the investigator would not have been aware of it); the answer is yes if the time period evaluated is longer than six years. Therefore, the qualified answer to the question depends on specifying the time of follow-up after the diagnosis is made. Clearly, the longer a patient is followed up, the greater the probability they will die (although not necessarily from IMHA). By convention, patients who do not experience the health outcome at the point that they are no longer observed at risk of it, because they were lost to follow-up, withdrew from the study, recovered, or died from a competing cause, are called "censored."

Suppose that the patient was lost to follow-up after four years, but was known to be alive up to that time. Did death from IMHA occur? The answer at the four-year time point is no, because the patient was not observed long enough for death to occur and be recorded. However, such an individual who did not die from IMHA after four years should not statistically be treated as equivalent to a patient still alive after an even longer period of observation. Because most patients are followed for different periods of time after disease diagnosis, an investigator would provide a distorted impression of the natural course of the disease by responding to the simplistic question, "What proportion of patients died?" A legitimate analysis would instead have to be limited to specifying an identical follow-up period for each patient, such as "What proportion of patients succumbed to IMHA within one year of diagnosis?" Of course, patients followed for less than one year would necessarily be excluded even from this analysis.

Because follow-up times vary so much in patients recruited over long periods of time, a preferable analytic approach takes into account not only if a patient eventually died from the disease, but also how long they were alive prior to death. The apposite question instead becomes: "What is the probability of patients dying from IMHA after accounting for different periods of time under observation following diagnosis?" The answer, a probability that depends on the time interval after diagnosis and characteristics of patients that influence survival, will fall between 0 and 1. This kind of analysis is generically known as a "survival analysis." One approach commonly used to estimate these probabilities is called the "product-limit method of survival/failure function estimation" or, equivalently and eponymously, a "Kaplan–Meier analysis."

To illustrate the distinction between counting the proportion of patients who die and the probability of a patient dying as a function of time, consider a hypothetical cohort of 12 patients. Four patients each have either five, six, or seven years of follow-up, and within each group of four patients, two die and two either do not die or are lost to follow-up at the end of their follow-up period.

The crude proportion of these 12 patients dying is 50%, but that figure is entirely misleading because of unequal follow-up times. In contrast, a statistical analysis projects that the probability of dying after five years is 17%, after six years is 38%, and after seven years is 69%. The latter analysis is valid because it accounts for not only whether or not death occurred, but also how long a patient was at risk of dying (by including censored patients).

It is also possible to estimate the time it takes to reach a certain probability of death. For example, the time it

takes for an estimated 50% probability of patients to die is called the median survival time. In the above example, the median time to death is seven years. With larger datasets, it would also be achievable to estimate the time it would take for a 10%, 25%, 75%, 95%, etc. probability of death.

In the less common case that patients are followed for identical periods of time, or inferences are restricted to briefer periods that most or all patients were followed through, it becomes possible to estimate the risk of outcomes for such time periods, either unconditionally or conditional on possible determinants of the outcomes. For example, the one-year risk of death from patients diagnosed with IMHA conditional on sex can be calculated, and expressed (typically) as a risk ratio (sometimes referred to as a relative risk). It is conventional to report ratio statistics accompanied by: (1) their respective 95% confidence intervals to demonstrate the degree of precision associated with the statistic, and (2) *P*-values corresponding to a test of the null hypothesis that the risk ratio = 1 (i.e., there is no difference in the risks of the outcome between the groups compared in an analysis), which are interpretable as the probabilities of finding risk ratios >1 at least as large (or risk ratios <1 at least as small) as those observed in the study when the null hypothesis (of no difference in risks) is correct.

In the preceding paragraph, the phrase "rate of death" was deliberately not used because a rate is neither a proportion nor a probability. Instead, a rate can be thought of as a "velocity" – how much of an event occurs as a function of time (e.g., miles traveled per hour). In this setting, it is possible to estimate such a rate: the number of expected deaths for each year(s) of being a patient. Using the example above, the average (constant) rate of death equals 0.0833 death/patient-year as a patient (obtained by dividing the number of deaths [6] by the total amount of time all patients spent alive and at risk of dying [72 years]). Although this number is admittedly difficult to understand because it is not possible to have a fractional death, it is better understood when inventorying multiple years as a patient: 8.3 deaths for every 100 patient-years alive, six deaths for every 72 patient-years alive, etc.

Using rate information is invaluable in assessing the course of a health outcome because it is possible for the probability of the outcome to be the same across groups for the same amount of follow-up, even while the rates of the outcome occurring are different. To illustrate this, consider two drugs (drug A and drug B) used to cure a particular disease, both of which are 100% effective. However, drug A cures the disease much faster than drug B, making drug A more desirable than drug B (ignoring other relevant issues such as cost, side-effects, etc.). This is equivalent to saying that the rate of cure under drug A is higher than the rate of cure under drug B.

We can assign hypothetical numbers to further the discussion. Suppose the six patients receiving drug A were cured at 1, 2, 3, 4, 5, and 6 weeks following administration; those receiving drug B were cured at 7, 8, 9, 10, 11, and 12 weeks following administration. In both groups the probability of cure by 12 weeks was 100%. However, the rate of cure in the drug A group is 0.29 case/week, while the rate of cure in the drug B group is 0.11 case/week (calculations not shown). This is illustrated in the Kaplan–Meier plot in Figure 3.1.

Having now calculated the rates of cure (by drug group), it becomes possible to finally ask the question: how does the rate of cure from drug A compare (relatively speaking) to the rate of cure from drug B? The answer to this is to simply take the rate from drug A and

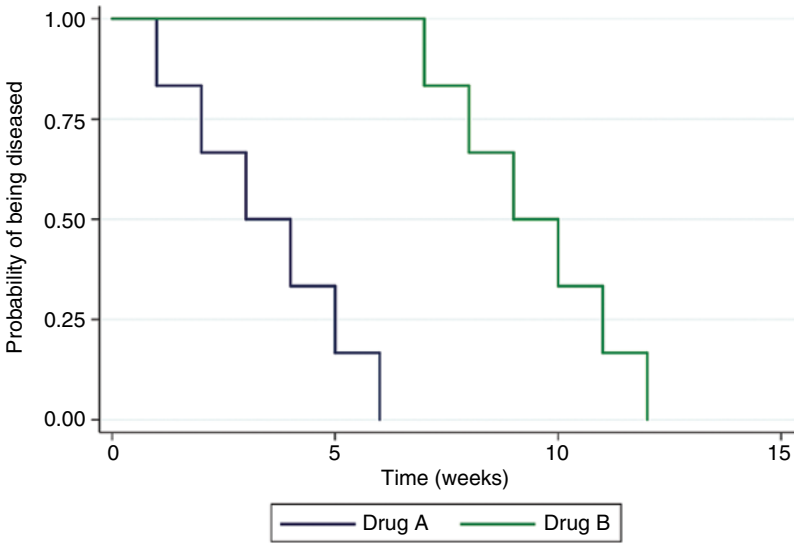


Figure 3.1 Rate of cure illustrated in a Kaplan–Meier plot.

divide it by the rate from drug B; this is called the incidence rate ratio, which is often equivalently reported as the hazard rate ratio or incidence density ratio. In this example, the rate ratio = 0.29 / 0.11 = 2.7; this can be interpreted to mean that the rate of cure from drug A is 2.7 times greater than the rate of cure from drug B, even though the eventual probability of being cured is 100% in both drug groups.

When the rates in the two groups being compared are identical, then no matter what those rates are, the rate ratio will always equal 1.0. Typical significance tests that are performed on such cohort data assume that the rate ratio equals 1.0 – this is the "null hypothesis." Rejection of the null hypothesis (using a type I error proportion of 5%) implies that the rate ratios at least as large (or small) as those observed are unlikely (with a probability of less than 5%) to have arisen when the null hypothesis and model assumptions are correct – and thus the data are relatively incompatible with the null hypothesis. It is conventional to report rate ratio statistics accompanied by: (1) their respective 95% confidence intervals to demonstrate the degree of precision associated with the statistic, and (2) *P*-values corresponding to a test of the null hypothesis that the rate ratio = 1 (i.e., there is no difference in the rates of the outcome between the groups), which are interpretable as the probabilities of finding rate ratios >1 at least as large (or rate ratios <1 at least as small) as those observed in the study when the null hypothesis (of no difference in rates) is correct.

There are, however, compelling reasons not to use hospital-based cohort studies to study treatment efficacy between groups of patients. In contrast to intervention studies, where treatment is randomly assigned, cohort study patients are intentionally (and, pointedly, non-randomly) administered a particular treatment by choice. For example, one treatment may have been available during earlier years of patient enrollment, but was later superseded by an alternative preferred treatment. A cohort study comparing these treatments would be unable to discriminate between any possible effects they had and any effects related to time (such as from amended standards of care, veterinarian experience and adeptness at treating cases over time, different clinicians of potentially different abilities treating patients across times, trends in disease severity seen over time at the hospital, etc.). In addition, clinicians administer treatments in part by using their acuity to judge patient severity; one treatment may be indicated for milder cases, while an alternative treatment, that may be more costly and risky but potentially superior, may be earmarked for cases with the poorest prognoses. Again, it would be problematic for the investigator to distinguish whatever treatment effects may exist that are distinct from the effects of disease severity (or any other influences) that inspired a particular treatment regimen by a veterinarian. This type of bias is called "confounding by indication," and all nonrandomized studies of treatment efficacy are potentially susceptible to it. The inability to statistically control for this bias, particularly in retrospective studies where the reason for selecting a treatment may not be in the medical record, should presumably dissuade investigators from conducting nonrandomized studies of treatment efficacy.

Case–Control Studies

In one sense, a case–control study is a size- and cost-efficient variant of a cohort study. Both are longitudinal (retrospective or prospective), can be performed on the same population, and are designed to investigate how one or more potential measured risk factors may affect the occurrence of measured specified health outcomes (such as becoming diseased). An important way in which they differ is in how populations are sampled for study inclusion. In cohort studies, investigators take a census of a population, unconditionally sample it, or sample it conditional on risk factor status. In contrast, in case–control studies, investigators always sample conditional on outcome (typically disease) status, selecting cases and controls. The studies also differ with respect to the statistical interpretation of their respective effect measures. Cohort studies, by virtue of their ability to estimate rates and risks, allow the use of these statistics to construct comparative measures of putative effect, such as risk ratios and incidence rate ratios. Case–control studies, because of their unique sampling design, estimate odds ratios (see Chapter 2 for a detailed explanation of this statistic).

For illustration, consider a study designed to test the hypothesis that vaccination leads to a transient (two months) increase in the risk of IMHA in dogs. A hospital-based cohort study could be undertaken by either: (1) enrolling some or all patients at risk of IMHA to the hospital, assessing their vaccination histories, and observing the subsequent incidence of IMHA conditional on vaccination histories, or (2) conditionally enrolling dogs known to have been vaccinated and comparing them to enrolled dogs confirmed to have not received vaccines, and then measuring subsequent IMHA incidence. Both approaches could be done retrospectively, provided vaccination histories were in the medical record and there was sufficient patient follow-up to determine if IMHA occurred, or could be done prospectively by placing the enrolled dogs with recorded vaccine histories under surveillance for disease onset.

The problem with this approach is that IMHA is a relatively rare disease, and regardless of whether the cohort study was done retrospectively or prospectively, it would

be unlikely to have many cases of IMHA enrolled unless the population was very large, adversely affecting statistical precision and jeopardizing the ability to make conclusions. Moreover, it would require comparing vaccination histories on a disproportionately large number of dogs that never developed IMHA for comparison to a disproportionately small number of dogs that did, adversely affecting study efficiency.

If an adequate number of cases exist in a hospital registry (or those of multiple hospitals or diagnostic laboratories, etc.), a far more efficient approach to studying factors affecting the incidence of a rare disease is to take a census or sample of the cases from the registry, and for comparative purposes take a sample of dogs (controls) never diagnosed with IMHA (but theoretically at risk of getting it later in life) from the same registry. The ratio of controls to cases is at the discretion of the investigator; if resources dictate that only a fixed number of cases and controls can be included in the study, a 1:1 ratio is most efficient. If the cost of obtaining risk factor information on the patients is not an important consideration, then a ratio of up to 4–5 controls per case is usually sufficient for statistical precision.

Although controls can be taken at any time during the period of case accrual, there are distinct statistical and interpretive advantages to selecting them at the same time that cases are diagnosed. Such matching on time can be extended to additional confounders, such as hospital (in a multicenter study) and age, but most other confounders can be controlled for by an appropriate matched analysis.

The advantages to matching controls to cases on time are several-fold. First, if time itself was a confounder of the risk factor–disease relationship (i.e., if disease incidence and the distribution of the risk factor in the population change over time), then effective analytic control of it would almost certainly be impossible without matching if the period of case accrual was long. Second, the odds ratio calculated from the case–control study can be interpreted as a risk ratio when the incidence of disease is believed to be rare in all categories of the risk factors (and confounders). Third, if the disease incidence is not rare, the odds ratio can still be interpreted as an incidence rate ratio, described earlier for cohort studies. However, analyses of matched case–control data are complex when more than one control is matched to a case, and require a computer with software capable of performing conditional logistic regression.

The most difficult design issue in case–control studies is that of proper control selection. Cases can be thought of as originating from an underlying source population of individuals at risk of developing the disease, and controls are, simplistically, a sample of that source population. Just as the distribution of risk factors is measured in the cases, the distribution of the same risk factors is also measured in controls. Setting aside the issue of matching, conceptually the distribution of risk factors in a control group not subject to selection bias effectively mirrors that same distribution in the source population. Matching is a technical violation of this principle, because matching on a confounder alters the distribution of the risk factors in the controls to be more aligned with that of the cases, but this intentional design feature that leads to an unintentional selection bias can be remediated through a proper matched statistical analysis.

The problem with this conception of a control group as a representative sample of a source population of cases is one of practicality: for a hospital that is not in a geographically restricted region, it is not at all clear what the source population is. There are many reasons, known and unknown, why owners elect to have their pets treated or not treated, and why they choose one hospital over another. The reasons why owners make such choices could be influenced in some way by the very risk factors being studied, so without appreciating the subtleties of selecting controls, it is possible to introduce selection bias into a case–control study.

To illustrate this point, suppose that an investigator at a community hospital wishes to determine if vaccinations lead to IMHA development, and observes that 50% of new cases had a history of vaccination in the prior two months. The odds of exposure to the risk factor is therefore 0.50 / 0.50 = 1.0. To obtain controls, a random survey by the investigator of pet owners in the community around the hospital reveals that 8.3% of their pets were vaccinated in the prior two months; the odds of exposure in the community-based controls is 0.083 / 0.917 = 0.091. The odds ratio relating two-month prior vaccination to IMHA incidence is 1.0 / 0.091 = 11.0.

The assumption behind using a random sample of dogs in the community as controls is that they represent the source population of cases of IMHA seen at the hospital; namely, had those dogs in the community developed IMHA, they would have been brought to the hospital and undergone the same diagnostic work-up as other cases of IMHA. In cases when only a single hospital serves a well-circumscribed region, this may be a tenable assumption. However, if there are multiple hospitals that serve communities, the reasons why some owners select one hospital over another may be related to factors associated with the study exposure. Moreover, the proportion of owners who are willing to bear the costs of seeking medical diagnosis and care for their pets for serious illnesses is likely to be lower than the proportion of people who would seek medical care for their own serious illnesses.

Now suppose that the investigator's hospital is known for higher medical costs relative to other hospitals that

serve the same community. For economic reasons, some pet owners utilize less expensive hospitals, and these owners are less likely (say, 50%, so assuming no month is any more or less likely for vaccination the two-month vaccination percentage is (2 months/12 months) × 50% = 8.3%) to provide consistent vaccination coverage for their pets. In contrast, the pet owners who utilize the investigator's hospital are more likely (90%) to provide such vaccination coverage; their pets' two-month vaccination percentage is substantially higher: (2 months/12 months) × 90% = 15%, with an exposure odds of 0.15 / 0.85 = 0.176 in the hospital-based controls. The odds ratio relating two-month prior vaccination to IMHA incidence is therefore 1.0 / 0.176 = 5.7, almost half that when using the random community controls.

This illustrates an important point of selecting controls for hospital-based case–control studies: the source population of cases to be sampled as controls should be restricted to those patients who, had they developed the disease under study, would have gone to the same hospital as the cases, and would have proceeded through the same mechanism of diagnosis and case ascertainment that occurred for the actual cases. There is no way to know whether such a hypothetical scenario would actually hold when randomly sampling members of a population; even asking the question of owners is conjectural at best.

To accommodate this concern about selection bias, an alternative approach involves selecting controls with particular diagnoses from the patient registry at the same hospital(s) or laboratory(s) that provide the cases. The singular advantage of this tactic is that whether or not an owner would utilize a particular hospital is no longer an issue; what remains unknown, of course, is what the owner would have done if their dog developed the actual disease of interest. While this too is conjectural, the choice of control diagnoses provides some guidance, if not assurance. That is, if alternative diagnoses could be identified for the case illness that are similar with respect to severity of clinical signs to warranting the owner to seek medical assistance, cost of diagnosis, and owner propensity to seek diagnostic confirmation, then those patients may be acceptable as controls. Using the IMHA example, diseases would be sought as control inclusion criteria that required presentation at the same hospital, with similar laboratory work and diagnostic procedures performed as that of the cases. Many alternative diagnoses could potentially qualify.

An additional critical requirement to impose on controls is that their medical condition should be unassociated with the exposure(s) of interest in the study (note: in this context unassociated means no more or less likely to be exposed than individuals in the source population; it does not mean unexposed). If this exposure were to cause both the case and control conditions, then the frequency distribution of exposure in the controls would become more like that of the cases than of the source population of cases, leading again to a selection bias, and specifically to an underestimation of the odds ratio. In the IMHA example, one diagnosis would be particularly ill advised: patients diagnosed with immune-mediated thrombocytopenia (IMTP). While vaccination may or may not be associated with its etiology, the hypothesis that it could lead to IMHA leaves room for the possibility that it could lead to other immune-mediated diseases affecting the bone marrow.

The choice of controls therefore necessarily depends on a decidedly thorough and insightful understanding of the relative benefits of particular control diagnoses for particular exposures and case conditions; acceptable controls for one hypothesis or study may be unacceptable for another. Control selection is perhaps the most contentious and challenging component of case–control study design, and should be carefully considered in advance of study commencement.

Clinical Trials

The defining characteristic of these studies is their interventional nature; unlike cohort studies, where treatments are not under investigator control, in clinical trials investigators have the ability to randomly assign treatments to their patients in a way that allows valid estimation of their effects. Although many experimental designs exist and have been adapted for clinical settings, this section will focus on the two most common: the randomized masked clinical trial, and the cross-over trial.

Randomized Masked Clinical Trials

The drawback of using hospital-based cohort studies to evaluate treatment efficacy, as noted earlier, is that of confounding by indication; it is difficult, if even at all possible, to distinguish actual treatment effects from those of the underlying indications (which may or may not be consciously evident) for treatment choice. Random assignment of treatment, known as "randomization," is the most powerful tool an investigator has to avoid this source of bias. The goal of randomization is beguilingly simple: to establish distinct but comparable groups of individuals whose incidence of the outcome of interest would be essentially identical if none received the treatment of interest. With such established groups, it could then be possible to isolate the treatment's effect if administered to one of them [2].

Randomization itself is not a guarantee of group comparability, however. Consider two patients enrolled in a study to compare a novel treatment to a placebo in treating a disease. Unknown to the investigator, one patient

was doomed to die from the illness regardless of treatment, and the other would have inevitably recovered even if treatment had been withheld; thus the correct (but unknown) interpretation would be that treatment could not have any effect on survival. Clearly, the two groups, composed of one individual each, are not comparable in the sense that their outcomes (death versus survival) would differ even if both received the placebo. But if treatment had been randomized, the study would remain invariably confounded, leading to incorrect conclusions. If the doomed individual received the treatment, then without knowing the individual was doomed the inference would erroneously be that treatment resulted in the patient's death. Conversely, if the recovered individual received the placebo, the incorrect conclusion would be that treatment prompted a recovery.

This example underscores an important characteristic and drawback of randomization: its effectiveness in establishing group comparability is proportional to the study size. In small studies, the possibility of group imbalances of characteristics or risk factors that could influence health outcomes cannot be discounted, but fortunately declines as study size increases. Sample size calculations therefore take on importance when undertaking a randomized study, and would be expected in any study proposal seeking approval from an institutional review board.

Sample size estimation for randomized studies is not trivial, however, and it is a fallacy to believe that there is a universal sample size that is adequate for all clinical trials. For example, information required to perform a sample size calculation to determine if two group means significantly differ requires an investigator to know *a priori* the type I (α) and type II (β) error percentages (the latter is one minus the "study power"), whether the test will be one- or two-tailed, the standard deviations of the outcome measurements in both groups, and the minimum difference in means the investigator believes is medically important enough to warrant a finding of statistical significance (the null hypothesis is that the means are equal, or equivalently the difference in means is zero). If instead the goal is to determine if the proportions of individuals in two groups that experience an outcome significantly differ, then the two expected proportions that are medically important enough to find significantly different must alternatively be specified (in addition to α and β). Issues related to sampling, sample size, and power can become complex [3], and separate calculations for these would ideally be undertaken for every independent hypothesis test in a study, with the necessary sample size being the largest of all the ones calculated. Once a study is completed, however, there is little value or justification in performing *post hoc* sample size or power calculations because the sample size has already been determined, and for any statistical test performed there was either sufficient power (i.e., $p \leq \alpha$) or not (i.e., $p > \alpha$) for a particular significance test.

The above examples present clinical trial outcomes as means and proportions. However, it is not uncommon in clinical trials to instead use interval-scaled ordinal variables, such as pain or severity indices, when quantitative measurements are unavailable. These variables generally require nonparametric statistical analyses for group comparisons, as well as for sample size and power calculations, rather than ones that assume that the group outcomes follow a normal (Gaussian) distribution. Nonparametric methods are invaluable for clinical research, particularly when sample sizes are small and underlying distributional assumptions are tenuous (as with interval-scaled data), and are discussed in more detail in Chapter 2.

Cross-over Trials

In studies of medical interventions with transient effects, there can be a distinct advantage of using each patient as her or his own control. Earlier, when groups composed of randomized individuals were compared, there was always an assumption that they were similar with respect to the distribution of unknown or unmeasurable variables (confounders) that could influence the outcome. This assumption becomes tenuous when group-specific sample sizes are small or there is so much variability in these factors that the groups would still not be comparable. In this case, sequentially administering different treatments to the same individual allows them to "cross over" between exposure states, permitting within-individual comparisons and controlling for confounding by intrinsic patient characteristics.

This approach requires two important assumptions. One is "temporal stability": that time itself is not a determinant of the study outcome. It implies that over the study period, the incidence of the outcome remains constant in the absence of any treatments. The second is "causal transience": that order of treatment administered (e.g., an experimental drug versus placebo) is irrelevant because there are no carry-over effects of either treatment (i.e., the effects of both are transient), which implies an eventual return to an original state. To make this assumption more tenable, a "wash-out" period is typically included between treatment options, being sufficiently long to ensure that any effects have become dissipated.

Measurements are characteristically taken at multiple times under the different treatments, allowing the assessment of time effects, treatment effects, and the interaction between these two main effects. It is also possible to extend such studies to include evaluating the effects of subgroups of different individuals, such as those defined by age and sex categories.

Studies where individuals serve as their own controls lead to collection of dependent data, in which measurements from the same individual are correlated. This arises, for example, when readings are taken from both eyes, when blood parameters are sequentially monitored, or when drug concentrations are evaluated for half-lives. Conventional statistical procedures assume that data are independent, but when data are paired or repeatedly collected from the same individual, the independence assumption is violated, which leads to invalid hypothesis test results, typically erroneously low *P*-values and higher than planned type I error proportions. Analysis of dependent data typically requires specialized statistical methods, from Student's t-tests or the nonparametric Wilcoxon signed-rank tests for paired data, to one-way repeated measures analysis of variance or the nonparametric Friedman test for sequential observations, to multivariate models, such as mixed effects analysis of variance or linear regression models for more complex designs.

Conclusion

Using data to make causal inferences is a hallmark of evidence-based medicine, but no inferences will be correct if the evidence used to establish them is flawed. Research can generate new knowledge, but it can also embed flawed conclusions in the literature if sedulous attention is not afforded to proper study design and conduct. Even the most sophisticated statistical methods cannot supplant biases that insidiously enter studies through flaws in study design. Despite the zeal that investigators have for finding statistically significant study results, reported point and variance estimates, confidence intervals, and *P*-values will be incorrect unless great care is exercised in designing and establishing the central features of a clinical study: thoughtful selection of comparison groups, unbiased and masked collection of information, diligent follow-up of patients, proper specification of statistical models, and verification of the model assumptions.

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Section 2

Endocrine Disease

4

Principles of Endocrinology

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Overview of Endocrinology

The classic definition of an endocrine tissue is a ductless gland specialized to release a hormone into the bloodstream to act on a distant target. Glands such as the pituitary, thyroid, islet cells in the pancreas, and adrenal fit this characterization. It is increasingly clear, however, that many (if not all) tissues in the body release substances into the blood (or at least locally) in a regulated fashion and these substances influence the activity of other cells. Examples include leptin and adiponectin from adipose tissue, natriuretic factors from the heart, and erythropoietin from the kidney.

Hormones regulate a vast array of biologic processes, including, but not limited to, fuel mobilization, storage, and distribution; maintenance of electrolyte concentrations in extracellular fluid; and control of metabolic rate. Each system employs checks and balances; most utilize some form of negative feedback control to maintain homeostasis. While some systems have as their principal goal maintenance of a steady level of a metabolite or electrolyte, others employ moving set points or thresholds that adapt to changing conditions. As an example of the latter, stress causes activation of the pituitary-adrenal system and increased adrenocorticotropic hormone (ACTH) release stimulates release of cortisol from the adrenal cortex. Normally, elevated cortisol concentrations suppress ACTH secretion via negative feedback, but in some long-term stressful situations, this negative feedback is overridden so that high ACTH concentrations in circulation are maintained in the presence of the steroid negative feedback signal.

Chemical Classes of Hormones

Classic hormones comprise three main chemical types. Each class has a different means of synthesis, storage, and mechanism of action on targets.

Protein/Polypeptide Hormones

Hormones in this class are composed at minimum of three amino acids. Some consist of subunits (e.g., the pituitary hormones luteinizing hormone [LH], follicle-stimulating hormone [FSH], and thyroid-stimulating hormone [TSH]) and may have additional modifications including additions of sugar residues (glycosylation), phosphates, and disulfide bonds.

Protein/polypeptides hormones are manufactured by classic transcription/translation of genes that are expressed in high amounts in the endocrine tissue of origin. Encoded in the genes are sequences that direct these molecules to the regulated secretory pathway, resulting in the storage of the hormone in vesicles, ready for release by exocytosis in response to the appropriate signal. The nature of this signal differs depending on the system involved. Most endocrine cells that produce and release hormones of this class store significant amounts of the hormone and have the ability to release a large amount of product if needed. Continual stimulation of release often causes induction of the gene necessary for its synthesis.

Protein/polypeptide hormones are released into circulation through the specialized capillaries in their tissue of origin and most circulate free or unbound in blood. Exceptions exist; for example, insulin-like growth factor-1 (IGF-1) and growth hormone are bound to varying extent to plasma proteins. In the case of IGF-1, the binding is significant, accounting for the prolonged half-life of this hormone. By contrast, most other protein/polypeptide hormones have relatively short half-lives, usually in the range of several minutes (e.g., the half-life of ACTH is less than 15 minutes). Protein/polypeptide hormones act on target cells by binding receptors located on the cell surface (see later), rapidly activating specific signal transduction systems in target cells.

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Steroids

Steroid hormones include the adrenocortical hormones (e.g., cortisol, aldosterone), reproductive steroids (e.g., estrogen, testosterone), and vitamin D. They are manufactured in their tissues of origin from cholesterol. In turn, most of the cholesterol used for synthesis is transported in blood, taken up, and stored in the endocrine tissue. Each endocrine cell expresses a unique set of enzymes used in the conversion of cholesterol to final product. These cells typically possess large amounts of smooth endoplasmic reticulum and enzymatic conversions occur in this location as well as other intracellular sites (e.g., mitochondria). The final products accumulate and simply diffuse out of the cell because of their hydrophobic nature.

Steroids are relatively insoluble in water and are found in circulation bound to carrier proteins, including globulins and albumin. Because of this protein binding, steroids generally have longer half-lives in blood than proteins/polypeptides. While the free or unbound portion is available to enter and act in target cells, the loosely bound albumin fraction is available to deliver steroid to targets as well. The globulin-bound portion serves as a reservoir, buffering steroids in circulation and also assisting in delivery to tissues by releasing bound steroid as the complex permeates through tissues. Steroids act on target cells primarily by binding to intracellular receptors; the receptor hormone complex then binds to specific DNA sequences and affects rates of gene transcription. Steroids are removed by the liver and kidney. Active hormones are inactivated by processes including removal of double bonds, conjugation to glucuronic acid and sulfate, and excretion in urine and feces.

Hormones Made from Amino Acids

The principal hormones in this chemical class are the catecholamines and thyroid hormones, which are derived from the amino acid tyrosine by different means. Catecholamines (epinephrine and norepinephrine) are made by a series of enzymatic events involving hydroxylation, decarboxylation, and methylation in adrenal medullary cells. Catecholamines have short half-lives in blood and bind to receptors on the cell surface. By contrast, thyroid hormones (T4 and T3) are made in thyroid follicles (colloid) by iodination and coupling of iodinated tyrosines and are stored in thyroglobulin until colloid is taken up into the thyroid follicular cells, broken down, and T4 and T3 are secreted. Thyroid hormones behave much like steroids; they are carried in blood primarily in protein-bound form and act on target cells by binding to intracellular receptors.

Hormones in Circulation

Concentrations of hormones in circulation may vary significantly depending on a variety of circumstances. Specific hormones show characteristic secretory patterns in blood. For example, ACTH and cortisol show periodic and, to some degree, irregular spikes and troughs throughout the day (Figure 4.1). Stressful conditions elevate levels of both of these hormones. In addition, ACTH and cortisol levels may also vary with time of day. In humans, ACTH and cortisol levels in circulation are higher in the early morning hours. This circadian variation is significantly less (or absent) in dogs and cats. By contrast, T4 levels in blood do not change as dramatically and instead are relatively steady, varying by approximately 15–20% during the day (see Figure 4.1). Growth hormone is secreted in bursts or pulses and in humans, greatest levels are observed shortly after going to sleep.

These patterns of secretion and resultant normal fluctuations have practical consequences. For example, resting cortisol measurement is of little value in the diagnosis of hyperadrenocorticism. Overall, cortisol levels are greater in dogs with hyperadrenocorticism but because of the normal fluctuating nature of its secretion, values overlap when comparing single baseline levels between dogs with normal adrenals and dogs with hyperadrenocorticism. An additional confounding factor in evaluating baseline cortisol concentrations is that stress associated with blood sample collection may result in an elevated cortisol level. The fact that T4 concentrations are more stable throughout the day permits the use of resting or baseline T4 determination as a screening test for hypothyroidism in dogs and hyperthyroidism in cats.

Hormone Receptors

Receptors for the majority of protein/polypeptide hormones (and catecholamines) reside on the target cell

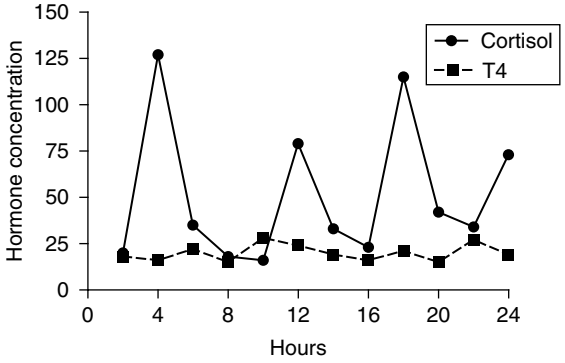


Figure 4.1 Fluctuations in levels of cortisol and T4 in a healthy dog during the day. Levels of cortisol show significant random variation, while levels of T4 are relatively stable.

surface. Hormone binding results in a subtle change in the three-dimensional structure of the receptor and this signal is carried into the cell where it is transduced into a message(s) that affects cellular biochemistry.

Cell surface receptors can be classified by their structure and the nature of the signaling pathway that they activate. Many protein/polypeptide hormones bind to G-protein (guanosine-protein) coupled receptors. This large family of receptors possess 7-transmembrane spanning domains and transfer signals to another membrane protein complex (the G-protein) consisting of three subunits (alpha, beta, and gamma). The alpha subunit at rest is bound to a GDP, hormone-receptor binding causes the G-alpha to replace the guanosine 5'-diphosphate (GDP) with guanosine 5'-triphosphate (GTP), resulting in activation of the G-protein and dissociation of its subunits. The free subunits then carry the signal to other downstream proteins, including enzymes (e.g., adenylyl cyclase) or ion channels. Hormone activation of a G-protein does not always result in activation of a cellular process, but may instead result in inhibition. For example, some G-alpha subunits (Gi), when activated, suppress the activity of adenylyl cyclase, reducing cyclic AMP production in cells.

Other types of cell surface receptors are enzymes themselves. For example, the insulin receptor has tyrosine kinase activity, meaning that after insulin binds, the intracellular portion of the receptor acts to place phosphates on tyrosine residues on the receptor itself and on substrate molecules that contact the activated receptor.

Cell surface receptor activation can activate many pathways in target cells, employing signal amplification and cross-talk. Signaling may also reach the nucleus, therefore affecting gene transcription.

Cell surface receptor number can change with conditions. Exposure to high levels of the activating hormone can result in receptor downregulation and reduce the target tissue response. In other situations, target cells express more receptors which can result in upregulation of the response. In many cases, "spare receptors" are present on targets, meaning that only a small percentage of receptors need to be occupied in order to obtain a maximal response in the cell.

Steroid and thyroid hormones principally affect their targets by binding to intracellular receptors followed by movement and binding of the hormone receptor complex to specific regions on DNA. This binding then affects (positively or negatively) the rate of gene transcription and ultimately the production of certain cell-specific proteins. The receptor molecules act in pairs. Thyroid hormone entry into target cells has been shown to be mediated by specific cell membrane transporters such as monocarboxylate transporter 8 and organic anion transporting polypeptide 1C1. Similar transporters have not been identified for steroid hormones. Evidence exists for steroid and thyroid hormone effects that do not involve the classic genomic signaling pathway, and in fact, membrane receptors for both steroids and thyroid hormones have been identified. In addition, these hormones may act inside cells by binding their receptors and then the hormone–receptor complex interacts with intracellular proteins, such as transcription factors, without the need to bind DNA. It is believed that much of the antiinflammatory activity of glucocorticoids comes about through this process, where the glucocorticoid receptor complex binds to nuclear factor kappa B (NFkappaB), preventing this molecule from stimulating the production of proinflammatory genes.

In general, activation of cell surface receptors results in rapid responses in target cells while the effects of steroid and thyroid hormones take longer to become apparent. This difference can be illustrated by comparing the response to ACTH (protein hormone) to that of thyroid hormone. When performing an ACTH response test, a post-ACTH blood sample is usually collected at one hour for cortisol measurement, the time it takes for the ACTH-induced cortisol secretion to reach maximum levels in circulation. On the other hand, noticeable clinical responses in a dog with hypothyroidism treated with T4 replacement therapy require several days (increase in activity) to weeks (stimulation of hair regrowth) to become apparent.

Regulation of Hormone Secretion

Although control of each endocrine system is unique, negative feedback is a dominant feature in most, if not all, systems. The nature of the feedback signal depends on the system; in some cases, it is an ion (calcium in the case of the parathyroid) or fuel molecule (glucose in the case of insulin) while in others it is a hormone itself (cortisol in the case of the ACTH-adrenal axis). Regulatory control in some systems is multifaceted and more complex; for example, regulation of aldosterone involves the renin-angiotensin system with sensing mechanisms tied to extracellular fluid volume and sodium levels. In others, such as calcium and parathyroid hormone, the relationship is straightforward with the parathyroid gland responding rapidly to a decline in calcium levels in the blood with an increase in secretion of parathyroid hormone that, in turn, works to restore calcium levels to a set point.

Feedback relationships are central to diagnostic testing and to localizing disease. Dexamethasone suppression testing relies on feedback, as this potent glucocorticoid activates negative feedback in the hypothalamus and pituitary, suppressing ACTH secretion and thus secretion (and therefore blood levels) of cortisol. ACTH-secreting

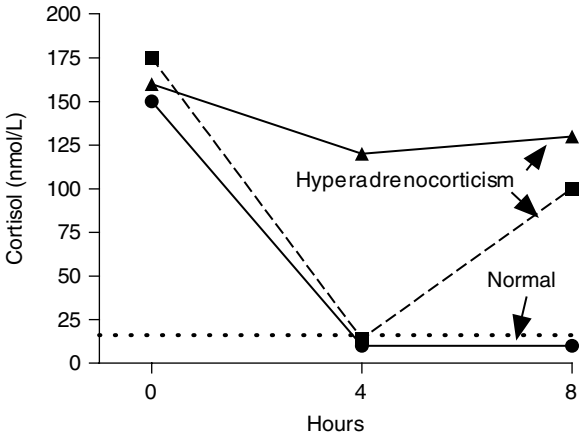


Figure 4.2 Low-dose dexamethasone (Dex) suppression patterns in dogs. Administration of Dex activates negative feedback in the hypothalamus and pituitary, resulting in a decline in ACTH secretion. In turn, the drop in ACTH rapidly results in a decline in levels of cortisol from the adrenal. In dogs with normal pituitary-adrenal function, cortisol levels are suppressed (stay below the dotted line) at four and eight hours after Dex. The pituitary tumor present in dogs with pituitary-dependent hyperadrenocorticism possesses resistance to feedback, so cortisol levels are not suppressed below the normal cut-off value at both time points.

pituitary tumors in canine hyperadrenocorticism (corticotroph tumors) have an inherent degree of resistance to feedback and therefore affected dogs do not demonstrate the same feedback responsiveness to a low dose of dexamethasone as do unaffected dogs (Figure 4.2).

Insulinomas also have abnormalities in negative feedback. Whereas the normal beta cell responds to a drop in circulating glucose levels by shutting off insulin secretion, in patients with insulinomas, the tumor cells do not respond appropriately to this decline in glucose and insulin secretion is maintained in the face of hypoglycemia. Documentation of an elevated insulin level in blood collected from a fasted animal experiencing hypoglycemia is diagnostic for this tumor. Levels of parathyroid hormone (PTH) should be evaluated in conjunction with calcium (total or free) levels. If normal parathyroid gland function is present, the presence of hypercalcemia will be accompanied by low levels of PTH. However, hypercalcemia occurring in conjunction with an elevated PTH concentration is consistent with a defect in parathyroid gland feedback, most likely related to a parathyroid adenoma (primary hyperparathyroidism).

Endocrine Disease

Endocrine diseases usually manifest as hypo- or hyperfunction of an endocrine tissue. In many cases, the cause of hypofunction involves the immune system (autoimmune attack) resulting in a gradual destruction of the endocrine tissue. Examples include primary hypothyroidism in dogs and hypoadrenocorticism (Addison disease) in dogs and cats. The immune-mediated destruction and gradual loss of hormone secretion activate negative feedback mechanisms so that a period of compensation typically occurs. For example, levels of TSH would be expected to rise in dogs with primary hypothyroidism, possibly even before clinical signs are noted. Eventually, the immune-mediated destruction results in loss of sufficient endocrine tissue so that the hormone secretion declines to the point that clinical signs of deficiency are seen.

Often, endocrine hyperfunction conditions result from overactivity of endocrine cells associated with either hyperplasia or neoplasia. Often, these affected cells not only possess increased cell division rates but also lose (or show lessened) negative feedback control. Examples include the most common form of hyperadrenocorticism in dogs (pituitary-dependent hyperadrenocorticism), primary hyperparathyroidism, and insulinoma. Feline hyperthyroidism is associated with a similar process occurring in follicles; these cells show increased activity (resulting in excessive secretion of T4) in the absence of trophic drive from TSH.

Endocrine diseases can result from many other potential mechanisms. Mutations in receptors can render them incapable of responding to the hormone ligand or can result in continual activation in the absence of hormone. In other situations, diseases occur as a consequence of receptor insensitivity to the hormone in the absence of mutations. For example, in type 2 or noninsulin-dependent diabetes, the insulin receptor has reduced responsiveness to insulin, often related to obesity.

Hormone Measurement

For many years, radioimmunoassay (RIA) was the standard method used to measure hormone concentration in blood. RIA employed a radioactive-tagged version of the hormone and an antibody made against it. Nontagged hormone, either in the form of standard, purified hormone or present in patient sample, was mixed with the tagged hormone and competed for a limited number of antibody-binding sites. In this way, displacement curves were generated, so that tubes containing increasing amounts of nontagged hormone displaced tagged hormone from antibody. Standard curves were generated by adding known amounts of nontagged hormone to tubes, and radioactivity in tubes with patient sample was then compared to that from the standards. Use of radioactivity as the mode of detection allowed for a high level of sensitivity in RIA, a must when attempting to measure substances circulating in pico- (10^{-12}) or nano- (10^{-9}) gram amounts.

While some diagnostic laboratories still use RIA, most hormone determinations today are made using reporters other than radioactivity. The basic methodology is similar to RIA (competitive binding to antibodies) but the tag employed is nonradioactive, using methods such as chemiluminescense or an enzyme label (as in enzyme-linked immunosorbent assay [ELISA]). Another method that is particularly well suited to the measurement of protein hormones employs two antibodies, directed against different regions of the molecule. The presence of the hormone allows for formation of a "sandwich" complex, which is reported by a tag present on one of the antibodies.

Measurement of hormones in companion and domestic animals presents some special challenges. Many assays are commercially available to measure hormones in samples from humans. Some, but not all, of these can be used to measure the hormone in samples from other animal species. Considerations involved in determining the usefulness of such assay methods include the fact that circulating levels of a particular hormone can vary significantly across species (e.g., T4 levels are approximately four times higher in humans compared with dogs and cats), protein binding differs across species and other materials in serum or plasma (e.g., lipid content) can impact results obtained in a particular assay. Protein hormones can vary structurally across species and this may have a profound effect on the usefulness of an assay to validate across species. For example, TSH levels cannot be determined in samples from dogs or cats using human TSH assay methods. Especially in the case of protein hormones, users should contact the reference laboratory to determine if the assay has been validated for use in that species.

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5

Neuroendocrinology

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Neuroendocrinology refers to the orchestration between the nervous system and the endocrine system to maintain homeostasis by regulating various bodily functions such as stress responsiveness, growth and development, and metabolism. To achieve homeostasis, the body appropriately senses and responds to alterations in the external and internal environment through the modulation of chemical messengers, or hormones. The key players of the neuroendocrine system are the hypothalamus and pituitary gland which are intricately linked via secretory peptides and neuronal connections, as well as target end-organs (adrenal, thyroid, gonads, liver, and breast tissue) whose role is to exert a physiologic response. These players are integrated with one another through a series of feedback loops that allow controlled secretions of endocrine hormones throughout the body. In this way, the hypothalamus, pituitary gland, and target tissues regulate physiologic function. Alterations to these pathways and regulatory mechanisms may result in hormone disturbances that lead to disease processes.

Anatomic Considerations of the Hypothalamus and Pituitary System

The Hypothalamus

The hypothalamus is a highly specialized region of the posterior forebrain that is critical to regulation of vital bodily functions, including temperature regulation, immune function, growth, stress responsiveness, water balance, sexual behavior and reproduction, and metabolism. It is situated below the thalamus just above the midbrain, and arises from the diencephalon during embryologic development.

The hypothalamus is composed of neurosecretory neurons that produce various peptide hormones and biogenic amines (dopamine), which enter the circulatory system and act as endocrine hormones on distant target tissues. The unique capability of the hypothalamus to convert neural signals into hormonal output is called neuroendocrine transduction.

Hypothalamic hormones enter the general circulation in one of two ways (Figure 5.1). Some hypothalamic hormones are transported along axons to the median eminence where they enter the portal circulation to reach the anterior pituitary. Here, they stimulate or inhibit anterior pituitary hormone release into the general circulation. Other hypothalamic nuclei have axons that terminate at the posterior pituitary. These particular hypothalamic hormones (e.g., vasopressin and oxytocin) are transported to the posterior pituitary where they can be released into the general circulation. The intermediate lobe of the pituitary gland is under direct neural control by the hypothalamus.

Hypophysiotropic hormones can be releasing or inhibitory in nature. The hypothalamic and pituitary hormones and their primary effects are listed in Table 5.1.

The Pituitary Gland

The pituitary gland is referred to as the *hypophysis*, and it is situated beneath the hypothalamus at the base of the brain. It is securely nestled within a depression of the sphenoid bone called the *sella turcica* whose shape is described as "saddle-like." The pituitary is composed of an anterior lobe (AL; *adenohypophysis*) and a posterior lobe (PL; *neurohypophysis*). Their diverse function is a reflection of their distinct embryologic origin.

Adenohypophysis and Intermediate Lobe

The adenohypophysis is the glandular portion of the pituitary gland. During embryologic development, it arises from an ectodermal pouch (Rathke's pouch) growing upwards from the oral cavity. In many mammalian species, there is a distinct intermediate lobe (IL) that

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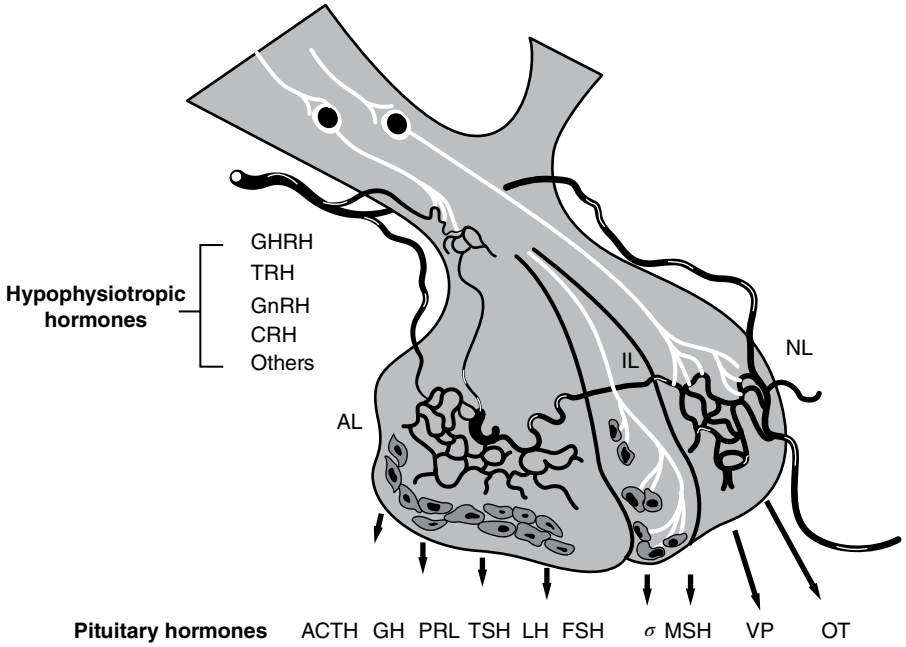


Figure 5.1 Schematic representation of the hypothalamus and pituitary gland. Hypothalamic hormones are released into the hypophyseal portal circulation for delivery to the anterior pituitary (AL) where they stimulate or inhibit release of the anterior pituitary hormones. The posterior pituitary (NL) is the direct neural extension of the hypothalamus. Vasopressin (VP) and oxytocin (OT) are produced by hypothalamic nuclei, and traverse the hypothalamic-pituitary stalk to reach the NL where they are stored for release. The intermediate lobe (IL) is under direct neuronal control by the hypothalamus. *Source*: Mol and Meij 2008. Reproduced with permission of Elsevier.

develops along with the adenohypophysis but is kept separate by a thin membranous remnant of Rathke's pouch. Therefore, it is often described as part of the adenohypophysis. The IL is absent or underdeveloped in humans.

The adenohypophysis contains specialized secretory cells that are classified according to the product(s) they secrete; thyrotrophs (thyroid-stimulating hormone [TSH]), gonadotrophs (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]), somatotrophs (growth hormone [GH]), lactotrophs (prolactin [PRL]), and corticotrophs (adrenocorticotropic hormone [ACTH]). The IL is primarily composed of melanotrophs (alpha-melanocyte-stimulating hormone [alpha-MSH]), which cause pigmentation of hair and skin. The composition of AL secretory cells varies between mammalian species, but is approximately as follows in humans; somatotrophs 50%; lactotrophs 15%; corticotrophs 20%; gonadotrophs 10%; and thyrotrophs 5%.

These secretory products are further classified into three families according to their structure and function: glycoprotein hormones, somatomammotropic hormones, and derivatives of proopiomelanocortin (POMC).

Glycoprotein Hormones

The glycoprotein hormones include TSH produced by thyrotropin cells, and LH and FSH produced by gonadotropin cells. Each hormone is a peptide made up of single alpha and beta subunit. The amino acid sequence of the alpha subunit is homologous between the glycoprotein hormones, while the beta subunit is unique.

Thyroid-Stimulating Hormone Thyroid-stimulating hormone is involved in the regulation of energy homeostasis and metabolism. TSH is secreted in response to thyrotropin-releasing hormone (TRH), which is produced in the paraventricular nucleus of the hypothalamus. Upon release, TSH circulates to the thyroid gland where it stimulates follicular cells to synthesize and release the thyroid hormones triiodothyronine (T3) and thyroxine (T4) into the circulation. As thyroid hormone levels rise, they exert negative feedback on the hypothalamus and pituitary gland to suppress TRH and TSH production, respectively, thereby decreasing thyroid hormone production. Somatostatin (SS), a hypophysiotropic hormone that is also produced by pancreatic islet D cells and gut mucosa, is also a known inhibitor of TSH release.

Luteinizing Hormone and Follicle-Stimulating Hormone Luteinizing hormone and FSH, known collectively as the gonadotropins, regulate sex steroid synthesis and reproduction. In females, FSH regulates ovarian follicular development, and LH stimulates ovulation and

Table 5.1 Hypothalamic-pituitary hormones and their primary functions

Endocrine gland	Hormone	Primary function	Target
Hypothalamus	Thyrotropin-releasing hormone (TRH)	Stimulates the release of thyroid-stimulating hormone (TSH) and prolactin (PRL)	Anterior pituitary
	Gonadotropin-releasing hormone (GnRH)	Stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH)	
	Corticotropin-releasing hormone (CRH)	Stimulates the release adrenocorticotropic hormone (ACTH) and proopiomelanocortin (POMC)-derived peptides	
	Growth hormone-releasing hormone (GHRH)	Stimulates the release of growth hormone (GH)	
	Prolactin-releasing hormone (PRLH)	Stimulates the release of prolactin (PRL)	
	Somatostatin (SS)	Inhibits the release of GH and thyroid-stimulating hormone (TSH)	
	Dopamine (AKA prolactin-inhibiting hormone)	Inhibits the release of PRL	
Posterior pituitary[a]	Vasopressin	Regulates blood volume	Distal convoluted tubules and collecting ducts of kidney
		Stimulates smooth muscle contraction	Blood vessels
	Oxytocin	Stimulates uterine contraction during parturition	Uterine smooth muscle
		Stimulates milk ejection during lactation	Myoepithelial cells of mammary gland ducts
Anterior pituitary	ACTH	Stimulates the release of glucocorticoids and sex steroids	Adrenal cortex
	GH	Promotes growth and development	Various tissues[b]
	Prolactin	Stimulates milk production	Mammary tissue
	TSH	Stimulates the release of thyroid hormone	Thyroid gland
	FSH	Stimulates estrogen production and promotes ovarian follicle development in the female. Stimulates spermatogenesis in the male	Gonads
	LH	Stimulates progesterone production and promotes ovarian follicle maturation in the female. Stimulates testosterone production in the male.	

[a] These hormones are synthesized in the hypothalamus and released from the posterior pituitary gland.
[b] See GH section.

maintenance of the corpus luteum. Together, the gonadotropins stimulate production of the sex hormones estradiol and progesterone. In male gonads, LH stimulates testosterone production by Leydig cells, and FSH stimulates Sertoli cell proliferation and maintains sperm quality.

Gonadotropin secretion is pulsatile, and release is stimulated by gonadotropin-releasing hormone (GnRH) binding to the anterior pituitary. LH and FSH circulate to target tissues and stimulate sex hormone production. As gonadotropin levels rise, LH and FSH exert negative feedback on the hypothalamus and pituitary to decrease their own production. Sex hormone products also feed back on the hypothalamus and pituitary gland to variably regulate gonadotropin production. Testosterone and estrogen inhibit LH and FSH release by the anterior pituitary, while estradiol may have variable effects on gonadotropin production depending on its plasma concentration, a feature that may be important during various stages of reproduction. High levels of estradiol exert positive feedback on GnRH to promote sustained gonadotropin release, while low levels negatively feedback to inhibit hypothalamic GnRH and pituitary gonadotropin release. Inhibin, a protein produced by ovarian granulosa cells in females and by Sertoli cells in males, inhibits FSH release both by direct feedback on

its production by the pituitary and indirectly by altering GnRH receptor sensitivity. Activin, a protein produced by the ovaries, and dopamine are known stimulators of FSH release. Endogenous opioids have an inhibitory influence on gonadotropin production through alteration of GnRH secretion.

Somatomammotropic Hormones

Growth hormone and prolactin (PRL) are grouped together as the somatomammotropic hormones. Their amino acid sequences are similar, which may account for some common functions.

Growth Hormone As the name suggests, GH regulates growth and development. In young animals, it stimulates growth of connective tissue, long bones, muscles, and endocrine glands. GH is a metabolic counterregulatory hormone, which opposes the actions of insulin and raises glucose by stimulating hepatic gluconeogenesis and impairing glucose uptake in muscle. GH stimulates lipolysis in adipose tissue, which results in increased circulating free fatty acids, and has an anabolic effect on protein synthesis. GH stimulates production of insulin-like growth factor 1 (IGF-1) by hepatocytes. IGF-1 is a primary mediator of the effects of GH.

Growth hormone is a single-chain polypeptide containing two disulfide bridges. The sequence is highly conserved among species; the sequences of canine and feline GH differ by only one amino acid, while those of canine and porcine GH are identical. Receptors for GH have been identified throughout the body, but are found in the highest concentrations in skeletal muscle, liver, adipose tissue, heart, kidneys, lungs, and cartilage. This diffuse distribution in part explains GH's diverse effects. GH receptors are known to have altered sensitivity to various secretagogues throughout life, which aids in preferential growth and development in young, and specialized metabolic function in adults.

Growth hormone secretion is pulsatile, and results from the complex interactions between growth hormone-releasing hormone (GHRH), SS, and peripheral factors (both neural and hormonal). GH release is primarily a reflection of the delivery and binding of hypothalamic GHRH to pituitary somatotropic cells. SS is a known inhibitor of GH secretion, thus high GHRH and low SS levels result in GH release. SS is a more potent inhibitor of GH release than of TSH release.

Insulin-like growth factor 1 is secreted in response to GH, but is also responsive to systemic alterations in energy balance and nutrition. Low levels of IGF-1 stimulate GH release. As GH and IGF-1 levels rise, they feed back on the hypothalamus to decrease GHRH and increase SS secretion, which results in reduced production of GH. Ghrelin, an endogenous ligand produced by enteral cells of the stomach, is a potent GH secretagogue. Other factors known to directly or indirectly influence GH secretion include nutritional states, stress, sex steroids, and exercise. For example, GH secretion is stimulated by alpha-adrenergic agonists and inhibited by beta-adrenergic agonists and hyperglycemia. Estradiol modulates GH levels indirectly via inhibitory effects on SS.

Prolactin Prolactin is involved in the regulation of lactation and reproduction. PRL works together with sex steroids to stimulate mammary gland development and regulate milk production during lactation. Although PRL is secreted in the male, its physiologic role is not yet fully elucidated.

Prolactin is a single-chain polypeptide containing three disulfide bridges. There is significant sequence variation between species. PRL secretion is pulsatile, and stimulated by the hypothalamic hormones prolactin-releasing hormone (PRLH) and TRH. PRL is also released in response to the neural stimulation of suckling during lactation. The definitive identity of PRLH is not yet known, but vasoactive intestinal peptide (VIP) has been suggested. PRL release is inhibited by dopamine, which is also referred to as prolactin-inhibiting hormone. In the regulation of PRL release, the inhibitory component is known to predominate over the stimulatory component.

Upon binding to its receptors in lactotropic cells, dopamine inhibits PRL release. PRL, in turn, acts in a short feedback loop by circulating and binding to PRL receptors on dopaminergic neurons in the hypothalamus. PRL release is also stimulated by oxytocin and angiotensin II, and inhibited by gamma-aminobutyric acid (GABA). Unlike other hypophyseal hormones, PRL is not subject to typical feedback inhibition by target tissue hormone products. Instead, its release is solely regulated through hypothalamic input and the suckling reflex.

Proopiomelanocortin-Derived Peptides

Proopiomelanocortin is a large prohormone which encodes numerous secretory products (Figure 5.2). It is synthesized by corticotropic cells of the anterior pituitary and melanotropic cells of the IL. Proteolytic enzymes hydrolyze POMC into ACTH and beta-lipotropin (beta-LPH). These products are then further cleaved into alpha-MSH, which stimulates melanin production by epithelial cells and leads to darkening of skin, beta-endorphin (an endogenous opioid), and other related peptides. The function of many of these peptides is not yet fully understood and remains under investigation.

Proopiomelanocortin synthesis is under direct neural control by the hypothalamus primarily through inhibitory dopaminergic innervation. Thus, dopamine exerts tonic inhibition of POMC release under normal

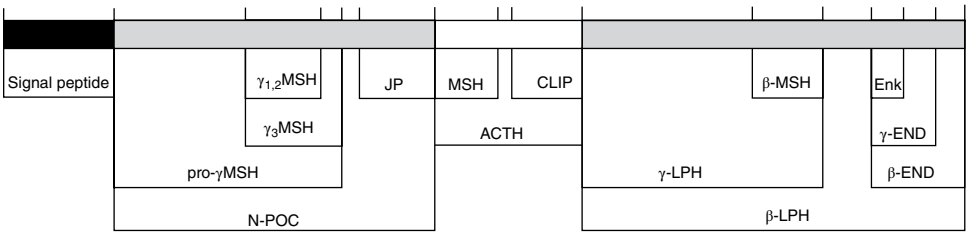


Figure 5.2 Schematic representation of proopiomelanocortin (POMC) and production of ACTH and related peptides. POMC contains four major domains: the signal peptide domain; the N-terminal peptide domain (N-POC) which contains the (pro) gamma-MSH peptide and joining peptide (JP); the ACTH domain which contains melanocyte-stimulating hormone (MSH) and corticotropin-like intermediate lobe peptide (CLIP); and the beta-lipotropin (beta-LPH) domain which generates metenkephalin (Enk) and the endorphin (END) family of peptides. Vertical lines represent potential sites of proteolytic cleavage. *Source*: Mol and Meij 2008. Reproduced with permission of Elsevier.

circumstances. Corticotropin-releasing hormone (CRH) will stimulate POMC production, which results in ACTH release.

Adrenocorticotropic Hormone Adrenocorticotropic hormone is a glycoprotein hormone that regulates the synthesis and release of cortisol. Its binding to adrenal cortical cells stimulates production of glucocorticoids, sex steroids, and, to a lesser extent, mineralocorticoids. ACTH also regulates growth of the adrenal cortex as evidenced by high ACTH causing hypertrophy of the adrenal cortex, and absent ACTH causing atrophy.

Adrenocorticotropic hormone secretion is pulsatile, and stimulated by the hypothalamic hormones CRH and vasopressin. These hormones act synergistically to stimulate ACTH release, but stress will variably modulate their production by the hypothalamus.

Adrenocorticotropic hormone stimulates cortisol release, and as cortisol levels rise, they feed back on the hypothalamus and pituitary to inhibit production of CRH and ACTH, respectively. Hypothalamic dopamine exerts tonic inhibition of ACTH release through dopaminergic neural connections terminating on the IL. Some factors that directly or indirectly influence ACTH release include leptin, vasoactive intestinal peptide (VIP), neuropeptide Y, cholecystokinin (CCK), cytokines such as interleukin-1 and tumor necrosis factor-alpha, serotonin agonists, and beta-adrenergic agonists. Additionally, ACTH release is triggered by exercise and hypoglycemia.

Neurohypophysis

The neural portion of the pituitary is called the *neurohypophysis*, and it is composed of axons that extend downward as a large bundle from the hypothalamus. During embryologic development, the neurohypophysis and hypothalamus both arise from the diencephalon and remain connected through life.

The hormones oxytocin and vasopressin are synthesized by the paraventricular and supraoptic nuclei of the hypothalamus. They are transported to the neurohypophysis through direct neuronal projections, and are stored in secretory vesicles in axon terminals. Upon appropriate neurogenic stimulation, they are released into the general circulation where they travel to distant target tissues and exert a physiologic effect.

Vasopressin; Antidiuretic Hormone, Arginine Vasopressin

Vasopressin (VP) regulates blood volume through alteration of water excretion in the kidneys. It also promotes vascular smooth muscle contraction, and stimulates ACTH release. These diverse effects are mediated by vasopressin receptors: V1 in vascular smooth muscle, V2 in the kidney epithelium, and V3 in the anterior pituitary.

Vasopressin secretion is pulsatile, and hypothalamic production is primarily stimulated when high plasma osmolality (hemoconcentration) or a significant decrease in blood volume (hypovolemia) is detected. In the absence of circulating VP, the epithelial cells lining the distal convoluted tubules and collecting ducts in the kidney are largely impermeable to water. As such, large volumes of dilute filtrate are excreted into the urine. Upon release, circulating VP binds to VP2 receptors and enhances the permeability of water-selective channel proteins (aquaporins) to water in renal epithelial cells. This results in the passive diffusion of water into the interstitial space due to the medullary osmotic gradient, thereby restoring blood volume and suppressing VP production by the hypothalamus.

The binding of VP to V1 receptors in blood vessels results in vasoconstriction through activation of calcium channels (vasopressor effects). VP binding to V3 receptors in the anterior pituitary stimulates ACTH release. The production of VP is stimulated by CRH and angiotensin II, and inhibited by glucocorticoids.

Oxytocin

Oxytocin (OT) regulates lactation and parturition. Similar to VP, OT is produced in hypothalamic nuclei, and transported to the posterior pituitary where it is stored for release. OT release is stimulated by suckling, during lactation, and in response to vaginal or cervical distension. Dopamine and opioids are also known to modulate OT secretion from the posterior pituitary, as well as extrareproductive factors such as stress.

In the uterus, OT binds to its receptors and stimulates the myometrium to contract. The sensitivity of uterine receptors to circulating OT is variable during different stages of reproduction. Receptor sensitivity is reduced during pregnancy, and greatly enhanced at the time of delivery when OT stimulates contraction of uterine smooth muscle and results in expulsion of the newborn. This OT-mediated uterine contraction is further augmented by the presence of estrogen, which increases at parturition. Conversely, OT-mediated uterine contraction is inhibited by progesterone, which is high throughout pregnancy but plummets at parturition.

During lactation, OT release is triggered by suckling. Circulating OT stimulates contraction of myoepithelial cells in mammary gland ducts, which results in milk ejection. As for PRL, its function in the male is not fully understood.

Regulation of the Neuroendocrine System

The neuroendocrine system tightly regulates hormone production by means of feedback mechanisms, which help ensure optimal hormone levels and activity. The hypothalamus and pituitary gland synthesize various regulatory hormones – both releasing and inhibitory in nature – that circulate to target endocrine glands (such as adrenal, thyroid, gonads) and modulate hormone release. These hormones bind to receptors in target tissues to generate a physiologic response, for example GH stimulating growth in long bones. This pathway is referred to as the hormone cascade, and it allows amplification of a signal in a closed system. When sufficient amounts of target hormone are produced, the target hormone exerts feedback on the hypothalamus and pituitary gland to inhibit previous steps in the pathway. Often there is also negative feedback on the hypothalamus by pituitary hormones, a principle referred to as short-loop feedback.

An excellent example of typical feedback regulation is illustrated by the thyroid hormone pathway (Figure 5.3). The hypothalamus produces TRH, which reaches the anterior pituitary via the portal circulation. Here, it stimulates release of TSH, which then is transported in the blood to the thyroid gland where it stimulates production of thyroid hormone. As thyroid hormone levels rise above a certain threshold, there is negative feedback on production of TRH and TSH, which thereby decreases thyroid hormone production. Subsequently, as thyroid hormone levels decay, negative feedback is relieved on the hypothalamus and pituitary, and production of thyroid hormone is once again restored through the hormone cascade. Neuroendocrine regulation predominantly relies on negative feedback, but there are instances when positive feedback is used in which target hormones influence the hypothalamus and pituitary to further augment their own production.

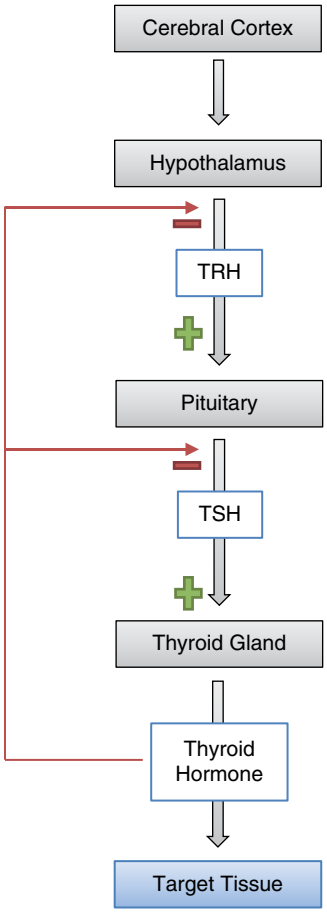


Figure 5.3 Typical feedback control of hormone secretion in the neuroendocrine system. The hypothalamus releases thyrotropin-releasing hormone (TRH) in response to a stimulus. TRH stimulates the anterior pituitary to releases thyroid-stimulating hormone (TSH). TSH targets cells in the thyroid gland to produce thyroid hormone, which circulates to target cells and elicits a response (increase energy expenditure). Thyroid hormone exerts negative feedback on the hypothalamus and pituitary to downregulate TRH and TSH production, respectively. Plus signs indicate stimulation of hormone production and release; minus signs indicate inhibition hormone production and release.

Vascular Supply

The vascular organization of the neuroendocrine system is responsible for the effectiveness of feedback regulation and the hormone cascade. The hypothalamus receives arterial blood from the circle of Willis, while the pituitary gland is supplied by the superior and inferior hypophyseal arteries (branches of the internal carotid artery). The hypophyseal portal circulation connects the hypothalamus with the anterior pituitary, thereby allowing direct transport of hypophysiotropic hormones to their corresponding hypophyseal receptors. Venous blood from the pituitary drains into the cavernous sinus where it enters the systemic circulation to reach target glands and tissues. Short portal veins connect the posterior and anterior lobes of the pituitary. A small portion of pituitary outflow is thought to ascend in retrograde to the hypothalamus where it can directly participate in regulation of hypophyseal hormone production. It is important to note that the blood–brain barrier is incomplete surrounding the portal system, which ensures exposure to circulating hormones emanating from peripheral tissues.

Regulation of Hormone Secretion

Hypothalamus

The hypothalamus is responsible for integrating sensory stimuli from the external environment with input from the internal environment to maintain homeostasis. Therefore, neuroendocrine transduction is regulated not only by hormonal feedback but also by neural input from higher brain centers that convey information about the external environment such as temperature, light, pain, and other sensory stimuli.

In the hypothalamus, cell bodies responsible for hormone synthesis are anatomically intermingled, and there is often redundancy in production of a single hormone by separate hypothalamic nuclei. A single hypothalamic hormone may exert an effect on multiple pituitary hormones, and multiple hypothalamic hormones may influence regulation of a single hypophyseal hormone. This overlap and redundancy throughout the neuroendocrine system allows for a high degree of regulation.

Pituitary Gland

Pituitary hormone regulation is not only under hormonal feedback but is also influenced by central and peripheral neural input, an example of which is illustrated by lactation and nursing. Suckling activates sensory pathways leading to the hypothalamus that trigger release of PRLH and TRH, and inhibit release of dopamine (prolactin-inhibiting hormone), and result in PL secretion by the anterior pituitary. Concurrently, suckling stimulates release of OT by the posterior pituitary, and together PRL and OT stimulate milk production and initiate milk ejection in mammary glands, respectively. Central factors also influence pituitary hormone release, as is seen when on occasion lactating mothers expel a small amount of milk upon the thought of their baby. The images stimulate the cerebral cortex, which results in release of OT and contraction of myoepithelium in mammary gland ducts.

The majority of pituitary hormones are released in a pulsatile manner, therefore regulation of target organs and tissues relies not only on absolute hormone concentrations but also on the frequency and amplitude of hormone pulses.

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6

Feline Acromegaly

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Etiology/Pathophysiology and Epidemiology

Feline acromegaly is a disease characterized by excessive growth hormone secretion leading to a wide array of clinical signs caused by the hormones' effects on multiple organ systems. These effects can be divided into two major classes. The first are the catabolic actions of growth hormone that include insulin antagonism, lipolysis, and gluconeogenesis with the net effect of promoting hyperglycemia. The second are the slow anabolic (or hypertrophic) effects of growth hormone, which are mediated by insulin-like growth factors. Growth hormone stimulates production of insulin-like growth factors in several different tissues. Insulin-like growth factor-1 (IGF-1), which is produced in the liver, is thought to be the key factor that facilitates the anabolic effects of growth hormone that are responsible for the characteristic appearance of acromegalic people, dogs, and cats.

Growth hormone is produced in the pars distalis (anterior pituitary), specifically by acidophilic cells, called somatotrophs. The release of growth hormone is regulated by many factors, the most important of which is growth hormone-releasing hormone (GHRH) produced by the hypothalamus. Recently, another hormone, ghrelin, has also been identified as a potent stimulator of growth hormone release. Ghrelin is produced by the stomach and released following ingestion of a meal.

Release of growth hormone is inhibited by the hypothalamic hormone somatostatin as well as by growth hormone and IGF-1 via negative feedback. Feline acromegaly is typically the result of a functional adenoma of the pituitary that releases growth hormone despite negative feedback resulting in excessive growth hormone production and release.

Feline acromegaly, thought to be an uncommon disease until recently, is likely underdiagnosed. Three studies have examined the incidence of acromegaly in the diabetic cat population. A recent study in the United Kingdom measured IGF-1 levels in variably controlled diabetic cats. Of the 184 cases, 59 (32%) had markedly increased IGF-1 concentrations. Eighteen of these 59 cats underwent pituitary imaging, confirming a diagnosis of acromegaly in 17/18 (94%). A second study examined 225 cats with variably controlled diabetes and 40 (17.8 %) had markedly high IGF-1 concentrations. In the largest study to date, of 1222 cats with diabetes, 323 (26.4 %) had IGF-1 suggesting acromegaly and 90% had a pituitary mass upon imaging (CT or MRI). This suggests that 18–32% of diabetic cats may have concurrent acromegaly and acromegaly may be one of the most important predisposing factors to feline diabetes through the induction of insulin resistance.

Etiology

Acromegaly in humans is usually sporadic, but up to 20% of familial isolated pituitary adenomas are caused by germline sequence variants of the aryl-hydrocarbon-receptor interacting protein (AIP) gene. The AIP gene is associated with xenobiotic metabolizing enzymes and endocrine disrupting chemicals in the environment, such as bisphenol A and PBDEs, have been linked to both feline acromegaly and hyperthyroidism. Feline acromegaly has similarities to human acromegalic families with AIP mutations. A recent study sequenced the feline AIP gene, to identify sequence variants and compare the AIP gene sequence between feline acromegalic and control cats, and in acromegalic siblings. A single nonsynonymous single-nucleotide polymorphism (SNP) was identified in exon 1 (AIP:c.9T > G) of two acromegalic cats and none of the control cats, as well as both members of one sibling pair. The region of this SNP is considered essential for the interaction of the AIP protein with its receptor. This sequence variant has not previously been reported in humans. Two additional synonymous

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sequence variants were identified (AIP:c.481C > T and AIP:c.826C > T). This was the first molecular study to investigate a potential genetic cause of feline acromegaly and identified a nonsynonymous AIP SNP in 20% of the acromegalic cat population evaluated, as well as in one of the sibling pairs evaluated.

History and Clinical Signs

Feline acromegaly most commonly affects middle-aged to older, male castrated cats. In one study, 13 of 14 cats with acromegaly were males with an average age of 10.2 years. This association may be biased, however, as most cats that are diagnosed with acromegaly present for insulin-resistant diabetes mellitus, which is also more common in older, male castrated cats. Based on available data, there is no known breed association for acromegaly.

Most patients with acromegaly present for insulin-resistant diabetes mellitus (insulin doses greater than 1.5–2.2 units/kg BID) with concurrent weight gain rather than weight loss. Growth hormone has effects on all the tissues in the body and therefore the disease has a range of clinical signs. Physical characteristics of acromegaly include increased body weight, a broadened face, enlarged feet, protrusion of the mandible (prognathia inferior), increased interdental spacing, stertorous breathing, organomegaly, and a poor haircoat. Cardiovascular signs include the presence of a heart murmur, hypertension, arrhythmia, associated with hypertrophic cardiomyopathy. Neurologic disease associated with feline acromegaly is uncommon but can occur with a pituitary macroadenoma. Neurologic signs that have been observed with acromegaly include dullness, lethargy, abnormal behavior, circling, and blindness. Glomerulopathy and secondary renal failure have also been associated with feline acromegaly. Histopathologic evaluation of the kidneys from acromegalic cats has revealed thickening of the glomerular basement membrane and Bowman's capsule, periglomerular fibrosis, and degeneration of the renal tubules. Arthropathy and peripheral (diabetic) neuropathy have been shown to cause lameness in acromegalic cats.

Diagnosis

Diagnosis of feline acromegaly starts with clinical suspicion, using a thorough history, signalment, and clinical signs. Many of the abnormalities in the minimum database of affected cats reflect concurrent diabetes mellitus and include erythrocytosis, hyperglycemia, increased liver enzymes (ALT, ALP), hypercholesterolemia, hyperphosphatemia, hyperglobulinemia, azotemia, glucosuria, ketonuria, proteinuria, and isosthenuria.

Growth hormone concentration is a common diagnostic for acromegaly in humans, but assays specifically for feline growth hormone are not widely available. An assay using ovine GH as the antigen has been validated for use in cats, but is only available in Europe. However, even if an assay were available, growth hormone concentrations alone may not be a reliable diagnostic for acromegaly. Growth hormone production is cyclic and levels may vary throughout the day. A single high value may not necessarily be diagnostic for acromegaly. Additionally, it has been shown that growth hormone may be elevated in nonacromegalic diabetic cats. This may be due to the fact that portal insulin is required for the liver to produce IGF-1. In diabetics being treated with insulin subcutaneously, portal insulin concentrations will remain low, resulting in decreased IGF-1 production and theoretically decreased inhibition of GH release. In addition, GH levels may also not be elevated early in the course of the disease, but later typically increase significantly.

Insulin-like growth factor-1 is the endocrine assay most commonly used to diagnose feline acromegaly and is widely available through the Michigan State University Diagnostic Center for Population and Animal Health (www.animalhealth.msu.edu/Forms/F.ADM.7.pdf). Unlike GH, IGF-1 concentrations are less likely to fluctuate over the course of the day as the majority of IGF-1 is protein bound, giving it a longer half-life in the body. In addition, IGF-1 increases in response to chronically elevated GH concentrations and is thought to be a reflection of GH levels over the previous 24 hours. However, just as with GH, elevations in IGF-1 concentration alone may not be diagnostic for acromegaly. One study found that IGF-1 levels in nonacromegalic cats on long-term insulin treatment (>14 months) had higher levels of IGF-1 than nondiabetics. It was proposed that insulin treatment allowed for beta cell regeneration and increased portal insulin, leading to elevations in IGF-1. A subsequent study evaluating IGF-1 levels in confirmed acromegalics, diabetics, diabetics, and healthy cats found that acromegalic diabetics had significantly higher levels of IGF-1 than diabetics and nondiabetics. This study concluded that IGF-1 was 84% sensitive and 92% specific for diagnosing feline acromegaly. No correlation between long-term insulin use and elevations in IGF-1 concentrations was found in this study.

Diagnostic Imaging

Radiographic findings associated with feline acromegaly are related to the hypertrophic effects of excessive GH. Hyperostosis of the calvarium, spondylosis of the spine, and protrusion of the mandible are common findings.

Periosteal reaction, osteophyte production, soft tissue swelling, and collapse of joint spaces are signs associated with the degenerative arthropathy linked to feline acromegaly. Thoracic radiographs may reveal cardiomegaly (hypertrophic cardiomyopathy) and/or congestive heart failure. Nonspecific signs such as abdominal organomegaly (hepatic, renal, and adrenal) may be revealed by abdominal ultrasound.

Advanced imaging is needed to document the presence of a pituitary macroadenoma. Computed tomography (CT) and magnetic resonance imaging (MRI) are both useful for identifying pituitary masses. However, one study found MRI to be the more sensitive imaging modality. The presence of a pituitary tumor alone is not diagnostic for feline acromegaly as other functional tumors of the pituitary may also result in insulin-resistant diabetes, such as adrenocorticotropic hormone (ACTH)-producing tumors in patients with Cushing disease. Conversely, the absence of a pituitary mass does not rule out acromegaly as there have been reported cases where a patient had a negative MRI but a pituitary mass was identified at necropsy and histopathology confirmed a GH-secreting adenoma.

Histopathology

Histopathology is needed for definitive diagnosis which makes antemortem diagnosis challenging. However, with advancements in surgical procedures such as transsphenoidal hypophysectomy, surgical excisional biopsy is possible. The main histopathologic change associated with acromegaly is acidophil proliferation in pituitary tumors.

Adrenocortical Function Testing

There is no single test for the diagnosis of feline acromegaly. Clinical suspicion based on a thorough history and physical exam is essential. As stated earlier, the most common presenting complaint for patients with acromegaly is insulin resistance with weight gain. The two most common causes of insulin resistance in cats are hyperadrenocorticism and acromegaly. Both of these diseases can be associated with a pituitary mass and bilateral adrenomegaly. As such, all suspected acromegalics should undergo adrenocortical testing via the ACTH stimulation test and/or low-dose dexamethasone suppression test. Normal results on these tests would then be an indication to screen for acromegaly.

Treatment

Medical Treatment

Somatostatin is a hypothalamic hormone that acts on the pituitary to inhibit GH release. Somatostatin analogs are commonly used in human medicine for the treatment of acromegaly and have efficacy rates of 50–60%. The somatostatin analog octreotide has been evaluated in a small number of feline acromegalics with limited success. One study in four cats found no change in GH following treatment. Another study measured the short-term effects of octreotide in five feline acromegalics and found a decrease in growth hormone concentrations for up to 90 minutes. A small study evaluating an octreotide analog (Sandostatin® LAR) showed no benefit in cats treated for 3–6 months.

However, a recent study examined the long-term medical management of acromegaly in cats using pasireotide, a novel somatostatin analog, which had been shown to decrease serum IGF-1 and improve insulin sensitivity in cats with acromegaly when administered as a short-acting preparation. The study used once-monthly administration of long-acting pasireotide (pasireotide LAR) for treatment of cats with acromegaly. Fourteen cats with acromegaly, diagnosed based on the presence of diabetes mellitus, pituitary enlargement, and serum IGF-1 >1000 ng/mL, were enrolled. Cats received pasireotide LAR (6–8 mg/kg SC) once monthly for six months. Fructosamine and IGF-1 concentrations, and 12-hour blood glucose curves (BGCs) were assessed at baseline and then monthly. Product of fructosamine concentration and insulin dose was calculated as an indicator of insulin resistance (Insulin Resistance Index). Eight cats completed the trial. Three cats entered diabetic remission. Median IGF-1 (baseline 1962 ng/mL [range 1051–2000 ng/mL]; month 6 1253 ng/mL [524–1987 ng/mL]; $P < 0.001$) and median Insulin Resistance Index (baseline 812 µmolU/L kg [173–3565 µmolU/L kg]; month 6 135 µmolU/L kg [0–443 µmolU/L kg]; $P = 0.001$) decreased significantly. No significant change was found in mean fructosamine (baseline 494 ± 127 µmol/L; month 6 319 ± 113.3 µmol/L; $P = 0.07$) or mean blood glucose (baseline 347.7 ± 111.0 mg/dL; month 6 319.5 ± 113.3 mg/dL; $P = 0.11$), despite a significant decrease in median insulin dose (baseline 1.5 [0.4–5.2] U/kg; month 6 0.3 [0.0–1.4] U/kg; $P < 0.001$). Adverse events included diarrhea (n = 11), hypoglycemia (n = 5), and worsening polyphagia (n = 2). This initial study indicates that pasireotide LAR has potential as a long-term management option for cats with acromegaly.

Conflicting results with various somatostatin analogs may be related to difference in somatostatin receptor subtypes. Future studies are required to identify the somatostatin receptor subtypes in GH-secreting feline pituitary tumors to determine if they are similar to the ones found in humans.

Dopamine agonists and more recently GH receptor antagonists are also used in human medicine for the treatment of acromegaly. The use of GH receptor antagonists

has not been reported in cats but in humans, response rates have been reported to be as high as 90%. However, it has been noted that the medication has no effect on tumor size and thus would be of no benefit in patients with neurologic signs. A single case study using a dopamine agonist (L-deprenyl) for the treatment of feline acromegaly showed no effect on reducing insulin requirements or clinical signs of disease. In humans, dopamine agonists are typically only 10–20% effective, but are often used in combination with other medications.

Increasing the dosage of insulin to improve glycemic control and clinical signs of diabetes is the most conservative choice for treating insulin-resistant diabetic acromegalics. However, there have been reports that some patients suddenly and inexplicably become sensitized to insulin, resulting in hypoglycemic crises. In one study, several acromegalic cats were euthanized after experiencing hypoglycemic coma.

Surgical Treatment

Surgical removal of the pituitary tumor (adenectomy) is the treatment of choice for acromegaly in human medicine. The procedure can be performed in cats and dogs, usually employing complete removal of the entire pituitary (hypophysectomy).

In veterinary medicine, a transsphenoidal approach is used involving only a small incision through the soft palate and then approaching the pituitary gland through the basisphenoid bone. Complications associated with the surgery include hemorrhage and incision dehiscence. Post surgery, patients are treated with cortisone, L-thyroxine, and desmopressin. The same surgical procedure is also used to treat pituitary-dependent hyperadrenocorticism in both dogs and cats. A study in which seven cats with pituitary-dependent hyperadrenocorticism were treated with transsphenoidal hypophysectomy resulted in five cats showing complete resolution of the disease. Four of these cats had concurrent diabetes mellitus, two of which showed increased insulin responsiveness after surgery.

A few case reports exist for the treatment of feline acromegaly with transsphenoidal hypophysectomy. Prior to surgery, one patient was an insulin-resistant diabetic that was still exhibiting clinical signs despite receiving 25 U of insulin (Levemir® Novo Nordisk) four times per day. Three weeks after surgery, the patient no longer required insulin therapy and up to one year later the patient's IGF-1 and GH concentrations were within normal limits.

In another single case report, a 13-year-old male castrated domestic shorthair was treated for acromegaly with transsphenoidal hypophysectomy. The patient had a history of insulin-resistant diabetes mellitus (15 units of glargine BID) and was diagnosed with acromegaly via elevated IGF-1 (447 nmol/L) and visualization of a pituitary mass on MRI. The diabetes resolved two weeks postoperatively and remained in remission for eight months at which time the patient was euthanized as a result of feline infectious peritonitis.

In more recent studies, hypophysectomy has been offered to owners who presented diabetic cats with confirmed acromegaly (IGF-1 >1000 ng/mL, pituitary mass) to the Royal Veterinary College since 2012. All cats were operated on by one neurosurgeon. Hypophysectomy was performed by manual extirpation using fine surgical tools via a transoral transsphenoidal approach. Cats received intensive peri- and postoperative monitoring of electrolytes, glucose and blood pressure, and were initially administered conjunctival desmopressin (DDAVP), intravenous infusions of insulin and hydrocortisone, before being transitioned to conjunctival DDAVP, oral hydrocortisone and levothyroxine and subcutaneous glargine insulin. In total, 21 diabetic cats underwent hypophysectomy from April 2012 to October 2014 (median, range; age: 10.3 years, 5.4–14.8; pituitary height: 6.0 mm, 4.0–10.6; IGF-1: 1833 ng/mL, 1138 to >2000; fructosamine: 574 µmol/L, 339–1076). Other than mild pelvic limb weakness, no cat displayed overt neurologic deficits prior to surgery. Three (14%) cats died postoperatively. Two cats did not recover from anesthesia and were euthanized within 24 hours; one cat developed septic meningitis and was euthanized 17 days postoperatively. All surviving cats (n = 18) had a reduction of serum IGF-1 and 16 cats (89%) showed IGF-1 normalization (median postoperative serum IGF-1: 38 ng/mL (15–1955), $P < 0.001$). Fourteen of the 18 surviving cats (78%) achieved diabetic remission; the remaining four achieved superior glycemic control with lower insulin dosages (median fructosamine pre- and postoperatively: 692 and 547µmol/L respectively; median insulin dose pre- and postoperatively: 20.5 and 3.5 units/kg/day respectively). Congestive heart failure was encountered as a transient problem in 4/19 cats that recovered from the surgery; all four cases occurred prior to implementing a reduction in volume of intravenous fluid delivered as part of the postoperative protocol. Two cats developed paresis of the left orbicularis oculi muscle, which resolved in the surviving cat. Cardiac arrest occurred in one cat postoperatively at time of jugular catheter placement, which was successfully revived and made an uneventful recovery. One cat developed a left pelvic limb monoparesis, which improved but did not resolve. Palatal wound breakdown was not encountered. This large case series suggests that hypophysectomy as a treatment for feline acromegaly results in a high incidence of diabetic remission and resolution of acromegaly.

An alternative procedure, cryohypophysectomy, has been reported in a small number of cats but the procedure has been less effective and results in a higher complication rate.

Radiation

Radiation therapy is another option for the treatment of feline acromegaly, especially if the tumor is inoperable, the patient is not a suitable candidate for anesthesia, or surgical treatment is not available in the area. In human medicine, radiation therapy is regarded as a second-line treatment as beneficial effects may take years to develop and the patient typically experiences undesired late-term CNS radiation effects.

The majority of studies that have been performed in veterinary medicine focus on radiation treatment of pituitary masses regardless of functional status. There is no standard treatment protocol for pituitary masses in veterinary medicine and varying methods have been used, including both single and multiple dose fractions administering total dosages ranging from 1500 to 4000 cGY. The majority of the cats included in these studies had insulin-resistant diabetes (suspected acromegaly or Cushing disease) and/or neurologic signs. Radiation therapy was shown to be successful in improving insulin resistance and neurologic signs. Neurologic improvement was generally seen within weeks to months and an improved insulin response was seen within the first month, but most patients still required insulin therapy. In cases where repeat imaging was available, a decrease in tumor size was also noted.

Disadvantages of radiation therapy are the early and delayed effects of radiation, repeated anesthesia, and expense. Early effects from radiation therapy include hair loss, skin pigmentation, and otitis externa. Reported late-term side-effects include brain necrosis, tumor regrowth, and visual and hearing impairment.

In one study, 12 cats with pituitary tumors were treated with a coarse fractionated radiation protocol delivering a total dose of 37 Gy in five once-weekly doses. Eight of these cats had insulin-resistant diabetes mellitus secondary to acromegaly. Of these eight cats, five no longer required insulin therapy, two became stable diabetics, and one required less insulin. In addition, 3/4 cats had improved neurologic signs. The mean survival time of cats in this study was approximately 18 months. In another study, 14 cats with confirmed acromegaly and insulin-resistant diabetes were treated with a total dose of 3700 cGy divided into 10 fractions (three per week). Thirteen of the 14 cats had improved insulin responses. The average insulin dosage reduction was approximately 75%. Six of the cats went into complete diabetic remission and at the time the article was written, 3/6 remained in remission. The median survival time of cats in this study was 28 months.

The most promising results with radiation may involve the use of stereotactic radiation therapy (SRT). Fifty-three client-owned cats were referred to Colorado State University for

SRT to treat pituitary tumors causing poorly controlled diabetes mellitus (DM) secondary to acromegaly. Diagnosis of acromegaly was based on history, physical examination, laboratory results, and cross-sectional imaging of the pituitary. Signalment, radiation protocol, insulin requirements over time, adverse effects, and survival were recorded. Median survival time was 1072 days. Of the 41 cats for which insulin dosage information was available, 95% (39/41) experienced a decrease in required insulin dose, with 32% (13/41) achieving diabetic remission. Remission was permanent in 62% (8/13) and temporary in 38% (5/13) cats. Median duration to lowest insulin dose was 9.5 months. Of the treated cats, 14% developed hypothyroidism and required supplementation after SRT. Cats treated with SRT have improved survival time and control of their DM when compared to previously reported patients treated with non-SRT.

Conclusion

Feline acromegaly is likely an underdiagnosed disease in older male cats, especially in patients with insulin-resistant diabetes. There is no single diagnostic test for acromegaly. The diagnostician should use history, clinical signs, laboratory tests (GH and IGF-1), and advanced imaging to arrive at a diagnosis. There are several treatments options, but clinical studies on long-term safety and efficacy are limited and often lack controls. Until more work is done evaluating medical treatments such as somatostatin analogs and growth hormone antagonists, most patients are best treated with either surgery or radiation therapy to control GH levels, improve glycemic control, and improve or prevent the development of neurologic signs.

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7

Pituitary-Dependent Hyperadrenocorticism in Dogs and Cats

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Etiology/Pathophysiology and Epidemiology

Pituitary-dependent hyperadrenocorticism (PDH), also known as Cushing disease, is a common endocrine disorder in older dogs though relatively uncommon in cats. This disorder is caused by a pituitary adenoma (PA) that secretes inappropriate amounts of adrenocorticotropic hormone (ACTH), which results in bilateral adrenal hyperplasia and disorderly and excessive production of cortisol by the adrenal gland.

Classification

Basics of Classification

As with all central nervous system tumors, the Tumor–Node–Metastasis (TNM) system used by the World Health Organization does not apply. Current classification systems for PAs in veterinary patients are based primarily on secretory characteristics of the tumor. However, in humans, PAs are currently classified based upon:

- tumor size and degree of invasiveness (Box 7.1)
- tumor endocrine activity (hormone secretion)

or *functional* classification based on immunohistologic findings such as ACTH, thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), etc. immunostaining.

In both humans and animals, pituitary corticotroph adenomas that are responsible for Cushing disease (i.e., PDH) are classified as functional ACTH-secreting PAs (ACTH-PAs).

Further Classification

The World Health Organization classification system for PAs in humans has been refined to include designations for benign adenoma, atypical adenoma, and pituitary carcinoma on the basis of proliferation indices (p53 immunoreactivity, MIB-I Index, mitotic activity) and the absence/presence of metastases.

More comprehensive molecular classification systems based on relevant gene expression have not been systematically used to further characterize pituitary tumors. Similar work to classify canine pituitary tumors both morphologically and functionally is currently under way.

Prevalence

Humans

In humans, PAs are common tumors, with an overall prevalence in the general US population estimated at 16.7%.

- Corticotroph adenomas, comprising functional (ACTH-PAs) and silent corticotroph adenomas, represent approximately 10–15% of all PAs.
- Functional ACTH-PAs are the most common cause of Cushing syndrome (hypercortisolemia from any source), accounting for an estimated 70% of all cases.
- Prevalence of Cushing disease is estimated to be 1.2–2.4 per 1 million people, and affects approximately 12 000 people in the US. This number, however, may be much higher, given that Cushing disease is frequently misdiagnosed and diagnosis is often delayed.

Dogs

Functional ACTH-PAs have a reported incidence of 0.2% in all dogs (1–2 cases/1000 dogs/year), with approximately 100 000 dogs affected yearly in the US. PDH accounts for approximately 85–90% of cases of hyperadrenocorticism, with the remainder of cases resulting from functional adrenal tumors, meal/food-induced cases, occult or atypical disease.

Meal- or food-induced Cushing syndrome is thought to occur as the result of a congenital defect resulting in the aberrant expression of the gastric inhibitory polypeptide

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Box 7.1 Classification of pituitary tumors in humans by size and anatomic location

Classification by size based on radiologic findings

Microadenomas	Less than 10 mm diameter
Macroadenomas	Equal to or greater than 10 mm diameter

Classification based on radioanatomic findings

Stage I	Microadenomas (<1 cm) without sella expansion
Stage II	Macroadenomas (≥1 cm); may extend above the sella
Stage III	Macroadenomas with enlargement and invasion of the floor or suprasellar extension
Stage IV	Destruction of the sella

(GIP) receptor in the adrenal cortex. Stimulation of this receptor by GIP, normally released by the stomach in response to a meal, leads to clinical signs of hyperadrenocorticism in younger dogs. Occult hyperadrenocorticism refers to the presence of elevated adrenal steroid concentrations in the absence of clinical signs and has been best described in Scottish terriers with elevated serum alkaline phosphatase (SAP) and vacuolar hepatopathy. Atypical hyperadrenocorticism refers to animals with clinical signs of classic hyperadrenocorticism secondary to excess sex steroid production rather than excessive cortisol secretion.

Pathogenesis

The pathogenesis of pituitary tumors that produce ACTH is becoming more evident based on ongoing studies evaluating gene and protein expression in both humans and dogs. This information will aid our understanding of tumorigenesis and point us toward targeted specific therapies.

Two theories have been put forward to explain the development of an ACTH-producing pituitary tumor (ACTH-PA, corticotrophinoma):

- hypothalamic theory
- monoclonal theory.

Hypothalamic Theory

In this theory, the hypothalamus stimulates corticotrophs through enhanced secretion of corticotropin-releasing hormone (CRH) and vasopressin. In addition, concurrent defects in the pituitary glucocorticoid receptors (GR) on the corticotroph cells lead to decreased negative feedback by cortisol on CRH and ACTH synthesis.

Gene Mutation

Karl and colleagues and Lamberts described a mutation in the gene in humans that encodes the GR, with a reduction in the sites of DNA binding, while maintaining affinity for cortisol. This *de novo* mutation promotes GR resistance that precedes the formation of the corticotrophinoma.

Recent studies by Teshima and colleagues, using trilostane to decrease cortisol, demonstrated pituitary tumor growth as a consequence of a reduction in negative feedback. Their studies on canine ACTH tumor cells suggest that reduced negative feedback might first lead to corticotroph hyperplasia followed by a subsequent somatic mutation that could lead to tumor development.

Dopaminergic Actions

Other possibilities for a hypothalamic theory of PDH include:

- dopaminergic neurodegeneration in aged individuals
- decreased expression of the D2 dopaminergic receptor in the corticotroph cells, resulting in decreased dopaminergic inhibition and subsequent hyperplasia. With this possibility, adenomas would evolve secondary to somatic mutations in hyperplastic cells.

The hypothalamic theory is reinforced by the recurrence of ACTH-producing tumors following surgery or in patients in which no tumor was found on MRI or when exploring the sella. Both of these scenarios suggested stimulation or lack of inhibition of ACTH-producing cells from higher centers (hypothalamus or hippocampus). This hypothesis is also supported by the fact that individuals with chronic stress and greater activation of the hypothalamic–pituitary–adrenal axis show corticotroph hyperplasia.

Monoclonal Theory

The main evidence against the hypothalamic theory is the presence of tumor clonality in the majority of the adenomas studied in humans. The monoclonal theory argues that the adenoma occurs in the pituitary outside of other influences and arises through the somatic mutation of a corticotroph cell, resulting in a tumor clone. This mutation precedes the clonal expansion of the tumor.

It is unknown which mutation(s) result in the development of a tumor. Taking into account microadenomas and macroadenomas, the existence of a variety of corticotrophinomas is suggested. The majority of microadenomas in dogs do not progress to macroadenomas based on the low percentage of dogs that develop such tumors during treatment with adrenolytics or adrenal enzyme blockers. Macroadenomas can display a variety of behaviors, from limited growth and indolent course to more aggressive behavior as seen in human patients with

Box 7.2 Genes and proteins expressed in pituitary tissue in humans with functional ACTH-PAs

Genes

NEUROD1 + hPTTG1	*Overexpressed* in 3 studies
HIGD1B + HSD11B2	*Overexpressed* in 2 studies
CDKN1B	*Underexpressed* in 4 studies
CDKN2A	*Underexpressed* in 2 studies
let-7	*Underexpressed* in 2 studies

Proteins

c-myc	*Overexpressed* in 2 studies
p27Kip1	*Underexpressed* in 4 studies
p16	*Underexpressed* in 2 studies

Nelson syndrome in which the pituitary tumor grows rapidly following bilateral adrenalectomy or suppressive medical therapy.

Gene Origin

In humans with functional ACTH-PAs, studies have identified 43 genes and 22 proteins as overexpressed and 58 genes and 15 proteins as underexpressed compared with normal pituitary tissue (Box 7.2).

In dogs, we are just beginning to learn more about genes and protein expression in patients with PDH. The recent demonstration of expression of somatostatin receptor subtypes and dopamine receptor subtype 2 (D2) in canine corticotroph adenomas offers the possibility for novel medical treatment of PDH with somatostatin analogs and dopamine agonists.

Pituitary Size and Proliferation Markers

The ratio between pituitary height and area of the brain (P/B) has been used to evaluate pituitary size.

- P/B ratio >0.31 indicates an enlarged pituitary
- P/B ratio ≤0.31 indicates a nonenlarged pituitary.

A recent study investigated the expression of proliferation markers Ki-67 and minichromosome maintenance-7 (MCM7) in canine corticotroph adenomas in enlarged and nonenlarged pituitaries, and evaluated their relation to the size of canine pituitary corticotroph adenomas.

- Canine corticotroph adenomas in enlarged pituitaries showed greater proliferation potential compared with adenomas in nonenlarged pituitaries.
- MCM7 expression was significantly greater than Ki-67 expression in canine pituitary corticotroph adenomas.

Thus, MCM7 may be superior to Ki-67 as a proliferation marker in canine pituitary tumors.

Corticotroph and Melanotroph Cell Marker: Tpit

In the pituitary glands of humans and mice, corticotrophs and melanotrophs have a specific marker in common, the *T-box transcription factor* (Tpit or Tbx19), which regulates the late differentiation of corticotrophs and melanotrophs and therefore may contribute to the pathogenesis of corticotroph adenomas.

A recent study in 14 dogs with PDH examined the expression and mutation analysis of Tpit in normal canine pituitary and corticotroph adenomas.

- Tpit was expressed in corticotroph and melanotroph cells of normal and adenomatous canine pituitary, and remained present in nonadenomatous corticotrophs of pituitaries from PDH dogs.
- No tumor-specific mutation in Tpit cDNA from corticotroph adenomas was found; however, a missense polymorphism (see Polymorphism versus Mutation) in the highly conserved DNA-binding domain, the T-box, was discovered in one dog.

The study concluded that Tpit can be used as a reliable marker for corticotroph and melanotroph cells in canine pituitary tissue, but that mutations in the Tpit gene are unlikely to play a major role in pathogenesis of canine corticotroph adenomas.

Corticotroph Differentiation Markers: LIF and LIFR

Leukemia inhibitory factor (LIF) is a cytokine of the interleukin (IL)-6 family that activates the hypothalamic–pituitary–adrenal axis and promotes corticotroph differentiation during development. LIF and leukemia inhibitory factor receptor (LIFR) expression were studied in pituitary glands of control dogs and specimens of corticotroph adenoma tissue were collected from dogs with PDH. The results demonstrated that:

- LIFR is highly co-expressed with ACTH and alpha-melanocyte-stimulating hormone in the control canine pituitary gland and corticotroph adenomas
- there was a strong co-expression of LIFR and ACTH1-24 in the cytoplasm of cells in the pars distalis and pars intermedia of control pituitary tissue. In pituitary glands harboring an adenoma, the cytoplasmic expression of LIFR followed that of ACTH1-24. Nontumorous cells of the pars distalis showed no cytoplasmic staining but did demonstrate nuclear to perinuclear immunoreactivity for LIFR in 10 of 12 tissue specimens from PDH dogs. This nuclear immunoreactivity was not observed in the control pituitary tissues or in the pituitary gland with corticotroph hyperplasia.

Role of ACTH Production and Glucocorticoids

As mentioned earlier, a characteristic biochemical feature of corticotroph adenomas is their relative resistance to negative feedback by glucocorticoids. In a recent study,

gene expression related to ACTH production and secretion and the negative feedback by glucocorticoids in canine corticotroph adenoma was evaluated in pituitary tumors in 10 dogs with Cushing disease. The results demonstrated increased ACTH production and resistance to negative feedback by glucocorticoids in canine corticotroph adenomas.

Therapeutic Role of EGFR

Since tumors in dogs and humans express epidermal growth factor receptor (EGFR), in another study we examined whether EGFR might provide a therapeutic target for Cushing disease.

- In cell cultures from surgically resected human and canine corticotroph tumors, blocking EGFR also suppressed expression of proopiomelanocortin (POMC), the ACTH precursor.
- In mouse corticotroph EGFR transfectants, ACTH secretion was enhanced and POMC promoter activity was increased.

In mice, blocking EGFR activity with gefitinib, an EGFR tyrosine kinase inhibitor:

- attenuated POMC expression
- inhibited corticotroph tumor cell proliferation and induced apoptosis
- decreased both tumor size and corticosterone levels
- reversed signs of hypercortisolemia, including elevated glucose levels and excess omental fat.

These study results indicate that inhibiting EGFR signaling may be a novel strategy for treating Cushing disease.

History and Clinical Signs

Clinical signs, as well as laboratory abnormalities, seen in patients with PDH are secondary to the effects of steroid excess, well recognized, and similar in scope to those seen with exogenous glucocorticoid supplementation (Boxes 7.3 and 7.4).

The clinical signs of polyuria and polydipsia occur as the result of excessive cortisol interfering with pituitary release of antidiuretic hormone (ADH) or the binding of ADH to receptors in the renal tubules. Abdominal distension and thinning of skin occur due to the catabolic effects of cortisol on tissues such as muscle and connective tissue. Hepatomegaly steroid-induced vacuolar hepatopathy also contributes to the "pot-bellied" appearance. The endocrine alopecia mirrors the known distribution of sex hormone receptors in the skin with endocrine alopecias often sparing the head and extremities. Panting occurs in both dogs and humans and is felt to be due to steroid-induced stimulation of ventilator centers in the brainstem. Pyoderma and urinary tract infections reflect the immunosuppressive effects of glucocorticoids. The mechanism(s) behind the steroid induction of calcinosis cutis is poorly understood although the condition does occur with both iatrogenic and spontaneous hyperadrenocorticism and the condition can take months to resolve following resolution of hyperadrenocorticism or withdrawal of the exogenous steroid.

Awareness of PDH has increased over time, resulting in the presentation of patients with only mild clinical signs, clinical signs affecting only one organ system (e.g.,

Box 7.3 Common clinical signs of PDH in dogs and cats

Polyuria and polydipsia
Polyphagia
Abdominal distension
Bilaterally symmetric endocrine alopecia
Panting
Hypertension
Urinary tract infections
Additional dermatologic signs:
– Thin skin
– Pyoderma
– Calcinosis cutis

Box 7.4 Common laboratory findings of PDH

Hematologic abnormalities

"Stress" leukogram (uncommon in cats):
– Neutrophilic leukocytosis
– Lymphopenia
– Eosinopenia
Mild thrombocytosis
Mild erythrocytosis

Serum biochemical abnormalities

Increased serum alkaline phosphatase
Milder increased in alanine aminotransferase
Hypercholesterolemia
Hypertriglyceridemia
Hyperglycemia

Urinalysis

Decreased urine specific gravity <1.018
Proteinuria
Urinary tract infection (even in absence of pyuria and bacteriuria)

polyuria and polydipsia or alopecia), absent clinical signs, or unusual isolated manifestations of the disease.

Diagnosis

Diagnosis of PDH requires incorporating information from the history, physical examination, and routine laboratory tests. Specific endocrine tests and imaging modalities are available to diagnose hyperadrenocorticism (HAC) and distinguish between the various causes of hypercortisolism. No single test is perfect and if the initial screening test is negative and high clinical suspicion of HAC exists, additional tests should be performed. Endocrine evaluation of patients with HAC and nonadrenal illness can be difficult, and it is important to eliminate or manage the concurrent illness before undertaking adrenal function tests.

ACVIM Consensus Statement

In 2012, the American College of Veterinary Internal Medicine (acvim.org) issued a consensus statement addressing the diagnosis of spontaneous canine hyperadrenocorticism, which provides a thorough review of the diagnostic approach to patients with PDH and addresses many common clinical concerns. Access this statement at onlinelibrary.wiley.com/doi/10.1111/jvim.12192/epdf.

Baseline Diagnostics

In all patients being screened for PDH, the following initial diagnostics should be performed prior to endocrine diagnostics.

- Thorough history including prior treatment with systemic or topical glucocorticoids.
- Physical examination.
- Complete routine database, including complete blood count, serum biochemical profile, urinalysis, urine culture, and blood pressure.

These diagnostics are important as the clinical signs of PDH are rarely pathognomonic, and patients are generally older and may have co-morbidities, which affect endocrine function tests and impact therapeutic options and prognosis.

If a patient has a concurrent serious illness, postpone testing until the illness or injury has resolved or been controlled to minimize false-positive test results.

Endocrine Diagnostics

Specific endocrine tests and imaging modalities are available to both diagnose PDH and distinguish between the various causes of HAC (Tables 7.1 and 7.2). No single test is perfect and if the initial screening test is negative and high clinical suspicion of PDH exists, additional

Table 7.1 Diagnostic tests to evaluate patients with suspected PDH

Test	Components	Procedures	Results
Low-dose dexamethasone suppression (LDDS)	Dexamethasone sodium phosphate *or* polyethylene glycol: 0.01–0.015 mg/kg IV[a] (dog), 0.10 mg/kg IV (cat)	Obtain blood samples: 1) Before administration 2) 4 h after administration 3) 8 h after administration	Consult with your reference laboratory for specific reference ranges
ACTH stimulation	Cosyntropin *or* tetracosactrin: 5 µg/kg IV or IM (dog), 0.125 mg IV (cat)	Obtain blood samples: 1) Before administration 2) 60 min after administration	Consult with your reference laboratory for specific reference ranges
Urine cortisol to creatinine ratio (UCCR)[b]	Urine collected from dog in the morning[c]	Have owner collect urine at home for at least 2–3 consecutive mornings; submit an aliquot of the pooled samples to diagnostic laboratory	Consult with your reference laboratory for specific reference ranges

[a] Calculate dose using parent compound.
[b] High UCCRs in dogs without a high degree of clinical suspicion of hyperadrenocorticism should be interpreted cautiously.
[c] Urine collected by the owner is less likely to be influenced by stress; in addition, morning urine is preferred because it usually represents several hours of urine production.
Notes:

- The effect of feeding on LDDS or ACTH stimulation test results is unknown; however, feeding during these tests is not recommended. Fasting before testing is not necessary unless lipemia affects the cortisol assay results (check with your laboratory for specific details).
- In veterinary medicine, the ability of glucocorticoids, progestagens, and ketoconazole to suppress cortisol secretion is known. However, no effect on LDDS, ACTH stimulation, or UCCR has been documented in dogs treated with phenobarbital.

ACTH, adrenocorticotrophic hormone; IM, intramuscular; IV, intravenous.

Table 7.2 Diagnostic tests that differentiate between PDH and ADH

Test	Components	Procedures	Results
Low-dose dexamethasone suppression (LDDS)[a]	Dexamethasone sodium phosphate *or* polyethylene glycol: 0.01–0.015 mg/kg IV[b] (dog), 0.10 mg/kg IV (cat)	Obtain blood samples: 1) Before administration 2) 4 h after administration 3) 8 h after administration	• With LDDS, suppression to <50% baseline in a dog with HAC confirms PDH. • If no suppression with LDDS, cACTH measurement or abdominal ultrasound is recommended. • With LDDS or HDDS, lack of suppression does not confirm AT (approximately 25% of dogs with PDH fail to suppress)
High-dose dexamethasone suppression (HDDS)[a]	Dexamethasone sodium phosphate: 0.1 mg/kg IV[c] (dog), 1.0 mg/kg IV (cat)		
Endogenous ACTH	cACTH	Collect blood into chilled, silicon-coated glass or plastic EDTA tubes. Centrifuge within 15 min (ideally cooled centrifuge). Transfer plasma to plastic tubes and freeze immediately; samples must stay frozen until analysis[d]	Normal or elevated concentrations are consistent with PDH, suppressed values are consistent with AT

[a] LDDS and HDDS results cannot be considered 100% absolute; when imaging and endocrine test results conflict, the latter should be given preference.
[b] Calculate dose using parent compound.
[c] For HDDS, avoid the free alcohol form.
[d] Addition of the protease inhibitor aprotinin prevents ACTH degradation by plasma proteases and greatly facilitates sample handling. Check with your laboratory regarding suitability because, with some assays (i.e., Immulite), aprotinin introduces an artifactual decrease in results.
AT, adrenal tumor; ATCH, adrenocorticotrophic hormone; cATCH, canine adrenocorticotrophic hormone; HAC, hyperadrenocorticism; IV, intravenous.

tests should be performed to determine a definitive diagnosis.

Several endocrine screening tests are available to arrive at a diagnosis of HAC, including:

- low-dose dexamethasone suppression (LDDS)
- ACTH stimulation
- urine cortisol to creatinine ratio (UCCR).

Additional tests may be required to differentiate PDH from other causes of hypercortisolemia, such as endogenous ACTH measurement and advanced imaging.

Initial Endocrine Screening

Low-Dose Dexamethasone Suppression

Low-dose dexamethasone suppression demonstrates decreased pituitary sensitivity to negative feedback from glucocorticoids.

Indications Most consider LDDS the screening test of choice for HAC unless the patient history suggests iatrogenic HAC, in which case ACTH stimulation is preferred.

Sensitivity/Specificity In veterinary medicine, the reported sensitivity and specificity of the LDDS test range from 85% to 100% and from 44% to 73%, respectively.

Test Results Blood samples are obtained (1) before, (2) four hours after, and (3) eight hours after dexamethasone administration (0.01 mg/kg IV). Diagnosis of HAC is based on lack of suppression of cortisol concentration eight hours after dexamethasone administration.

ACTH Stimulation

Adrenocorticotropic hormone stimulation assesses adrenocortical reserve. Sensitivity of ACTH stimulation for all forms of spontaneous canine HAC ranges from 57% to 95%. In dogs with PDH, sensitivity is 80–83%. Specificity ranges from 59% to 93%.

Due to greater purity and quality control, use of synthetic ACTH is recommended. Use of compounded ACTH is discouraged, especially when monitoring patients on adrenolytic agents or adrenal enzyme blockers (see Synthetic versus Compounded ACTH).

Indications Adrenocorticotrophic hormone stimulation is the gold standard for diagnosis of iatrogenic HAC and spontaneous Addison disease (hypoadrenocorticism). A diagnosis of HAC is based on finding an elevated post-ACTH cortisol concentration based on the reference range established by the laboratory.

Sensitivity/Specificity Due to its low sensitivity, it is inferior to LDDS as a screening test for spontaneous HAC. However, many clinicians still use ACTH stimulation because of its convenient study duration of 60 minutes and relative effectiveness in the clinical setting,

especially when combined with abdominal ultrasound evaluation and interpreted in light of the history and physical examination.

Synthetic vs Compounded ACTH Synthetic polypeptides, such as Cortrosyn® (cosyntropin) or Synacthen® (tetracosactrin), contain the biologically active first 24 amino acids of ACTH; however, their potencies have not been compared.

In several studies, after administration of cosyntropin (5 µg/kg or 250 µg/dog IV or IM), peak cortisol concentrations occurred at 60–90 minutes. After administration of 5 µg/kg IV, no difference was detected between 60- and 90-minute cortisol concentrations. Cosyntropin can be reconstituted, divided into aliquots in plastic syringes, and frozen at –20 °C for six months. Whether tetracosactrin can be frozen has not been investigated; according to the manufacturer, store it at temperatures from 2 to 8 °C.

Compounded ACTH products have been evaluated in healthy dogs. Sixty minutes after administration, cortisol concentrations were similar among four compounded products (2.2 U/kg IM) and cosyntropin (5 µg/kg IV). However, at later times, cortisol concentrations varied considerably with the compounded products.

Urine Cortisol to Creatinine Ratio

The UCCR provides an integrated reflection of cortisol production, adjusting for fluctuations in blood concentrations. Determination of basal UCCRs can be performed alone or in tandem with other endocrine testing.

Indications The UCCR can be used as a screening test for hypercortisolemia, although a single positive result should not be overinterpreted. Adding oral dexamethasone suppression to UCCR testing (see later) has the advantage of potentially demonstrating both increased cortisol production and decreased sensitivity to glucocorticoid feedback.

Sensitivity/Specificity When a single, random urine sample is collected in veterinary hospitals, reported sensitivity and specificity of UCCR for diagnosis of HAC range from 75% to 100% and 20% to 25%, respectively. In some dogs, there is considerable day-to-day variation in UCCR results.

However, in dogs with physical and biochemical changes consistent with HAC, when two basal UCCRs were above the cut-off level:

- sensitivity was 99%; 95% confidence interval 94–100%
- specificity was 77%; 95% confidence interval 64–87%.

Evaluation of Pituitary–Adrenal Axis

Evaluation of the pituitary–adrenal axis is indicated in the following circumstances.

- Patients with clinical signs and laboratory findings consistent with PDH and in whom nonadrenal illness has been ruled out or is well controlled.
- Patients in whom an adrenal/pituitary mass or bilateral adrenal hyperplasia has been discovered in conjunction with compatible clinical signs.
- Patients with an incidentally discovered adrenal mass, with adrenalectomy being considered.
- Diabetic dogs with insulin resistance.

Differentiating PDH from ADH: Laboratory Analysis

Given that PDH and adrenal-dependent hyperadrenocorticism (ADH) are the most common forms of HAC, and that their treatment options and prognoses differ, it is important to recommend additional testing to determine the exact etiology of HAC. Several diagnostic modalities are commonly used to differentiate between PDH and ADH.

- Endogenous ACTH
- Dexamethasone suppression
- Dexamethasone suppression with UCCR

Endogenous ACTH

Canine ACTH is secreted from the pituitary gland in an episodic, pulsatile fashion in both healthy dogs and those with PDH. A circadian rhythm has not been convincingly demonstrated, although one study reported higher plasma concentrations of canine ACTH (cACTH) in the late afternoon than in the morning.

Indications Concentrations of cACTH do *not* differ between healthy dogs and those with PDH, and its measurement is not useful to screen for HAC. However, measurement of cACTH is the most accurate stand-alone biochemical test for differentiating PDH from adrenocortical tumor (AT), but the sensitivity of the assay differs with methodology. Normal or elevated concentrations of cACTH are consistent with PDH while suppressed values are consistent with AT.

Sensitivity/Specificity The most common problem with the cACTH assay is poor sensitivity. The largest study of cACTH in dogs with HAC used a two-site solid-phase chemiluminescent immunometric assay (Immulite 2000 Immunoassay System for ACTH; healthcare.siemens.com) and showed excellent discrimination between PDH and AT.

The likelihood of falsely low ACTH values in dogs with PDH is increased by:

- intraassay and interassay variability (increased at lower cACTH concentrations)
- pulsatile ACTH secretion
- inappropriate sample handling allowing ACTH degradation.

Dexamethasone Suppression

Dexamethasone administration in:

- *normal dogs:* causes rapid and prolonged suppression of cortisol secretion
- *patients with an AT:* at any dosage does *not* suppress cortisol secretion
  dogs with PDH:
  - does *not* appropriately suppress ACTH secretion (therefore does not suppress cortisol) when a low dose (0.01 mg/kg) is administered
  - in 75% of dogs with PDH, ACTH and cortisol concentrations decrease when a high dose (0.1 mg/kg) is administered
  - in 25% of dogs with PDH, suppression of ACTH and cortisol does not occur even after administration of higher dosages; in these patients, a large pituitary tumor or tumor developing from the pars intermedia is more likely.

Test Results The largest study evaluating both suppression tests (LDDS and high-dose dexamethasone suppression [HDDS]) included dogs with PDH (n = 181) and ATs (n = 35). With LDDS, criteria for identifying dogs with PDH included:

- four-hour post-LDDS cortisol concentrations below laboratory cut-off *or* <50% of basal cortisol concentration
- eight-hour post-LDDS cortisol concentrations <50% of the basal cortisol concentration *and* greater than the laboratory cut-off.

With HDDS, criteria for cortisol suppression were a four- and/or eight-hour cortisol concentration below the laboratory cut-off *or* <50% of the basal cortisol concentration.

Approximately 75% of dogs with PDH met at least one criterion for suppression on either LDDS or HDDS. Of those with PDH, 88% suppressed with the LDDS and 12% demonstrated suppression with HDDS.

Dexamethasone resistance (i.e., no criteria were met) occurred in all dogs with AT and the remainder (25%) of the dogs with PDH. In another study of 41 dogs with AT, 28 LDDS and 30 HDDS tests were performed, with no suppression seen on any test.

In dogs demonstrating lack of suppression with LDDS, use of endogenous ACTH rather than HDDS is recommended to differentiate PDH from ADH. Since suppression in response to dexamethasone supports a diagnosis of PDH, a dog with dexamethasone resistance can have either AT or PDH.

Dexamethasone Suppression with UCCR

Decreased blood cortisol concentration after dexamethasone administration is reflected in decreased UCCR.

Test Results After the patient's owner/handler collects a morning urine sample on two consecutive days, three doses of dexamethasone (0.1 mg/kg PO) are administered at 6–8-hour intervals, with a third urine sample collected the next morning.

Decrease in the third UCCR to <50% of the mean cortisol basal values is consistent with PDH. Lack of suppression does not confirm AT. In 160 dogs with HAC (49 with ATs, 111 with PDH), the UCCR in 72% of dogs with PDH suppressed to <50% of the basal UCCR, while the other 28% of those with PDH were dexamethasone resistant. In dogs with ATs, maximum suppression was 44% of the baseline sample.

Differentiating PDH from ADH: Imaging

While imaging can be very helpful in differentiating PDH from ADH, it cannot be used to establish a diagnosis of HAC. Moreover, finding normal adrenal glands on imaging studies does *not* rule out HAC.

Radiography

Imaging results may include:

- abdominal distension
- good contrast due to abdominal fat deposition
- hepatomegaly
- bladder distension
- mineralization of bronchi and pulmonary interstitium, and of dermal and subcutaneous tissues in areas predisposed to calcinosis cutis.

A small liver makes HAC unlikely. An AT may be visualized due to either mass effect or tumor calcification.

Adrenal Gland Imaging

Adrenal gland width is the most informative parameter identified on ultrasonography. However, the following may affect correct measurement.

- The long axis of adrenal gland often is misaligned with either the medial or dorsal plane of the body.
- Cross-sectional images may lead to oblique views and miscalculation of glandular dimensions.
- Breed and body size differences.
- Macronodular hyperplasia (a rare form of PDH) and some ATs can be difficult to differentiate.

Test Results In dogs with PDH, ultrasonography reveals normal-sized or enlarged adrenal glands that are typically symmetric; however, mild asymmetry may occur. In dogs with ATs, ultrasonography reveals moderate asymmetry, contralateral adrenocortical atrophy (adrenal width <4–5 mm), destruction of normal tissue architecture, or some combination of these findings.

Ultrasonography can also estimate AT size and possibly vascular or local soft tissue invasion. Although most ATs are unilateral, bilateral tumors may occur and in these patients, endogenous ACTH concentrations should be determined.

Metastasis When an AT has been confirmed, certain thoracic and ultrasonographic findings suggest malignancy.

- Adrenal gland width >4 cm.
- Invasion into the vena cava or adjacent tissues.

However, computed tomography (CT) and magnetic resonance imaging (MRI) are more sensitive techniques to identify vascular invasion and detect metastases.

Adrenalectomy should not be performed without confirming the presence of an AT (and atrophy of contralateral adrenal gland) by abdominal ultrasonography, CT, MRI, or some combination of these. Metastasis can be confirmed by ultrasound-guided biopsy, but differentiating benign from malignant AT often is difficult, even with histopathologic examination.

Pituitary Imaging

Pituitary imaging provides valuable information regarding treatment options and prognosis. Pituitary lesions range from microscopic nests of hyperplastic cells to large tumors. Absence of neurologic abnormalities does not exclude pituitary macrotumors (i.e., tumors that are >1 cm in diameter, extend above the sella turcica, or have a pituitary:brain ratio of >0.31).

Indications Pituitary imaging should be considered for all dogs at the time of PDH diagnosis, especially if hypophysectomy or radiation therapy is being considered. If clinical features suggest a pituitary macrotumor, confirmation requires imaging. Clinical signs of a macroadenoma include disorientation, aimless wandering, severe polyuria/polydipsia, lethargy, hyporexia to anorexia, visual impairment and possibly seizures.

Test Results Because pituitary lesions may be quite small, contrast-enhanced CT and MRI may identify normal-sized pituitary glands in dogs with PDH. However, dynamic contrast-enhanced CT takes advantage of the pituitary gland's blood supply.

- The posterior pituitary gland's blood supply is direct (arterial).
- The anterior pituitary gland's blood supply is mainly indirect via the pituitary portal system.

In dogs with normal pituitary glands, after IV administration of contrast medium, the posterior pituitary gland can be identified first – this phase is called the "pituitary flush." Its absence indicates atrophy due to compression by a pituitary tumor. Displacement or distortion of the flush can be used to identify and localize anterior pituitary microtumors.

Dorsal displacement and decreased signal intensity of the posterior lobe on T1-weighted MRI indicate the presence of a microtumor.

Treatment

In humans, while pituitary surgery is considered the first line of treatment for patients with Cushing disease, medical therapy now plays a more important role in the armamentarium available to patients after failed surgery. Repeat surgery, bilateral adrenalectomy, and pituitary radiation are also frequently employed.

In dogs, medical management is far more common than surgical approaches and generally involves the use of medications directed toward reducing adrenal glucocorticoid production. However, recent work on newer medical and surgical therapies as well as work on emerging treatments provides the clinician with multiple therapeutic options.

Medical treatments can be classified based on their mechanism of action and categorized as (1) adrenal-directed steroidogenesis inhibitors or adrenolytics, (2) centrally acting agents, and (3) glucocorticoid receptor blockers (Box 7.5).

Adrenal-Directed Therapies

In dogs, op-DDD (mitotane, Lysodren®; Bristol Pharmaceuticals), trilostane (Vetoryl®; Dechra Pharmaceuticals) and ketoconazole are the most commonly used agents although several other agents have been used or are under investigation. In cats, mitotane and trilostane are most commonly used.

Mitotane

Mitotane is derived from the insecticide DDT and is a potent adrenocorticolytic agent. The drug causes progressive necrosis of the zona fasciculata and zona reticularis of the adrenal gland and at higher doses may also cause necrosis of the zona glomerulosa. Other effects of mitotane include fatty degeneration, centrilobular

Box 7.5 Treatment of canine hyperadrenocorticism

Adrenal-directed therapy

Mitotane
Trilostane
Ketoconazole
Aminogluthemide
Metyrapone
Etomidate
LCI699*
Normocort*

Pituitary-directed therapy

Somatostain receptor agonists (octreotide, pasireotide)
D2 receptor agonists (cabergoline, bromocriptine)
Tyrosine kinase inhibitors (gefitinib)
Cyclin-dependent kinase inhibitors (roscovitine)*
PPAR-gamma agonists (rosiglitazone)*
Retinoic acid
Temozolamide*
mTor inhibitors (everolimus)*

Glucocorticoid receptor blockade

Mifepristone*

* = Currently no data in dogs with PDH.

atrophy, and congestion of the liver. Normal dogs and cats are clinically quite resistant to the effects of the drug.

Therapy with mitotane in both dogs and cats is begun at a dose of 50 mg/kg divided q12h. Glucocorticoids are not usually administered concurrently, but a small supply of prednisone should be made available to the owner for emergencies. Mitotane at induction doses is typically administered for 5–10 days, until water consumption decreases to <100 mL/kg/day. It should be discontinued immediately if decreased appetite, depression, diarrhea, or vomiting are observed. At this point, the pet should be reevaluated and an ACTH stimulation test performed. Prednisone treatment (0.2–0.5 mg/kg/day) should be initiated in patients showing clinical signs of hypocortisolemia, until the results of the ACTH stimulation test are known. In patients that are not polydipsic, patients in which water consumption cannot be monitored, and patients in which polydipsia is due to another underlying disease (e.g., diabetes mellitus), mitotane should be administered for a maximum of 5–7 days prior to ACTH stimulation testing.

The goal of treatment is to have both the pre- and postcortisol measurement in the normal resting range (2–6 µg/dL). Maintenance therapy (50 mg/kg q7–10 days) is started once the ACTH stimulation test shows adequate suppression (pre and post less than 5 µg/dL) and prednisone therapy (if necessary) has been discontinued. Failure to use maintenance therapy will result in regrowth of the adrenal cortex and recurrence of clinical signs. Efficacy of maintenance therapy is monitored by an ACTH stimulation test in one month and every 3–4 months thereafter. The dose of mitotane required for long-term maintenance is quite variable (26–330 mg/kg/week).

Reasons for treatment failure include incorrect diagnosis, the presence of an adrenal tumor (although some adrenal tumors will respond well), loss of drug potency due to poor storage or compounding of mitotane, or a need for a higher dose or duration of treatment in some dogs. Side-effects of mitotane include gastric irritation, hypoadrenocorticism, and very occasionally neurologic signs. Mean survival time of 200 dogs treated with mitotane was 2.2 years (range 10 days to 8.2 years).

Trilostane

Trilostane is a synthetic hormonally inactive steroid analog, which is a competitive inhibitor of the 3-beta-hydroxysteroid dehydrogenase system. The drug blocks synthesis of adrenal steroids, including cortisol and aldosterone. Trilostane is rapidly absorbed orally (peak concentrations within 1.5 hours), although suppression of plasma cortisol concentrations is short-lived (<20 hours). The medication should be administered with food (including the days when ACTH stimulation tests are scheduled to be performed) to aid in absorption.

Current recommendations for use of trilostane in dogs are to start at a dose of 1–2 mg/kg q12–24h and then increase or decrease the dose based on evaluation of ACTH stimulation tests performed 4–6 hours after drug administration. While there is no difference in whether the samples are drawn four or six hours post pill, it is important that the same sampling times are used in a given patient. The hormonal endpoints are postcortisol concentration of less than 6–9 µg/dL in conjunction with remission of clinical signs. Twice-a-day therapy at a starting dose of 1–3 mg/kg may result in good control of clinical signs at a lower total daily dose with less risk of adverse effects than higher doses q24h. In addition, BID dosing may be more effective in controlling hypercortisolemia more consistently throughout the day and may be appropriate as a starting dose in dogs with diabetes and other Cushing-related complications.

We have recently evaluated the safety and efficacy of trilostane therapy in 15 cats with PDH at starting doses of 1–2 mg/kg q12–24h. Clinical signs (13 of 15 cats) and ACTH stimulation testing results (13 of 15) improved with trilostane therapy. Diabetes mellitus was reported in 9/15 cases. Insulin requirements decreased by 36% within two months in 6/9 diabetic cats. Median survival

time was 617 days for all cats (range 80–1278 days). Complications included weight loss, urinary tract infections, chronic kidney disease, seizures, and recurrent pancreatitis. Hypocortisolemia was documented in one case. Cause of death occurred as a result of nonadrenal or nondiabetic illnesses (renal failure, seizures [caused by hypoglycemia or unknown]), or lymphoma. Trilostane ameliorates clinical signs of HAC in cats, is tolerated well in the long term, and can lead to improved regulation of diabetes. It should be considered as first-line therapy for cats undergoing medical management of PDH.

Adrenocorticotropic hormone stimulation testing should be performed 10, 30, and 90 days after start of treatment and 30 days after each dose adjustment. Trilostane is well tolerated in most dogs. Adverse effects that are usually mild and self-limiting include diarrhea, vomiting, and lethargy in up to 63% of treated dogs.

The ACTH stimulation test is the monitoring method for patients on trilostane therapy for which we have the most clinical experience and have reliably used for clinical decision making for a decade. However, the correlation of test results with the patient's clinical well-being has been questioned by multiple researchers. As with many endocrine tests, there is not one definitive methodology that can be applied to all patients.

The ACTH stimulation test remains the test of choice in any canine patient found to be clinically unwell by either the owner or the veterinarian. Oversuppression of cortisol production can occur with any medical therapy for hyperadrenocorticism and can develop insidiously or acutely.

Recently in Europe, the cost of cosyntropin has increased significantly. This, along with the multiple publications showing a lack of correlation between the ACTH stimulation test results and patients' clinical well-being, led a group of researchers to investigate the value of examining a single, unstimulated, cortisol result prior to the administration of trilostane.

Procedure/Protocol

1) Owners are instructed to bring their dog to the veterinary hospital prior to receiving the morning dose of trilostane.
2) The owners are then asked questions regarding control of clinical signs, with or without the use of a questionnaire. If any signs of cortisol oversuppression are noted, such as vomiting, anorexia, hyporexia, or lethargy, trilostane is not given, and a baseline cortisol and/or an ACTH stimulation test is performed to rule out hypoadrenocorticism.
3) A serum sample is collected for the measurement of cortisol.

Based on the above literature review, we offer the following recommendations for monitoring canine patients receiving trilostane therapy.

Unwell Dogs, Stressed Dogs, and Dogs With Concurrent Illness

- Perform an ACTH stimulation test.
- Perform an electrolyte panel and evaluate for signs of mineralocorticoid suppression.

Clinically Well and Controlled Dogs (Per Client Questionnaire and/or History)

- Pre-trilostane cortisol <1.4 µg/dL: decrease dose by 10% or perform an ACTH stimulation test.
- Pre-trilostane cortisol 1.4–5 µg/dL: continue current dose.
- Pre-trilostane cortisol >5 µg/dL: reevaluate history and consider splitting dose to twice daily (if currently once daily), or a small dose increase, based on clinical signs.

Clinically Undercontrolled Dogs

- Pre-trilostane cortisol <1.4 µg/dL: reevaluate history and diagnosis; perform an ACTH stimulation test; consult with a specialist.
- Pre-trilostane cortisol 1.4–5 µg/dL: this is currently a gray zone. Depending on the patient, consider splitting the dose to twice daily, if currently on once-daily dosing, or consider a dose increase if >3 µg/dL.
- Pre-trilostane cortisol >5 µg/dL: increase dose frequency (from once daily to twice daily) or dose.

Occasionally, dogs have developed hypoadrenocorticism, which is generally glucocorticoid deficient only, although dogs with evidence of mineralocorticoid deficiency have been reported. Hypoadrenocorticism induced by trilostane is generally reversible, although in rare cases this may take several months, likely because of adrenocortical necrosis. There have been anecdotal reports of acute death shortly after starting trilostane treatment.

Mitotane vs Trilostane

Studies have been performed comparing trilostane with mitotane in dogs with PDH or adrenal tumors. In a retrospective study of dogs treated with either mitotane (n = 25) or trilostane (n = 123), long-term survival was not statistically different between the groups. Median survival in the mitotane group was 708 days (range 33–1399), and in the trilostane group was 662 days (range 8–1971). Of the dogs that died in this study, 11% died due to causes that were attributed to the underlying PDH, and a further 17% died of causes that could have been related to their underlying PDH. In 38% of cases, the cause of death could not be directly attributed to PDH, and in 34% the cause of death was unknown.

Ketoconazole

While ketoconazole was used more frequently in the past, its use now is generally in countries where mitotane and trilostane are not available or when these agents have failed to correct hypercortisolism or resulted in adverse reactions. Its systemic use has recently been restricted or banned in several countries due to the potential of significant hepatoxocity in humans.

Specifically, ketoconazole has been shown to inhibit cholesterol side-chain cleavage enzyme, which converts cholesterol to pregnenolone, 17-alpha-hydroxylase and 17,20-lyase, which convert pregnenolone into androgens, and 11-beta-hydoxylase, which converts 11-deoxycortisol to cortisol.

A paper in 2008 examined the safety and efficacy of ketoconazole in 48 dogs with PDH. Data collected from each record included signalment, clinical signs, results of ACTH stimulation tests before and after treatment with ketoconazole (10 mg/kg PO BID), serum alkaline phosphatase (ALP) and alanine aminotransferase (ALT) activities, dosage of ketoconazole, clinical response, and survival time. Forty-three of 48 (90%) dogs had evidence of clinical improvement during the treatment period. In all dogs, treatment with ketoconazole resulted in significantly lower serum cortisol concentrations as measured before and after ACTH stimulation testing; 69% (33/48) of serum cortisol concentrations measured after ACTH stimulation were within the basal resting range. Serum ALP and ALT activities significantly decreased after treatment with ketoconazole.

Survival time after diagnosis of PDH ranged from 2 to 61 months (mean 26.9 months; median 25 months). Another study evaluating ketoconazole found that after diagnosis, 50% of the dogs died approximately 1.8–2 years (range 0.6–3) after starting therapy.

Several other adrenal steroidogenesis inhibitors have been used in man and at times in dogs.

Aminoglutethemide (Cytadren®; Novartis)

Aminoglutethemide blocks the conversion of cholesterol to pregnenolone by inhibiting the enzyme P450scc and consequently decreases synthesis of all hormonally active steroids. Its use in dogs has been limited. In one study, 10 dogs were diagnosed with PDH based on clinical and laboratory data, adrenal function tests, ACTH stimulation test and UCCR combined with a high-dose oral dexamethasone suppression test, and ultrasonographic evaluation of the adrenal glands. Aminoglutethimide was administered daily at a dose of 15 mg/kg body weight for one month. Median basal cortisol concentration and post-ACTH cortisol concentration one month after treatment were significantly lower than pretreatment values. Complete response was achieved in one dog, and partial response was obtained in three dogs. Severe side-effects of anorexia, vomiting, and weakness occurred in one dog and medication was withdrawn. Two further dogs developed progression of concurrent diseases and medication was stopped in these animals as well. Mild toxicity occurred in four dogs. Moderate to severe elevations in liver enzymes occurred in all dogs. The efficacy of this drug is lower than that observed using mitotane, trilostane and ketoconazole, and adverse effects limit its use.

Metyrapone (Metopirone®; Novartis)

Metyrapone is a pharmacologic agent used in the diagnosis of adrenal insufficiency and occasionally in the treatment of Cushing disease in humans. The primary inhibitory target is 11-beta-hydroxylase and to a lesser extent 17-alpha-, 18-, and 19-hydroxylase. The availability of metyrapone varies by country.

In dogs, it has been used in patients with Cushing syndrome in an attempt to distinguish PDH from a functional adrenal tumor. No reports exist on its use in treating Cushing syndrome in dogs.

Etomidate (Amidate®; Hospira)

Etomidate is a short-acting intravenous hypnotic nonbarbiturate anesthetic agent used for general anesthesia which suppresses steroidogenesis by dose-dependent inhibition of 11-beta-hydroxylase and desmolase. It plays a particular role in human cases with significant biochemical disturbance, sepsis and other serious complications such as severe psychosis, as well as in patients who have acute contraindications to surgery and cannot tolerate oral medications.

Its use in canine surgical patients has been reported revealing adrenal suppression for 2–6 hours following a single bolus injection of 1.5–3.0 mg/kg. Its use as a continuous-rate infusion (CRI) in the management of Cushing syndrome has not been reported.

LCI699 (Novartis)

LCI699 is a potent inhibitor of aldosterone synthase and 11-beta-hydroxylase. The mechanism of action of LCI699 is similar to that of metyrapone, but LCI699 is more potent and has a longer plasma half-life (approximately 4 vs 2 h), which allows for twice-daily dosing. LCI699 is currently under investigation in a Phase III prospective safety and efficacy study in human patients with Cushing disease. No information on its use in canine patients has been reported.

NormoCort (COR-003; Cortendo)

COR-003 is a single 2S, 4R enantiomer of ketoconazole in development as a possible new drug for the treatment of endogenous Cushing syndrome. This 2S, 4R enantiomer of ketoconazole is expected to be a more potent inhibitor of key enzymes in the cortisol synthesis

pathway, and also a less potent inhibitor of a metabolic enzyme, cholesterol 7-alpha-hydroxylase (Cyp7a), than its counterpart. COR-003 is presently in Phase III studies in humans though no information is available regarding its use in dogs.

Pituitary-Directed Therapy

Recent work on somatostatin and dopaminergic receptor changes in humans and dogs with Cushing disease has opened the door to targeted therapy of pituitary tumors. Such therapies result not only in decreased ACTH production but also a reduction in tumor size. Several agents have been studied or are in clinical trials.

Pasireotide (SOM230; Signifor®; Novartis)

Pasireotide is a somatostatin receptor (SSR) ligand with high binding affinity for multiple receptor isoforms (SST1-3 and SST5). SST5 and SST2 are highly expressed in ACTH pituitary adenomas, and animal studies documented that SSR mediates inhibition of cAMP and regulation of ACTH secretion. While SST5 is most commonly overexpressed in humans, SST2 appears to be most common in dogs. Pasireotide has recently been approved for use in humans for the treatment of adult patients with Cushing disease for whom pituitary surgery is not an option or has not been curative.

SOM230 was tested in dogs suffering from Cushing disease (10 animals were treated continuously during six months, and another 10 were treated with three cycles consisting of two months of treatment followed by a two-month rest period). The dose was 0.03 mg/kg SOM230, SC q12h. Clinical and biochemical variables were evaluated at different times: before treatment and at three and six months of treatment. MRI studies at three and six months were performed. A significant decrease in ACTH, urinary cortisol creatinine ratio, adenoma size (magnetic nuclear resonance), and improvement of clinical signs were obtained, without side-effects. In this study, tumor size did not decrease in patients whose tumors were >7 mm, but there was no increase either, and there were variations in the paramagnetic signal intensities, becoming isointense. AtT20 cells treated with SOM230 suppressed proopiomelanocortin (POMC) promoter activity through SSTR2, via the G_i alpha-subunit, and reduced Nur77/Nurr1 transcriptional activity. It was concluded that SOM230, in addition to its well-described antisecretory effects, inhibits, as shown in AtT20 cells, ACTH synthesis at the POMC transcriptional level, an effect mediated mainly through SSTR2, and limits tumor growth. The controlled Cushing disease in the dogs that received the treatment indicates that SOM230 has a potential therapeutic use in dogs suffering from Cushing disease.

We recently evaluated nine client-owned dogs with PDH and macroadenoma in which PDH had been successfully managed with adrenal-directed treatment (trilostane or mitotane). Dogs were given pasireotide (0.03 mg/kg [0.014 mg/lb], SC, q12h) for six months, while adrenal-directed treatment was continued. Physical examination, basic clinicopathologic testing, ACTH stimulation testing, and plasma ACTH concentration measurement were performed before (baseline) and three and six months after treatment began. Measurements of pituitary gland volume and pituitary gland-to-brain ratio were performed via MRI at baseline and six months after treatment began. No dog developed neurologic abnormalities or signs of adverse effects during the study period. No differences from baseline were identified in clinicopathologic values, ACTH stimulation test results, or plasma ACTH concentration at the three- or six-month assessment points. After six months of pasireotide treatment, six dogs had decreases in MRI-measured values, and three had increases. Pasireotide as administered in this study had no noted adverse effects on dogs with PDH and macroadenoma successfully managed with standard treatment. Placebo-controlled, randomized studies are needed to determine whether pasireotide protects from the development of neurologic signs or improves outcome in dogs with pituitary macroadenomas.

As mentioned, while dogs seem to overexpress the SST2 receptor, a recent paper showed no decrease in cortisol concentrations in dogs treated with octreotide, a selective SST2 receptor antagonist.

Cabergoline (Dostinex®; Pfizer)

Cabergoline is a dopamine D2 receptor agonist with a higher affinity and a longer half-life than bromocriptine. In humans, its effectiveness and tolerance in the treatment of prolactinomas and growth-hormone secreting adenomas have been demonstrated. Pivonello described reduction in size of the aggressive corticotroph adenoma, which causes Nelson syndrome, while the antineoplastic effects of cabergoline have been reported in the treatment of nonfunctional tumors of corticotroph cells.

A study with follow-up for over four years was conducted in 40 dogs with PDH that were treated with cabergoline (0.07 mg/kg/week). Out of the 40 dogs, 17 responded to cabergoline (42.5%). A year after the treatment, there was a significant decrease in ACTH (P <0.0001), alpha-MSH (P <0.01), UCCR (P <0.001), and tumor size (P <0.0001) evaluated by nuclear magnetic resonance. Dogs responding to cabergoline lived significantly longer (P <0.001) than those in the control group (ketoconazole). Cabergoline may be useful in 42.5% of dogs with PDH, justifying its use as a treatment especially if a pars intermedia tumor is documented or suspected based on hormonal (elevated MSH) and imaging data.

Selegilene (L-deprenyl)

The monoamine oxidase B inhibitor L-deprenyl, which serves to raise concentrations of dopamine in the brain, has been used to treat hyperadrenocorticism in dogs. The medication appears effective in some patients (20–30%) with pars intermedia disease with few side-effects. Today, the medication is generally used in PDH patients where the cost of monitoring ACTH stimulation tests and electrolytes would prohibit treatment with adrenal enzyme blockers or adrenolytics.

Retinoic Acid

Retinoic acid is an agent that has been shown to inhibit proliferation, invasion, and tumor growth *in vivo* and induces differentiation and apoptosis in different cell types. Some of these effects are mediated by a reduction in binding of the transcription factors AP-1 and Nur77 to their cognate DNA sites; these factors are also essential in the control of the POMC gene, which gives rise to the precursor to ACTH and alpha-MSH. Recently, it was shown that retinoic acid inhibits ACTH secretion both *in vitro* and *in vivo* through an action on POMC gene transcription and also inhibits corticotrophinoma development and proliferation.

A randomized study comparing treatment with 2 mg/kg/day of 9-cis retinoic acid (n = 22) vs 20 mg/kg/day of ketoconazole (n = 20) in dogs with Cushing disease was recently performed. Clinical signs, plasma ACTH and alpha-MSH, UCCR, and pituitary MRI were assessed and compared at different time points for six months. A significant reduction in plasma ACTH, alpha-MSH, and UCCR was seen in the dogs treated with retinoic acid. Pituitary adenoma size was also significantly reduced at the end of treatment. Survival time and all the clinical signs evaluated showed an improvement in the retinoic acid-treated dogs. No adverse events or signs of hepatotoxicity were observed, suggesting that the drug is not only effective but also safe. Retinoic acid treatment controls ACTH and cortisol oversecretion as well as tumor size in dogs with ACTH-secreting tumors, leading to resolution of the clinical signs. This study highlights the possibility of using retinoic acid as a novel therapy in the treatment of ACTH-secreting tumors in humans with Cushing disease.

EGFR Receptor Antagonists

We recently demonstrated that in surgically resected human and canine corticotroph cultured tumors, blocking EGFR suppressed expression of POMC, the ACTH precursor. In mouse corticotroph EGFR transfectants, ACTH secretion was enhanced and EGF increased POMC promoter activity, an effect that was dependent on mitogen-activated protein kinase (MAPK). Blocking EGFR activity with gefitinib, an EGFR tyrosine kinase inhibitor, attenuated POMC expression, inhibited corticotroph tumor cell proliferation, and induced apoptosis. As predominantly nuclear EGFR expression was observed in canine and human corticotroph tumors, we preferentially targeted EGFR to mouse corticotroph cell nuclei, which resulted in higher POMC expression and ACTH secretion, both of which were inhibited by gefitinib.In athymic nude mice, EGFR overexpression enhanced the growth of explanted ACTH-secreting tumors and further elevated serum corticosterone levels. Gefitinib treatment decreased both tumor size and corticosterone levels; it also reversed signs of hypercortisolemia, including elevated glucose levels and excess omental fat. These results indicate that inhibiting EGFR signaling may be a novel strategy for treating Cushing disease and studies in dogs and humans are under way.

Pituitary Surgery

Several groups have described successful use of transsphenoidal hypophysectomy (TSH) as a method of treating PDH in dogs. Recently, we described a technique for transsphenoidal removal of pituitary adenomas in 26 dogs with PDH using a high-definition video telescope. Pituitary tumors were removed using a modification of a transoral transsphenoidal approach. Surgery was observed using a high-definition video telescope (VITOMTM) and localization of the sella was performed by drilling pilot holes in the basisphenoid bone followed by CT. There were no postoperative cerebrospinal fluid leaks, wound dehiscence, or surgical site infections. Overall postoperative mortality was 19%, with no mortality observed in the last 16 dogs, indicating an initial learning curve. Follow-up times ranged from three to 36 months. Sustained tumor control and hormonal remission based on normalized ACTH and UCCR measurements were observed in 20/21 (95%) of dogs at one-year follow-up.

Surgical experience and tumor size are likely important variables in dogs undergoing TSH. The survival rates at one, two, three, and four years in the study by Hanson *et al*. evaluating 181 patients were 86%, 83%, 80%, and 79%, respectively. Disease-free intervals (DFI) were 90%, 77%, 72%, and 68%, respectively.

In our study, one-year survival was 81% (all five deaths occurring within the first five days) with 100% of the surviving dogs in remission at three months and 95% (20/21) in remission at one year. To date, seven dogs have survived >2 years and one dog >3 years.

Another important variable is tumor size. All the dogs in our study had tumors with P/B ratios >0.32 and a median P/B ratio of 0.73. Both the tumor size and extent of removal were typical for this series. Median tumor volume was 820 mm^3, which is nine times larger than the median volume of 89 mm^3 reported by Hanson *et al*. In

that series of 181 dogs with PDH, mean tumor height was 6 mm, mean width 6.2 mm, and mean height 5.4 mm with a median P/B ratio of 0.3.

Forty-three percent of the dogs had a normal P/B ratio. Interestingly, Hanson *et al*. concluded that pituitary size (height) was the most significant predictor of postoperative survival and mortality. In those studies, initial remission of PDH occurred in 85% of dogs with relapse in 28% by three years.

Similarly, Hara *et al*. evaluated outcomes in 25 dogs that had TSH using the protocol of Meij *et al*. Median P/B ratio was 0.38 (range 0.24–0.71) with 24% of dogs having a normal P/B ratio. Initial remission was attained in 84% with 12% of dogs having relapse within four years. Survival at one, two, three, and four years was 92%, 81%, 81%, and 81%. No data on DFI were reported.

Continued experience with surgery for pituitary tumors in both dogs and cats will be important not only in improving survival and DFI, but it will also allow for the continued collections of tumor tissue allowing for additional studies regarding pathogenesis and novel therapies for both man and pets.

Prognosis

With medical treatment, survival time after diagnosis of PDH ranges from two to 61 months (mean 26.9 months; median,25 months). Another study evaluating ketoconazole found that after diagnosis, 50% of the dogs died approximately 1.8–2 years (range 0.6–3) after starting therapy. A recent study evaluated survival times in dogs left untreated for PDH. Median survival time for the trilostane group was not reached (95% confidence interval 443 days–not applicable) and was significantly longer than the 506 days (95% confidence interval 292–564 days; $P = 0.016$) for the untreated group.

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8

Polyuria and Polydipsia

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Physiology of Water Metabolism

Maintenance of water balance is very tightly regulated between the hypothalamus, pituitary gland, and kidneys. The main hormone involved in this system is arginine vasopressin (AVP) or antidiuretic hormone. AVP is produced in the hypothalamus and stored in the posterior pituitary. The primary stimulus for AVP release is an increase in plasma osmolality sensed by osmoreceptors in the hypothalamus or a decrease in extracellular fluid volume sensed by baroreceptors in the aortic sinus, left atrium, and carotid sinuses. Other factors known to stimulate AVP release include alterations in blood pressure, hypoglycemia, angiotensin II, fever, stress, nausea, pain, exercise, and various drugs, hormones, and metabolic disturbances. *Osmolarity* is the concentration of a solutionin termsof osmoles of solutes per liter of solution. Inveterinary medicine, *osmolarity* is used to estimate the osmolality or tonicityof the extracellular fluid (ECF) space.

Once released into the circulation, AVP binds to receptors on the basolateral surface of cells in the renal distal convoluted tubules and collecting ducts. This initiates insertion of aqueous (aquaporin) channels into the luminal membrane of these cells. The hypertonicity of the renal medulla can then draw free water from the urine filtrate into the distal portion of the nephron, resulting in concentrated urine. Production of concentrated or dilute urine depends on functional kidneys; once greater than two-thirds of nephrons have been lost, the patient will be unable to produce concentrated urine despite the effects of AVP. Decreased concentrating ability may be noted before azotemia is evident on routine laboratory tests.

Etiology/Pathophysiology

Polydipsia is defined as a fluid intake >90–100 mL/kg/day in dogs and >45 mL/kg/day in cats. Patients may be categorized as having primary polydipsia with secondary polyuria or primary polyuria with compensatory polydipsia.

Primary polydipsia may arise from psychogenic causes (such as behavioral or environmental issues), liver disease, neurologic disease, fever, and pain. These patients will often have hyposthenuric urine (1.001–1.005) and have low levels of AVP secondary to excessive thirst and decreased osmolality (285–295 mOsm/kg).

Causes of primary polyuria can be divided into those which result in an osmotic diuresis versus manifestations of diabetes insipidus (DI) in which there is AVP insufficiency or insensitivity.

Osmotic diuresis occurs when an osmotically active solute (e.g., glucose or urea) is present in the glomerular filtrate at a high concentration. This creates a gradient, which impedes passive reabsorption of water in the distal tubules and results in increased water loss. Illnesses such as diabetes mellitus (DM), chronic renal failure, primary renal glycosuria, and postobstructive diuresis can cause polyuria with secondary polydipsia as a result of osmotic diuresis.

Diabetes insipidus can be further categorized as central or nephrogenic. Central DI (CDI) is the less common variant of this disorder and results from a complete or partial deficiency in AVP production. Trauma, infection, congenital anomalies, neoplasia, or idiopathic processes can cause CDI.

Nephrogenic DI (NDI) refers to problems at the level of the kidney, which prevent the patient from being able to concentrate urine appropriately in response to changes in serum osmolality. These patients are insensitive to the antidiuretic effects of AVP and excrete higher than normal amounts of urine (Box 8.1).

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Box 8.1 Diseases associated with secondary nephrogenic diabetes insipidus

Renal failure	Hyperadrenocorticism
Hyperglycemia	Hypoadrenocorticism
Hypercalcemia	Hypokalemia
Pyelonephritis	Hepatic disease
Pyometra	Hyperthyroidism (cats)
Leptospirosis (dogs)	Polycythemia
Acromegaly	Neoplasia
Renal medullary solute washout	Drugs (i.e., anticonvulsants, glucocorticoids, diuretics)

Nephrogenic DI can be further classified as primary and secondary. The primary form of NDI is due to an extremely rare congenital structural or functional defect of the kidneys. Secondary NDI is the most common cause of polyuria and polydipsia in veterinary medicine and is due to nonrenal causes, which interfere with the kidneys' ability to respond to AVP.

Signalment

Polyuria and polydipsia (PU/PD) can occur in any breed of dog or cat and at any age. However, certain diseases are associated with specific age groups and breeds. For example, primary polydipsia would be a consideration for a young dog whereas hyperadrenocorticism may be suspected in a middle-aged patient. Reproductive status should also be considered as conditions such as pyometra can result in these clinical signs. In addition, diseases such as Fanconi syndrome have been described in basenjis and Norwegian elkhounds.

History and Clinical Signs

A thorough history is critical when evaluating a patient with polyuria and polydipsia. A recent history of trauma, drug administration, (including topical medications), or environmental change will help narrow the list of differentials. Loss of appetite and lethargy may raise the possibility of liver or renal disease whereas polyphagia may increase the index of suspicion for hyperthyroidism in cats or hyperadrenocorticism in dogs. Diet should be discussed as well as salt content may affect water intake.

Diagnosis

First-Tier Diagnostic Tests

Physical examination findings in patients with PU/PD may be unremarkable or nonspecific. Special attention should be paid to body condition, muscle mass, hydration status, and recent changes in weight. Organomegaly and/or lymphadenopathy may raise suspicion of a neoplastic process. In cats, palpation for thyroid nodules may be useful in evaluating for possible hyperthyroidism. Females should be examined for evidence of vulvar discharge. Pyelonephritis should be suspected in patients with flank or abdominal pain.

Before embarking on a diagnostic work-up for the cause of PU/PD, it is often useful to make sure the problem truly exists. This can be done through a combination of history and evaluation of the urine specific gravity to document isosthenuria or hyposthenuria.

It may also sometimes be useful to ask the owners to quantify water intake at home (remember to discuss access to other sources of water such as ponds, pools, toilets, etc.). Water consumption may vary from day to day so assessing water intake over several days may be necessary. Polydipsia is documented in a patient with a water intake in excess of 100 mL/kg/day for dogs and 45 mL/kg/day in cats.

The urine should also be evaluated for other diagnostic clues.

- *Urine specific gravity (USG)*: Patients with normal renal function who are truly polydipsic should have a USG <1.030 in dogs and <1.035 in cats. If the USG is consistently >1.035, other problems such as incontinence or dysuria should be considered.
- *Glycosuria*: The presence of glucose may be suggestive of diabetes mellitus or, in some cases, primary renal glycosuria.
- *Proteinuria*: In conjunction with a low USG, proteinuria may be seen in patients with hyperadrenocorticism, pyelonephritis, lower urinary tract infection, or glomerulonephritis. A urine culture and/or urine protein:creatinine ratio may be warranted.

Initial diagnostics should also include a complete blood count (CBC), chemistry profile with electrolytes, and a total thyroxine level in middle-aged to older cats. A urine culture should be performed even in the face of an inactive sediment. Patients with underlying diseases such as hyperadrenocorticism or diabetes may be unable to mount an appropriate immune response so pyuria may not be noted. In addition, dilute urine can make it difficult to identify bacteriuria.

These initial tests often provide some direction as to the underlying cause (e.g., presence of azotemia or an elevation in liver values). In dogs, leptospirosis should be considered as a cause of PU/PD in endemic areas even in the absence of liver or renal abnormalities although the exact mechanism for why this occurs is not clearly understood.

The serum sodium concentration may also provide some insight into whether the patient has primary

polydipsia with secondary polyuria or polyuria with compensatory polydipsia.

- Primary polyuria (results in excess loss of free water) > elevated Na concentration > osmoreceptors sense increase in osmolality > trigger thirst response > compensatory polydipsia
- Primary polydipsia (results in excess intake of free water) > decreased Na levels > osmoreceptors sense decrease in osmolality > decrease AVP release > compensatory polyuria

It is important to note, however, that patients with hypoadrenocorticism will have a low sodium level due to mineralocorticoid deficiency despite primary polyuria.

Plasma osmolality can also be used to determine if a patient has primary polydipsia. In clinical practice, this can be estimated by calculating serum osmolality using the following formula:

$$2 \times [Na] + [BUN \text{ in } mg/dL]/2.8 + [Glu \text{ in } mg/dL]/18$$

Low osmolality is suggestive of primary polydipsia and further evaluation for hepatic disease or hyperthyroidism are indicated.

Second-Tier Diagnostic Tests

Further diagnostics will depend on physical and laboratory examination findings. For example, an abdominal ultrasound should be considered for patients with flank/abdominal pain in whom pyelonephritis is suspected. For patients in whom adrenal disease is suspected, an adrenocorticotrophic hormone (ACTH) stimulation test should be considered. It is important to remember that approximately 15% of dogs with pituitary dependent and 40% of dogs with adrenal-dependent hyperadrenocorticism can have a normal ACTH stimulation test. If hyperadrenocorticism is strongly suspected and the dog is otherwise healthy, a low-dose dexamethasone suppression test is a better option.

Other tests that may be considered, depending on laboratory findings, clinical signs, and signalment, include pre- and postprandial bile acids and imaging studies of the chest and abdomen. Imaging will be particularly useful for patients suspected of a neoplastic process and in any patient with hypercalcemia. Abdominal ultrasonography may be useful in looking for masses, enlarged abdominal lymph nodes, or adrenal enlargement.

Modified Water Deprivation Test (WDT) or DDAVP trial

A modified WDT should only be considered for patients in whom more common causes of PU/PD have been ruled out and central DI, primary NDI, or psychogenic polydipsia is strongly suspected. Fortunately, very few cases of PU/PD require performing this test.

In addition to being time-consuming and difficult to perform, for patients with underlying undiagnosed illness, this test is contraindicated and may increase the risk for complications, including death. This test should never be performed in patients who are azotemic or dehydrated. In addition, diseases such as hyperadrenocorticism may show some positive response, thereby complicating the diagnosis or resulting in misdiagnosis.

Steps for Conducting the Modified WDT

Phase 1

Patients that have had PU/PD for a prolonged period of time may have wash-out of their renal medullary concentration gradient and therefore, may be unable to concentrate their urine in the face of water deprivation. For this reason, it is recommended that once the pet's water intake has been quantified, the total amount of water given should be gradually restricted over 3–5 days until the goal of 60–80 mL/kg/day is reached. To avoid prolonged periods of water restriction, the total daily water should be calculated and provided in frequent small portions. A dry food diet should be fed during this phase. This testing will require that the owners pay very close attention to the pet for any signs of illness. Patients with severe polyuria are at increased risk for hypertonic dehydration and hospitalization during this phase of the WDT should be considered. A USG should be measured at the conclusion of this phase in case the patient has already reached a USG >1.030 (supportive of a diagnosis of psychogenic polydipsia) and the WDT is no longer required.

Phase 2

- The patient should be admitted to the hospital for a complete physical examination and assessment of hydration and mentation status.
- An indwelling urinary catheter is placed. The bladder should be emptied completely, and the USG measured.
- A blood urea nitrogen (BUN), creatinine, packed cell volume (PCV), total solids (TS), and electrolytes should be measured.
- Obtain patient's body weight.
- Patient should not have access to food or water.
- Patient should have the following performed every 1–2 hours.
  - Physical examination to assess hydration and mentation
  - Completely empty bladder and check USG
  - Obtain weight
- Every 4–6 hours check BUN, creatinine, PCV, TS, and electrolytes.
- The test should be stopped when *any* of the following occur:

Table 8.1 Currently available DDAVP preparations and common dosages

Preparation	Strength	Dose
Intranasal	100 µg/mL (1 drop = 1.5–4.0 µg desmopressin)	1–2 drops in conjunctival sac one to two times daily Or 2 µg SC one to two times daily (can be administered SC if sterilized through a bacteriostatic filter)
Injectable	4 µg/mL	2 µg SC one to two times daily
Oral	0.1–0.2 mg tablets (each 0.1 mg = approximately 4 µg desmopressin)	0.05–0.2 mg PO twice daily Bioavailability of the oral preparation may be a concern

PO, orally (*per os*); SC, subcutaneously.

- The patient loses 5% of body weight. Maximal stimulation of AVP release occurs at this point but the time required to reach dehydration may be a few hours or up to 12 hours in some patients.
- There is evidence of clinical dehydration or any vomiting, lethargy, or altered mentation is noted.
- Any evidence of azotemia.
- The USG is >1.030.

Phase 3

- If the patient is 5% dehydrated and has not produced an adequately concentrated urine, desmopressin acetate (DDAVP, a synthetic AVP analog) should be administered (see Table 8.1 for a list of desmopressin formulations).
  - Assess mentation and measure weight, BUN, creatinine, PCV, TS, electrolytes.
  - Bladder should be emptied.
  - Administer injectable DDAVP (2-10 µg IV). Alternatively, an intranasal DDAVP formulation may be administered into the conjunctival sac (1–4 drops/dog).
- Empty the bladder in 30 minutes and measure USG. Repeat every 30 minutes for up to two hours until USG >1.015. Bladder should be emptied at each time point. If USG is still below 1.015, empty bladder and measure USG every hour for up to 8 hours. At the conclusion of the test, water can be reintroduced slowly (10-20 mL/kg every 30 minutes for 2 hours).

Interpretation

If the patient achieved an adequate urine concentration during phase 1 of the test, then a diagnosis of primary (psychogenic) polydipsia can be made. AVP secretion and responsiveness are intact.

If concentrated urine was not noted at the end of phase 1, then the patient has primary polyuria – either CDI or primary NDI (causes of secondary NDI should have been ruled out prior to the WDT). Administration of DDAVP differentiates between these two possibilities.

A patient with CDI will achieve an increase in USG (>1.015) after DDAVP administration whereas a patient with NDI will show little to no response. Again, patients with secondary causes of NDI (i.e., hyperadrenocorticism) may also fail to show an elevation in USG after DDAVP administration, which is why it is imperative that secondary causes be ruled out prior to the WDT.

Interpretation may also be complicated in cases of patients with concurrent primary polydipsia and CDI or NDI.

DDAVP Response Test

In cases where more common causes of PU/PD have been ruled out and where there is a high index of suspicion for CDI, a DDAVP response test may be conducted in lieu of a WDT. This can be conducted at home as the owner continues to monitor water intake.

- Measure USG on day 1 and administer DDAVP intranasal preparation (1–4 drops) into the conjunctival sac twice daily for 5–7 days. Alternatively, the owner may administer oral DDAVP (tablet) at a dose of 0.1–0.2 mg every 8 hours for 5–7 days.
- After 5–7 days, the USG is measured again.

Animals with CDI should demonstrate an increase in the USG as well as a decrease in water intake. An animal with NDI or PP will show no response.

Patients with primary polydipsia may continue to drink excessively despite the DDAVP and there is a risk of water intoxication in these patients, which is why appropriate patient selection and owner vigilance are imperative.

Therapy

Treatment will need to address the underlying disorder. For patients with CDI, DDAVP will need to be administered daily. DDAVP can be administered topically in the conjunctival sac or a subcutaneous injection. An oral preparation is also available but may be more costly and has been shown to be less effective than parenteral administration in some patients. See Table 8.1 for recommended dosing schedules.

Regardless of the route of administration, the DDAVP dose should be titrated up gradually as needed to control the PU/PD as the effects last 8–24 hours.

For patients with primary psychogenic polydipsia, gradual water restriction and behavioral modification therapy may be warranted. Consultation with or referral to a behaviorist may be considered.

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9

Canine Hypothyroidism

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Etiology/Pathophysiology and Epidemiology

Canine hypothyroidism, while a common endocrinopathy in the dog, may be overdiagnosed due to confusion/inconsistencies in establishing a definitive diagnosis. Hypothyroidism is due to decreased thyroidal production of the thyroid hormones thyroxine (T4) and triiodothyronine (T3). Greater than 90% of cases are primary and are due to acquired immune-mediated destruction of the thyroid gland which is preceded by thyroiditis, idiopathic atrophy or, less commonly, neoplasia. Secondary forms of the disease include thyroid-stimulating hormone (TSH) deficiency, pituitary neoplasia, and cystic Rathke's pouch. Tertiary hypothyroidism with thyrotropin-releasing hormone (TRH) deficiency has not been documented in dogs. Congenital cases have been reported in both dogs and cats.

Hypothyroidism most commonly occurs in young to middle-aged dogs with an average age of 7 years. Dogs with autoimmune disease tend to develop hypothyroidism at a younger age. While thyroid values decrease within the reference range in senior dogs, hypothyroidism is very uncommon and other factors (see later) are likely responsible for the observed decreased thyroid concentrations in euthyroid older patients. Spayed females and neutered males are at increased risk when compared to sexually intact animals. Breed predispositions have been reported for golden retrievers and Doberman pinschers. Thyroiditis is heritable in the beagle, borzoi, golden retriever, Great Dane, Irish setter, Doberman pinscher, and old English sheepdogs. No known environmental factors have been identified.

History and Clinical Signs

As thyroid hormone regulates the metabolic rate and influences the functions of many organs, clinical signs are often nonspecific and insidious in onset. Many other diseases can have similar clinical signs to hypothyroidism, which may lead to an incorrect diagnosis. As such, laboratory testing of thyroid function is often performed as part of the diagnostic work-up in animals with nonthyroidal illness.

Common clinical signs include lethargy, mental dullness, weight gain, exercise intolerance, alopecia, and obesity. Many metabolic, infectious, neoplastic, congenital, degenerative, and inflammatory diseases can cause similar clinical signs and biochemical abnormalities seen with hypothyroidism.

Diagnosis

Laboratory Diagnosis

Thyroxine is the major secretory product of the thyroid while the majority of T3 is derived from extrathyroidal sources. Both T4 and T3 are highly protein bound to serum carrier proteins such as thyroid-binding globulin, transthyretin, and albumin. Only unbound (free) hormone is able to penetrate cell membranes, bind to receptors, and result in biologic activity. Protein-bound hormone acts as a reservoir to maintain steady concentrations of free hormone in the plasma despite rapid alterations in release and metabolism of T3 and T4 and changes in the plasma protein concentrations.

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Serum Total T4

Serum T4 is a sensitive (>90–95%) but not specific test (70–75%) for the diagnosis of canine hypothyroidism. The vast majority of dogs with hypothyroidism have a serum T4 below normal, but some normal dogs and those with a variety of other problems may have a low serum T4. A diagnosis of hypothyroidism can be ruled out if the T4 is in the upper 50% of the reference range. Autoantibodies to T4 occur in about 15% of hypothyroid dogs, and these antibodies may falsely increase the serum T4 concentration from below normal into or above the normal range. In-house testing of total T4 is not recommended.

Serum Total T3

Serum T3 concentration is an unreliable test for evaluation of thyroid function.

Serum Free T4 (fT4)

Thyroxine is highly (99.9%) protein bound in the circulation. Protein binding can be altered by many nonthyroidal illnesses and by certain drugs. Measurement of the unbound or free hormone can provide a more accurate assessment of thyroid function in these cases (sensitivity >95%, specificity >97%). The sensitivity of fT4 is equivalent to or slightly better than total T4 in diagnosing hypothyroidism in routine cases. More importantly, fT4 is more specific, particularly when nonthyroidal factors that can influence total T4 are present. Free T4 is less affected by most nonthyroidal illness and drugs, but still can be altered in cases of moderate to severe illness. In addition, fT4 by equilibrium dialysis is not affected by the presence of T4 autoantibodies that will falsely elevate total T4. Measurement of fT4 by equilibrium dialysis should be performed when uncommon clinical signs of hypothyroidism are present, the dog is being treated with a drug that may affect thyroid function, when nonthyroidal illness is present, and if autoantibodies to T4 are detected.

Serum TSH

Primary hypothyroidism results in a decrease in T4 and thus decreased negative feedback on the pituitary gland. In response, the pituitary secretes more TSH and plasma TSH levels increase. In humans, TSH is elevated prior to any decrease of T4 or fT4 outside the normal range. In the dog, TSH concentration is elevated in only 65–75% of cases of hypothyroidism, and thus it lacks sensitivity for use as a screening test. The combination of decreased total T4 or fT4 with an elevated serum TSH is diagnostic of hypothyroidism (specificity >95%). Therefore, a normal TSH does not rule out hypothyroidism, but an elevated TSH combined with a low T4 or fT4 provides a definitive diagnosis.

Diagnosis of Thyroiditis

Antibodies against either T4 or T3 or both are sometimes present in dogs with thyroiditis with or without hypothyroidism. The presence of these antibodies does not indicate that the dog is hypothyroid, but suggests that autoimmune thyroid disease is present. These antibodies frequently cause false elevation of T4 or T3 concentrations that can result in marked elevation of the hormones. Autoantibodies to T4 are present in about 10–15% of hypothyroid dogs.

Dogs with autoimmune thyroiditis may have circulating antibodies to thyroglobulin, the primary protein in the colloid of the thyroid gland. This is not a test of thyroid function but rather a marker for the presence of autoimmune thyroiditis. In one long-term study at Michigan State University, 20% of asymptomatic, antithyroglobulin-positive dogs with normal thyroid function progressed to hypothyroidism in one year. The presence of these antibodies in a dog with borderline laboratory evidence of hypothyroidism and clinical signs supports a diagnosis of hypothyroidism.

Additional Considerations

Breeds

Certain breeds have normal ranges of thyroid hormones that are different from most other breeds. Few have been evaluated but greyhounds have serum total T4 and fT4 concentrations that are considerably lower than most other breeds. Scottish deerhounds, salukis, and whippets also have total T4 concentrations that are well below the mean concentration of dogs in general. Alaskan sled dogs have serum T4, T3, and fT4 concentrations below the reference range of most pet dogs, particularly during periods of intense training or racing.

Time of Day

In one study 50% of normal dogs had a low serum T4 concentration at some time during the day.

Medications

The drugs that are known to commonly alter thyroid function tests are glucocorticoids, phenobarbital, sulfonamides, clomipramine, aspirin, and some other NSAIDs. Glucocorticoids suppress total T4 and sometimes fT4 as well. Phenobarbital causes decreased total T4 and mild increases in TSH. Sulfonamides can induce

overt primary hypothyroidism with clinical signs and thyroid function tests that support the diagnosis. The changes may be reversible when the medication is discontinued. There are dozens of drugs that affect thyroid function and thyroid function tests in humans, so many others likely affect the dog as well.

Nonthyroidal Illness

Illness not involving the thyroid gland can alter thyroid function tests and has been labeled "nonthyroidal illness" or "euthyroid sick syndrome." Any illness can alter thyroid function tests, causing a fairly consistent decrease in total T4 and T3 concentrations in proportion to the severity of illness. Serum TSH concentration is increased in 8–10% of dogs with nonthyroidal illness. Serum fT4 measured by equilibrium dialysis is less likely to be affected, but can also be increased or decreased. However, in dogs with substantial nonthyroidal illness, the fT4 is likely to be decreased. It is recommended that testing of thyroid function be postponed until the nonthyroidal illness is resolved. If this is not possible, measurement of T4, TSH, and fT4 is indicated.

Ancillary Testing

Thyroid Gland Ultrasound

Although rarely necessary, ultrasound of the thyroid glands (by an experienced ultrasonographer) can aid in differentiating dogs with primary hypothyroidism from those with nonthyroidal illness. Thyroid glands of hypothyroid dogs tend to be smaller, less homogeneous, and hypoechoic than those of euthyroid dogs. There is considerable overlap with the ultrasonographic appearance and size of the thyroid glands of euthyroid and hypothyroid dogs. Thyroid ultrasound can only be used to help support a diagnosis of hypothyroidism if the thyroid glands are quite small.

Treatment

Levothyroxine is the only hormone that appears necessary for treatment of hypothyroidism. The frequency of levothyroxine dosing is controversial, and the only study to closely evaluate the response to treatment showed that once-daily treatment is adequate. However, in clinical practice some dogs seem to respond better to twice-daily treatment.

The initial starting dose is 0.02 mg/kg PO q24h. In general, you will never have to exceed 0.8 mg as an initial daily dosage even in very large dogs. If the dog has significant cardiovascular disease, diabetes mellitus, or hypoadrenocorticism, treatment should be instituted at 25% of the standard dose, with the dosage increased by 25% every two weeks based on clinical response and postpill testing. Most dogs show improvement within the first 1–2 weeks, with increased activity, improved attitude, and partial or complete resolution of neurologic signs. The cutaneous manifestations of hypothyroidism may take several weeks to months to resolve.

Posttreatment monitoring may be carried out but clinical response is the most important monitoring tool. Peak T4 concentrations generally occur 4–6 hours after administration of levothyroxine and should be in the high normal to slightly above normal range (40–70 nmol/L). However, the bioavailability of thyroxine ranges from 13% to 87% in the same dog from day to day, bringing into the question the utility of random postpill monitoring of TT4. It is likely more meaningful (though more expensive) to measure TSH (especially if the TSH concentration was elevated pretreatment) or fT4 concentrations after replacement therapy has been started, especially in animals that show a poor clinical response to therapy. Serum TSH concentrations should be in the normal range or undetectable and fT4 concentrations should be in the normal range. Serum concentrations of TSH and fT4 should not be performed until the patient has been on supplementation for at least two weeks. If the patient was initially started on twice-daily therapy, treatment can be reduced to once-daily treatment when a good clinical response has been obtained.

Hyperthyroidism is the most common complication of treatment with levothyroxine, but it is rare in dogs. Clinical signs are similar to those of hyperthyroidism in cats and the diagnosis is confirmed by documenting a substantial elevation of serum T4. Treatment consists of stopping levothyroxine treatment for 2–3 days, then instituting treatment at a lower dose.

Prognosis

Response to therapy should be observed in the first 4–8 weeks post treatment. Improvements in mentation and physical activity may be noted within the first week though some abnormalities, especially dermatologic signs, may take several months to resolve. An absent or incomplete response to therapy may be due to an incorrect diagnosis, poor owner compliance, inadequate dosing, or poor absorption.

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10

Feline Hyperthyroidism

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Etiology/Pathophysiology and Epidemiology

Two recent large studies have looked at possible environmental or dietary factors involved in the pathogenesis of hyperthyroidism. One of the studies with a case–control design looked at 100 cats with hyperthyroidism and 163 control cats. The cats' medical records were reviewed and the owners were asked to complete a mailed questionnaire. Data included demographic variables, environmental exposures, and diet to include the preferred flavors of canned cat food. In this study, housing, exposure to fertilizers, herbicides, regular use of flea products, and the presence of a smoker in the house were not associated with an increased risk but cats that preferred fish or liver and giblets flavors of canned cat food had an increased risk. The results suggested that cats that prefer to eat certain flavors of canned cat food may have a significantly increased risk of hyperthyroidism.

In the second case–control study, owners of 379 hyperthyroid and 351 control cats were questioned about their cats' exposure to potential risk factors, including breed, demographic factors, medical history, indoor environment, chemicals applied to the cat and environment, and diet. The association between these hypothesized risk factors and outcome of disease was evaluated. Two genetically related cat breeds (Siamese and Himalayan) were found to have diminished risk of developing hyperthyroidism. Cats that used litter had higher risk of developing hyperthyroidism than those that did not. Use of topical ectoparasite preparations was associated with increased risk of developing hyperthyroidism. Compared with cats that did not eat canned food, those that ate commercially prepared canned food had an approximate twofold increase in risk of disease. When these four variables (breed, use of cat litter, consumption of canned cat food, and use of topical ectoparasite preparations) from the univariate analysis were selected for further, a persistent protective effect of breed (Siamese or Himalayan) was found. In addition, results suggested a 2–3-fold increase in risk of developing hyperthyroidism among cats eating a diet composed mostly of canned cat food and a threefold increase in risk among those using cat litter. In contrast, the use of commercial flea products did not retain a strong association. The results of this study indicate that further research into dietary and other potentially important environmental factors (cat litter) is warranted.

Altered G protein expression was found in thyroid gland tissue from hyperthyroid cats compared to normal control cats. Adenomatous thyroid glands obtained from eight hyperthyroid cats and thyroid glands obtained from four age-matched euthyroid cats were examined for expression of G inhibitory protein (Gi) and G stimulatory protein (Gs). Expression of Gi was significantly reduced in thyroid gland adenomas from hyperthyroid cats, compared with normal thyroid gland tissue from euthyroid cats. Expression of Gs was similar between the two groups. A decrease in expression of Gi in adenomatous thyroid glands of cats may reduce the negative inhibition of the cAMP cascade in thyroid cells, leading to autonomous growth and hypersecretion of thyroxine. What we don't know is what causes the reduction in Gi in hyperthyroid cats. The factors mentioned above in the studies of environmental and dietary risk factors may play a role in altering the G protein expression found in this study.

Oncogenes and the tumor suppressor gene p53 were examined in cats with hyperthyroidism. Formalin-fixed, paraffin-embedded thyroid glands from 18 cats diagnosed with hyperthyroidism were evaluated immunohistochemically for overexpression of the products of oncogenes c-ras (a mitogenic oncogene) and bcl2 (an apoptosis inhibitor) and the tumor suppressor gene p53.

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Fourteen thyroid glands from euthyroid cats without histologically detectable thyroid lesions were examined similarly as controls. Results from these investigations showed that all cases of nodular follicular hyperplasia/adenomas stained positively for overexpression of c-Ras protein using a mouse monoclonal antihuman pan-Ras antibody. The most intensely positively staining regions were in luminal cells surrounding abortive follicles. Subjacent thyroid and parathyroid glands from euthyroid cats did not stain immunohistochemically for pan-Ras. There was no detectable staining for either Bc12 or p53 in any of the cats. These results indicated that overexpression of c-ras was highly associated with areas of nodular follicular hyperplasia/adenomas of feline thyroid glands, and mutations in this oncogene may play a role in the etiopathogenesis of hyperthyroidism in cats. As with the study on G protein abnormalities, c-ras mutations could either be an initiating cause of hyperthyroidism or simply mediate the effects of an as yet unidentified dietary or environmental initiator.

Alterations in the thyrotropin (TSH) receptor were also examined in cats with hyperthyroidism. The authors used the polymerase chain reaction (PCR) to amplify codons 480–640 of the previously uncharacterized feline thyrotropin receptor (TSHR) gene, and determined the DNA sequence in this transmembrane domain region. They then analyzed single-stranded conformational polymorphisms in thyroid DNA from 11 sporadic cases of feline thyrotoxicosis and leukocyte DNA from two cases of familial feline thyrotoxicosis. They also determined the DNA sequence of this region of the TSHR in five of the cases of sporadic feline thyrotoxicosis and the two familial thyrotoxic cats. The normal feline TSHR sequence between codons 480 and 640 is highly homologous to that of other mammalian TSHRs, with 95%, 92%, and 90% amino acid identity between the feline receptor and canine, human, and bovine TSHRs, respectively. Thyroid gland DNA from 11 cats with sporadic thyrotoxicosis did not have mutations in this region of the TSHR gene. Leukocyte DNA from two littermates with familial feline thyrotoxicosis did not harbor mutations of this region of the TSHR gene. These studies suggested that TSHR gene mutations are likely not involved in feline hyperthyroidism.

Since its first description in 1979, the incidence of hyperthyroidism has dramatically increased, prompting veterinarians and researchers to hypothesize whether exposure to environmental thyroid-disruptor chemicals or other environmental, genetic or dietary factors are involved in the pathogenesis of hyperthyroidism. Potential exposure to several substances has been implicated, including organohalogen compounds such as polychlorinated biphenyls and polybrominated diphenyl ethers, fertilizers, soy isoflavones, bisphenol-A primarily released from "pop-top" canned cat food lids, and consumption of commercial canned food. One theory as to why the number and percentage of unexpected outliers becomes accelerated over the age of 9 years is that it may take several years of exposure to such environmental, dietary, and genetic factors before they express themselves clinically and hyperthyroidism ensues, although this topic requires further investigation.

History and Clinical Signs

With time, we have seen both an increase in the diagnosis of hyperthyroidism and a decrease in the severity of the clinical signs associated with thyrotoxicosis. This is most likely due to an increased awareness on the part of the pet owner and the veterinarian as well as the increased use of T4 concentrations as an integral part of routine feline health screening. We have also seen additional work on some of the less obvious manifestations of hyperthyroidism such as hypertension which may be clinically silent and/or present initially with ocular signs, as well as the effects of hyperthyroidism on the cardiovascular and renal system (to be discussed later).

As stated earlier, the clinical signs associated with hyperthyroidism have been decreasing in severity over the years (Box 10.1). A paper examined the electrocardiographic and radiographic changes seen in hyperthyroid cats today versus those seen 10–12 years ago. Two populations (1992–1993 and 1979–1982) of confirmed hyperthyroid cats were compared to determine whether the incidence of certain cardiovascular specific manifestations of feline thyrotoxicosis had experienced similar changes. Sinus tachycardia, which is the most commonly recognized cardiac manifestation of feline thyrotoxicosis, was not as prevalent in the 1993 group when compared to the 1982 group. This was also true for the finding of an increased R-wave amplitude on lead II electrocardiography. Both groups had a similar low incidence of atrial and ventricular dysrhythmias; however, the 1993 group had a significantly higher occurrence of right bundle branch block. Thoracic radiographs were deemed necessary in a larger proportion of the 1982 group compared to the 1993 group. Although there were

Box 10.1 Clinical signs of feline hyperthyroidism

Weight loss and poor hair coat
Aggressive or "cranky" behavior
Periodic vomiting
Polyuria and polydipsia
Increased appetite, activity, restlessness, and heart rate
Occasionally, difficulty breathing, weakness, and depression

no significant differences in radiographically defined cardiac size between the two groups, a larger number of cats in the 1982 group had evidence of congestive heart failure. These findings suggest that feline hyperthyroidism is being diagnosed earlier and with less severe clinical signs than when studied a decade ago.

Diagnosis

Diagnosis most often is based on the presence of one or more typical clinical signs and increased serum total thyroxine (T4) concentration. However, up to 10% of all hyperthyroid cats and 40% of those with mild disease have serum T4 values within reference range. The diagnosis of hyperthyroidism should not be excluded on the basis of a single normal serum T4 value, especially in a cat with typical clinical signs, a palpable thyroid nodule and serum T4 in the upper half of the normal range. In these cases, serum free T4 (fT4), measured by equilibrium dialysis, may provide an alternative means of diagnosing hyperthyroidism in cats with normal serum total T4 values. Studies document that up to 20% of sick euthyroid cats can have increased fT4 concentration. Therefore, it is most appropriate and reliable to interpret the two values together. Mid-to-high reference range total T4 and increased fT4 concentration are consistent with hyperthyroidism. In contrast, low total $T4_4$and increased fT4 values are usually associated with nonthyroidal illness. In cases where a strong index of suspicion exists for hyperthyroidism and test results are equivocal, thyroid imaging can be of benefit.

Treatment

Once hyperthyroidism has been diagnosed, all management options (thyroidectomy, radioactive iodine, antithyroid drugs, nutritional management) should be discussed with pet owners. All options can be ≥90% effective for controlling hyperthyroidism when used appropriately. The selected management option will differ for each cat based on several considerations (Table 10.1). Radioactive iodine therapy is considered the gold standard for treatment of hyperthyroidism but most pet owners currently opt for medical management. Until recently, this included oral or transdermal antithyroid drugs. Now nutritional management using a limited-iodine food is another option for cats with hyperthyroidism.

Radioactive Iodine

Radioiodine treatment is often considered the best option for many hyperthyroid cats because:

- it has the potential to eliminate a benign thyroid tumor or abnormal thyroid tissue with a single treatment
- it treats extrathyroidal thyroid tissue, which may occur in 10–20% of hyperthyroid cats
- no general anesthesia is required
- reported side-effects are minimal.

Cats should be stable prior to radioiodine therapy; those with clinically significant cardiovascular, renal, gastrointestinal, or endocrine (e.g., diabetes mellitus) disease may not be very good candidates, especially because of the time necessary for boarding after treatment.

Table 10.1 Advantages/disadvantages of options for managing cats with hyperthyroidism

Option	Advantages	Disadvantages
Thyroidectomy	Cures current tumor	High initial costs Requires anesthesia Hospitalization required Risk of postoperative hypocalcaemia **Irreversible**
Radioactive iodine	Cures current tumor Single treatment Effective for ectopic tissue Side-effects uncommon	High initial costs Limited availability Hospitalization required **Irreversible**
Antithyroid drugs	Routinely available Reversible Costs spread over time	Not curative (controls T4 and signs) Daily administration needed Drug side-effects
Limited-iodine food	Routinely available Reversible Costs spread over time	Not curative (controls T4 and signs) Cat can only eat a single food

After administration, radioactive iodine is actively concentrated by the thyroid gland and has a half-life of eight days. It emits both beta-particles and gamma-radiation; the beta-particles are responsible for the majority of tissue destruction, but are only locally destructive, traveling a maximum of 2 mm. Therefore, no significant damage to adjacent parathyroid tissue, atrophic thyroid tissue, or other cervical structures is expected. The main limitation to widespread use of radioactive iodine is the requirement for special licensing and the isolation of the cat for variable periods after treatment. This can range from several days to several weeks depending on state or local radiation regulations and the dose administered.

The goal of treatment is to restore euthyroidism with the smallest possible single dose of radioactive iodine, while avoiding development of hypothyroidism. Controversy exists as to the best method of calculating the optimum dose for individual cats. Based on the majority of reported cases, posttreatment hypothyroidism is transient and generally uncommon (2–7% of cases); even fewer cats have clinical signs or appear to require thyroid hormone replacement. However, up to 30% (50 of 165 cats) were hypothyroid three months after radioactive iodine therapy in one study; of these, 56% (19 of 34 hypothyroid cats with available information) had clinical signs of hypothyroidism and 52% (23 of 44 cats) were given thyroid hormone supplementation. Thyroid hormone replacement may be needed in some cats, especially those with concurrent kidney disease, since hypothyroidism has been associated with azotemia and decreased survival time in previously hyperthyroid cats. Owners should be advised of this possibility, particularly if their motivation is to avoid long-term oral medication.

Antithyroid Drugs

Antithyroid drugs (e.g., methimazole, carbimazole) are commonly used for treatment of hyperthyroidism in cats. If administered appropriately, they reliably inhibit the synthesis of thyroid hormones and thereby lower serum thyroid hormone concentrations. These drugs do not affect the thyroid gland's ability to trap inorganic iodide or release preformed hormones. They are widely recommended to stabilize hyperthyroid cats prior to surgery and are the only drugs that can be used chronically for management of hyperthyroidism. Almost all cats are potential candidates unless thyroid carcinoma is suspected.

Antithyroid drugs used most often in cats include methimazole and carbimazole; both can be given orally or formulated for transdermal application. Custom formulation of transdermal products may increase the expense of therapy and stability of the product is not guaranteed. Results of a recent prospective study conducted in New Zealand showed that once-daily treatment for 12 weeks with transdermal methimazole in a novel lipophilic vehicle was as effective as twice-daily carbimazole administered orally.

While many cats have been successfully managed long term with antithyroid drugs, it is important to monitor for potential side-effects that have been associated with their use. In the study with the largest number of cats, 18% had side-effects associated with methimazole; a more recent study revealed that 44% of 39 cats had side-effects. In 44 cats receiving carbimazole for one year, 44% had associated side-effects, with gastrointestinal signs (decreased appetite, vomiting, diarrhea) being most common. In another study, 13% of 39 cats treated with carbimazole experienced side-effects. It is difficult to determine what percentage of side-effects are caused by the drug versus something else such as concurrent disease.

Most adverse reactions occur within the first few weeks to months after beginning therapy and include depression, inappetence, vomiting, and self-induced excoriations of the head and neck (facial pruritus). Gastrointestinal signs are less common with transdermal administration of methimazole. Mild to serious hematologic complications, including agranulocytosis and thrombocytopenia either alone or concurrently, and more rarely immune-mediated hemolytic anemia may also occur. Hepatic toxicity with marked increases in bilirubin concentration and hepatic enzyme activities has been described in less than 2% of cats treated with methimazole. Cessation of therapy is required if either serious hematologic or hepatic reactions develop. Serum antinuclear antibodies develop in approximately 50% of cats treated with methimazole for longer than six months, usually in cats on high-dose therapy (>15 mg/day). Although clinical signs of a lupus-like syndrome have not been reported, decreasing the daily dosage is recommended.

Nutritional Management

Production of thyroid hormone requires uptake by the thyroid gland of sufficient amounts of iodine, which is provided by dietary intake. The only function for ingested iodine is for thyroid hormone synthesis. This observation led to the hypothesis that limiting dietary iodine intake could be used to control thyroid hormone production and potentially manage hyperthyroidism in cats. After more than a decade of research and development, a limited-iodine therapeutic food (Hill's® Prescription Diet® y/d™ Feline) containing <0.3 ppm (mg/kg) iodine on a dry matter basis (DMB) is now available as an option for managing cats with hyperthyroidism.

Three studies were designed to determine the magnitude of iodine control necessary to return newly diagnosed cats to a euthyroid state; the maximum level of dietary iodine that maintains cats in a euthyroid state; and the effectiveness of a therapeutic food formulated based on the previous studies to control naturally occurring hyperthyroidism in cats. In summary, results of these studies demonstrated that a food with 0.17 or 0.32 ppm iodine (DMB) maintained normal thyroid hormone concentrations in hyperthyroid cats, helping to further define the range of iodine effective for managing hyperthyroidism.

After confirming the diagnosis and performing a thorough patient evaluation, nutritional management should be discussed along with other options for managing hyperthyroidism. If selected as the management option, gradual transition to the limited-iodine food over at least seven days is recommended. It is very important to counsel owners so they understand that success of nutritional management depends on the limited-iodine food being the sole source of nutrition for their cat.

The first recheck evaluation should be done four weeks after completing the transition to y/d Feline (i.e., once the cat has eaten y/d exclusively for four weeks) and as a minimum should include physical examination and measurement of T4, BUN, serum creatinine, and urine specific gravity. All cats should have decreased T4 concentrations compared with baseline and many will have returned to normal by the four-week evaluation. Clinical improvement including weight gain, improved hair coat, and decreased tachycardia/cardiac murmur also may be noted by the first evaluation. Clinical signs should continue improving by the next reevaluation at eight weeks and most cats will be euthyroid. Some require slightly longer to become euthyroid but it is expected that 90% will have normal T4 concentrations if the limited-iodine food is their sole source of nutrition.

If euthyroidism is not achieved within 4–12 weeks, a thorough history is indicated to confirm that only the limited-iodine food is being fed.

Managing Hyperthyroid Cats with Concurrent Kidney Disease

Chronic kidney disease (CKD) and hyperthyroidism are more likely to be diagnosed in older cats so it is not surprising that many hyperthyroid cats have CKD. Untreated hyperthyroidism complicates the diagnosis of CKD because it is associated with increased glomerular filtration rate (GFR) and therefore often masks biochemical markers of CKD. Regardless of the therapeutic modality (methimazole, surgical thyroidectomy, or radioiodine), decreased GFR, increased serum urea and creatinine concentrations, and development of overt clinical signs of kidney disease have been reported after successful treatment of hyperthyroidism. The presence of underlying CKD may affect the prognosis; one study documented a shorter survival time in hyperthyroid cats with azotemia. However, two recent studies comparing survival of cats that developed azotemia with those that did not after treatment of hyperthyroidism found no significant difference between the two groups if cats did not become hypothyroid post treatment.

The reported occurrence of azotemia after treatment of hyperthyroidism ranges from 15% to 49%. Iatrogenic hypothyroidism has been reported to decrease GFR in human patients. Posttreatment iatrogenic hypothyroidism has been reported in cats after radioiodine therapy and bilateral thyroidectomy, which constituted the predominant therapeutic modalities in previous studies. In one recent study, cats with iatrogenic biochemical hypothyroidism were almost twice as likely to develop azotemia post treatment as euthyroid cats. The hypothyroid cats with azotemia had shorter survival times than those without azotemia, whereas, consistent with previous reports, there was no difference in survival times of euthyroid cats with or without azotemia.

It is not possible to consistently predict which cats will develop overt CKD after treatment of hyperthyroidism or have progression of their kidney disease. This should be considered when deciding on treatment options, particularly those that are irreversible (thyroidectomy, radioactive iodine). Regardless of the option selected for managing hyperthyroidism, it is important to remember that the only intervention shown to improve quality of life and prolong survival time in cats with naturally occurring CKD is feeding a therapeutic renal food. Until the recent availability of limited-iodine food, nutritional recommendations have not generally been considered for hyperthyroid cats without azotemia. In cats with compromised renal function but without azotemia (IRIS Stage 1), the decrease in GFR associated with normalizing serum T4 levels may be sufficient to prevent effective clearing of protein metabolic by-products (BUN and creatinine) when dietary intake of protein and phosphorus is high. This could contribute to the occurrence of post-therapy azotemia in hyperthyroid cats.

Prognosis

Although older studies report survival times of two years after diagnosis, more recent data show that cats without concurrent CKD have a median survival of 5.3 years. Untreated hyperthyroidism is a progressive disease that can lead to significant morbidity and mortality. Morbidity and mortality in well-managed hyperthyroid cats are more strongly influenced by the presence and severity of the co-morbid disease than the hyperthyroidism itself.

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11

Hypoadrenocorticism in Dogs and Cats

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Hypoadrenocorticism in Dogs

Etiology/Pathophysiology

Primary hypoadrenocorticism (Addison disease, HOAC) results from the destruction of >90% of the adrenal cortex. Clinical signs are due to both cortisol and aldosterone deficiency in the majority of patients, although some patients only have signs of cortisol deficiency (atypical hypoadrenocorticism).

Aldosterone is the major mineralocorticoid secreted by the outermost layer of the adrenal cortex, the zona glomerulosa. Its main activities are the conservation of sodium and water, and excretion of potassium and hydrogen ions (acid), from the distal renal tubules. Aldosterone secretion is primarily regulated by the renin-angiotensin-aldosterone system, but secretion can also be stimulated by hyperkalemia. In patients with hypoadrenocorticism and subsequent aldosterone deficiency, hyperkalemia, hyponatremia, and hypovolemia are common.

Cortisol is the major glucocorticoid produced by the innermost layers of the adrenal cortex, the zonae fasciculata and reticularis. Its functions include stimulation of gluconeogenesis and erythropoiesis, suppression of the inflammatory response, and maintenance of gastrointestinal mucosal integrity. Cortisol also helps the body deal with stress. In dogs with HOAC, cortisol deficiency often results in lethargy, gastrointestinal signs, hypoglycemia, and anemia.

Cortisol release is regulated by the hypothalamic-pituitary-adrenal axis (HPAA). During times of stress (emotional, physiologic, other), corticotropin-releasing hormone (CRH) is secreted from the hypothalamus, and stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH then stimulates cortisol secretion from the adrenal cortex. Cortisol has a negative feedback effect on both the pituitary and hypothalamus, such that ACTH and CRH production are decreased when adequate cortisol concentrations are present.

Most naturally occurring cases of primary hypoadrenocorticism in dogs are idiopathic, likely due to immune-mediated destruction of the adrenal cortex. Rarely, infiltration of the adrenal cortex by fungus, neoplasia, other granulomatous disease, or amyloidosis has been reported. Trauma, hemorrhage, and infarction may also lead to Addison disease, as can drugs used to treat hyperadrenocorticism. Although proper use of mitotane usually leads to necrosis of only the zonae fasciculata and reticularis, improper monitoring, or use in a particularly sensitive patient, can result in destruction of all three layers of the cortex, causing both cortisol and aldosterone deficiency. Trilostane is an enzyme inhibitor that decreases cortisol concentrations, but also decreases aldosterone concentrations to a lesser extent. It can lead to cortisol deficiency and, occasionally, aldosterone deficiency. Additionally, trilostane has been reported to cause idiosyncratic adrenocortical necrosis, resulting in both cortisol and aldosterone deficiency.

Secondary hypoadrenocorticism can be caused by either a pituitary lesion, resulting in ACTH deficiency, or iatrogenically. Iatrogenic secondary hypoadrenocorticism is caused by abrupt cessation of exogenous glucocorticoids following long-term use. Long-term use of glucocorticoids suppresses production of ACTH. Without the trophic effects of ACTH, the zonae fasciculata and reticularis atrophy. When the exogenous glucocorticoid is abruptly discontinued (not tapered), ACTH production occurs, but the adrenal cortex is atrophied and incapable of producing adequate amounts of cortisol. Thus, signs of cortisol deficiency occur. Aldosterone deficiency is not present in cases of secondary hypoadrenocorticism, since ACTH has little regulatory control of aldosterone production.

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Epidemiology

Hypoadrenocorticism affects approximately 1/2000 dogs. Dogs with other immune-mediated endocrinopathies, such as hypothyroidism and diabetes mellitus, are at increased risk.

Signalment

Young to middle-aged female dogs are predisposed to Addison disease, although dogs at any age may be affected, with some studies revealing a more equal distribution between sexes. Poodles of all sizes, West Highland white terriers, Great Danes, bearded collies, Portuguese water dogs, Leonbergers, and Nova Scotia duck-tolling retrievers (NSDTRs) are predisposed. Notably, NSDTRs may develop clinical signs at a very young age (as young as 2 months). Heritability has been proven in standard poodles, bearded collies, and NSDTRs.

History and Clinical Signs

The clinical manifestation of hypoadrenocorticism is highly variable in presenting complaint, chronicity, and severity. Whereas some dogs present with chronic signs, others present acutely, in an "Addisonian crisis." The pathophysiology for chronic and acute hypoadrenocorticism is the same, and these presentations represent a continuum of disease progression. If not diagnosed and treated early in the course of disease, dogs with chronic signs may present in crisis.

Addison's disease often causes vague, nonspecific clinical signs that can be confused with other diseases, thus its nickname "The Great Pretender." Nonspecific signs such as lethargy, inappetence, and weight loss occur in most patients. A waxing and waning pattern, with exacerbations following stressful events or improvement following fluid or steroid administration, is often noted.

Gastrointestinal signs, including vomiting and diarrhea, are common and likely due to the loss of "trophic" effects of cortisol on the gastrointestinal mucosa. Melena and/or hematochezia, and abdominal pain, may be reported by the owners or found on rectal examination. Exacerbation or onset of gastrointestinal (GI) signs following a stressful event is often reported in dogs later diagnosed with Addison disease, so HOAC should be considered in patients with recurrent "stress colitis," particularly if accompanied by other GI signs, lethargy, or weakness.

Renal loss of sodium and water, and the resulting decreased renal medullary concentration gradient due to hyponatremia, sometimes lead to polyuria and polydipsia. Rarely, seizures due to hypoglycemia occur, and HOAC should be ruled out in all dogs with unexplained hypoglycemia.

Less common clinical signs include generalized or hindlimb muscle weakness, megaesophagus (ME), and muscle cramping. The etiology of these abnormalities is unclear, but is probably due to aberrant neuromuscular function caused by deranged electrolyte concentrations and/or hypocortisolemia. Muscle weakness can be severe, and the patient may present for inability to rise. Generalized debility could explain the weakness, but some of these dogs are specifically weaker in the hindlimbs. Regurgitation due to ME is a rare presentation for hypoadrenocorticism, but since the ME usually resolves with appropriate treatment, HOAC should be ruled out in all cases of ME.

Hair loss or a change in hair coat color are observed occasionally in dogs with hypoadrenocorticism, but the cause is unknown. Hypothyroidism should be ruled out in these patients following initial management of HOAC.

Approximately 30% of dogs with Addison disease present in hypovolemic shock, or Addisonian crisis. In addition to the aforementioned clinical signs, especially vomiting, diarrhea, and GI bleeding, these dogs sometimes experience collapse and/or severe generalized weakness. Classic signs of hypovolemic shock are usually present, including weak pulse, pale mucous membranes, and prolonged capillary refill time. Some dogs are also hypothermic. Heart rate is variable. Whereas most hypovolemic non-Addisonian dogs are tachycardic (>160 bpm), patients in an Addisonian crisis often have a normal to decreased heart rate. This is due to the effects of hyperkalemia on cardiac conduction. The presence of a decreased or normal heart rate in a patient in hypovolemic shock ("relative bradycardia") should raise suspicion of hyperkalemia and hypoadrenocorticism. In patients with cardiac changes associated with hyperkalemia, rapid treatment and correction are critical for the survival of the patient.

Gastrointestinal bleeding, including melena and hematochezia, is frequently seen during crisis. It may be present initially or appear within 2–3 days of presentation. Progressively decreasing hematocrit during treatment should increase suspicion of melena, and the possibility of GI bleeding should not be excluded despite the absence of melena or hematochezia on the initial examination. Hospitalization is recommended until the hematocrit stabilizes or increases. GI blood loss is occasionally severe enough to require blood transfusion.

Diagnosis

Since dogs with HOAC often present with nonspecific signs, most of the diagnostics are performed early in the work-up, prior to significant suspicion of hypoadrenocorticism. A complete blood count, serum biochemistry analysis, and urinalysis should be performed in each

patient with clinical signs consistent with hypoadrenocorticism. Electrolyte analysis must be included in the minimum database, as sodium and potassium abnormalities are often the first specific indicators of HOAC, and electrolyte disturbances are common in patients with gastrointestinal signs of any etiology, and need to be addressed during treatment.

Serum Biochemistry, Urinalysis, and Complete Blood Count

Most dogs with HOAC are hyperkalemic and hyponatremic at diagnosis. Dogs with "atypical" hypoadrenocorticism are not (see Atypical Hypoadrenocorticism later). Potassium concentrations usually remain below 8 mEq/L, but may be as high as 11 mEq/L. Sodium concentrations are usually 120–140 mEq/L, but may be as low as 100 mEq/L. Some dogs present with one abnormality without the other (e.g., hyponatremia without hyperkalemia). Hypochloremia follows hyponatremia in about half the patients. Metabolic acidosis is also common, due to the inability to excrete H+ ions from the distal tubule.

Electrolyte abnormalities are not always detected early in the course of the disease, and may appear as disease progresses. Emphasis is sometimes placed on calculation of the Na+/K+ ratio. The lower the sodium and the higher the potassium concentration, the lower the ratio. Although lower ratios make HOAC more likely, a high ratio does not rule it out, and dogs with low ratios do not always have HOAC. Therefore, the utility of the ratio is questionable. Any dog with hyponatremia and/or hyperkalemia should be considered a suspect for HOAC, regardless of the ratio.

Most patients experience some degree of azotemia, with increased BUN (90% of dogs) and creatinine (65%). This is due to a combination of decreased renal perfusion from hypovolemia, and GI blood loss (increased BUN). Phosphorus is usually increased, as well. Although the azotemia is primarily pre-renal in nature, most dogs with HOAC have a urine specific gravity <1.030 (often <1.020), which is more dilute than expected with pre-renal azotemia alone. For this reason, and the presence of hyperkalemia and hyponatremia, some Addisonian patients are initially misdiagnosed with acute kidney injury (AKI). Given the difference in prognosis and treatment, clinicians must consider HOAC in every suspected AKI patient, especially if the dog has a history of gastrointestinal signs. Severe azotemia caused by HOAC usually resolves quickly following appropriate rehydration. Primary renal damage is possible with prolonged hypovolemia, but most Addisonian patients recover renal function. Conversely, patients with AKI take much longer or never improve. Additionally, significant hyperkalemia and hyponatremia rarely occur in polyuric AKI patients, but often occur in anuric and oliguric AKI dogs. Addisonians may initially present with physiologic oliguria (appropriately decreased urine production in the face of hypovolemia and/or dehydration). However, rehydration results in polyuria. Thus, if a hypovolemic, azotemic, hyperkalemic, hyponatremic dog has significant improvement of attitude and becomes polyuric upon rehydration, HOAC should be strongly considered as a differential diagnosis.

Hypocholesterolemia and hypoalbuminemia occur in approximately 10% and 15% dogs with HOAC, respectively. Both might be due to decreased hepatic production and GI malabsorption. GI blood loss exacerbates the hypoalbuminemia in some cases.

Hypoglycemia is present in about 15% of HOAC dogs, probably due to decreased gluconeogenesis and increased insulin sensitivity. It is usually subclinical, but occasionally can be severe enough to result in seizures. Thus, hypoadrenocorticism should be a differential diagnosis in adult dogs with unexplained hypoglycemia.

Total and ionized hypercalcemia occurs in about 30% of Addisonians. It is not usually the presenting complaint, but HOAC should be considered a differential diagnosis in hypercalcemic patients.

Increased alanine aminotransferase (ALT), alkaline phosphatase (ALP), and aspartate aminotransferase (AST) are also frequently seen (20–30%) in HOAC dogs, possibly secondary to hepatic hypoperfusion and cholestasis.

At diagnosis, about 30% of Addisonian dogs are anemic. This increases to 70% following rehydration. It is usually a mild normochromic, normocytic, nonregenerative anemia, and GI blood loss should be suspected in patients with severe anemia. The lack of a stress leukogram (neutrophilia, lymphocytosis, monocytosis, and eosinopenia) in a sick dog is suggestive of HOAC. Occasionally, lymphocytosis and eosinophilia occur (10%), but neutropenia is rare.

Diagnostic Imaging

Diagnostic imaging is not required to diagnose HOAC in most patients, but abdominal imaging is often performed in the initial work-up of patients with gastrointestinal signs. Imaging is recommended, however, in Addisonian patients that do not respond to appropriate therapy. These patients may have concurrent disease or HOAC due to infiltrative disease (e.g., neoplasia or fungal disease invading the adrenal cortex).

In patients with primary idiopathic HOAC, abdominal radiographs and ultrasound may reveal a small liver, consistent with hypovolemia. Adrenal gland length and thickness might be smaller than in normal dogs, but the overlap in adrenal size between normal and HOAC patients does not allow definitive differentiation. Thoracic radiographs

often reveal nonspecific signs of hypovolemia, including microcardia. Megaesophagus is seen infrequently.

Electrocardiogram

Additional diagnostics for patients that present in hypovolemic shock include blood pressure measurement and electrocardiography. ECG abnormalities are caused by hyperkalemia. Although rigid criteria associating specific ECG findings with specific potassium concentrations do not exist, cardiac effects are rarely seen when K+ <7.0 mEq/L, and frequently observed when K+ >9 mEq/L (and may be fatal). With increasing severity of hyperkalemia, ECG changes may include increased T-wave amplitude ("spiked" T wave), shortened Q-T interval, decreased P-wave amplitude, prolonged P-R interval, absent P-wave, severe bradycardia, and asystole. Bizarre QRS complexes, including ventricular tachycardia and ventricular fibrillation, may also occur. Patients with ECG abnormalities require immediate interventions to prevent progression to a fatal arrhythmia.

Endocrine Diagnostics

The ACTH stimulation test is required for definitive diagnosis of hypoadrenocorticism. A baseline cortisol concentration alone can help rule out the diagnosis of HOAC, but cannot be used to definitely diagnose it.

During an ACTH stimulation test, a supraphysiologic dose of ACTH is administered, and the cortisol concentration is measured 1–2 hours later. In a dog with normally functioning adrenal glands, ACTH should cause a significant increase in cortisol concentration. In HOAC dogs, minimal to no increase in cortisol will occur.

To perform an ACTH stimulation test, a baseline serum sample is first obtained. Then, 1 µg/kg (up to 250 µg/dog) of synthetic ACTH (cosyntropin or tetracosactrin) is administered intravenously. One hour later, another serum sample is obtained. Cortisol concentration is then measured in both pre- and post-ACTH serum samples.

Protocols for the ACTH stimulation test vary when testing for HOAC or hyperadrenocorticism. The use of compounded ACTH gel is not recommended for the diagnosis of hypoadrenocorticism, due to inconsistent results. Additionally, since dogs with HOAC are often hypovolemic, intramuscular administration of ACTH is not recommended.

The diagnosis of HOAC requires a post-ACTH cortisol concentration <2 µg/dL (55 nmol/L), with a post-ACTH cortisol concentration >2 µg/dL ruling out the diagnosis. Rarely, dogs with HOAC have a post-stimulation cortisol between 2 and 3 µg/dL. Note that this test does not differentiate between primary, secondary, and iatrogenic Addison disease. However, iatrogenic HOAC, due to long-term administration of glucocorticoids, should be identified based on historical findings.

Administration of glucocorticoids prior to an ACTH stimulation test can interfere with and/or cause decreased response to the test. Most synthetic glucocorticoids, including prednisone and methylprednisolone, cross-react with the cortisol assay, which can result in falsely increased cortisol concentrations. Dexamethasone and triamcinolone do not. Thus, if a steroid is given just prior to the test, dexamethasone is recommended. Other short-acting glucocorticoids (such as prednisone) should be withheld for 12–24 hours prior to the test. Longer-acting glucocorticoids, such as methylprednisolone acetate, should be withheld for at least four weeks prior to the test to avoid cross-reactivity.

Administration of glucocorticoids decreases endogenous ACTH concentrations, which causes atrophy of the adrenal cortex (fasciculata and reticularis). A blunted cortisol response during the ACTH stimulation test is expected in patients that have received glucocorticoids (oral, parenteral, or topical) within a month of the test, or longer if longer-acting glucocorticoids (such as methylprednisolone acetate) have been administered. A post-stimulation cortisol between 2 µg/dL and 5 µg/dL is often the result of recent steroid administration and not hypoadrenocorticism.

One way to save money with ACTH stimulation tests is to freeze the unused portion of a vial of cosyntropin. Cosyntropin can be frozen in plastic syringes (not glass, as it binds to ACTH) for up to six months. The use of a frost-free freezer is not recommended, as the effect of the freeze/thaw cycles on the ACTH is unknown.

A baseline cortisol concentration is a less expensive way to rule out hypoadrenocorticism. Since the cortisol concentration in almost any patient with HOAC is <2 µg/dL, a baseline cortisol concentration of >2 µg/dL rules out the diagnosis in most dogs. However, if the patient has a baseline cortisol concentration <2 µg/dL, an ACTH stimulation test is required for definitive diagnosis of HOAC.

For the definitive diagnosis of primary hypoadrenocorticism, a potential alternative to the ACTH stimulation test is the cortisol-to-ACTH ratio (CAR). Since dogs with HOAC have low cortisol concentrations and high ACTH concentrations (due to lack of negative feedback), the CAR is significantly lower in patients with hypoadrenocorticism than in normal dogs or dogs with nonadrenal illness (Lathan et al, 2014, *JVIM*). Unfortunately, there is some overlap between dogs with Addison's and dogs with non-adrenal illness (Boretti et al, JVIM, 2015). Thus, at this time, the CAR cannot be recommended for definitive diagnosis of HOAC when synthetic cosyntropin is available.

Therapy

Acute Management

Patients with hypoadrenocorticism fall along a continuum of disease. While some patients present in hypovolemic shock with severe hyperkalemia, most are less critical, but require intravenous fluids and other supportive therapy. The most severe cases (true Addisonian crises) will be discussed in this section.

The initial goal of treatment of Addisonian crisis is to correct hypovolemia, hyperkalemia and associated arrhythmias, hypoglycemia, and acidosis. Aggressive intravenous fluid resuscitation is the top priority. In addition to correcting hypovolemia, it also helps treat hyperkalemia, hyponatremia, hypochloremia, and acidosis. One-third of a shock bolus of crystalloids is given initially, and response is assessed based on heart rate, pulse quality/blood pressure, capillary refill time, and mental status. Additional fluids are then given as necessary.

Historically, 0.9% NaCl has been recommended as the fluid of choice, since it contains sodium and chloride but no potassium. However, Normosol-R®, Plasma-Lyte A®, and/or lactated Ringer's solution (LRS) are preferred by some clinicians, since they are more alkalinizing than saline, thus correcting acidosis more efficiently. Although they contain a small amount of potassium, these crystalloids still allow for correction of hyperkalemia via dilution and increased renal perfusion. Hydroxyethyl starch can also be used in conjunction with crystalloids for more rapid fluid resuscitation, at a dosage of 5–10 mL/kg.

Sodium concentration should not be increased by more than 0.5 mEq/kg/h, as myelinolysis may occur with more rapid correction. Thus, hypertonic saline should not be used to treat an Addisonian crisis. Normosol-R, Plasma-Lyte A, and LRS all have lower sodium concentrations than 0.9% saline (140 mEq/L, 140 mEq/L, 130 mEq/L, and 154 mEq/L, respectively). Their use is sometimes preferred in patients with severe hyponatremia, as they are less likely to increase the serum sodium concentration as rapidly as 0.9% saline.

Hyperkalemia is often the most life-threatening consequence of HOAC, and must be addressed immediately. Mild to moderate hyperkalemia usually responds to fluid therapy alone. However, severe hyperkalemia (>9 mEq/L) and/or hyperkalemia accompanied by life-threatening arrhythmias (severe bradycardia, absent P-waves, idioventricular rhythm) require specific therapy.

Calcium gluconate is given for its cardioprotective effects, allowing time for fluids and other therapies to take effect. However, it does not directly decrease the potassium concentration. A dosage of 0.5–1.5 mL/kg of 10% calcium gluconate is given slowly over 15 minutes, while monitoring the ECG. Rapid administration may cause additional arrhythmias, such as shortened Q-T interval and more severe bradycardia.

Intravenous regular insulin helps drive the potassium intracellularly. Dosages of 0.2–0.5 U/kg regular insulin are administered, followed by 2 g of dextrose (diluted to 25% in an isotonic crystalloid) per unit of insulin administered. Dextrose should then be added to the intravenous fluids (e.g., 0.9% saline or LRS) to produce a 1.25–2.5% dextrose solution, and blood glucose should be monitored. Generally, 5% dextrose alone (D5W) should not be given, as it becomes hypotonic and enters the interstitial space once the dextrose is metabolized.

Hypoglycemia is uncommon, but should be treated with an IV dose of 1 mL/kg of 25–50% dextrose in a 1:1 solution of dextrose and 0.9% saline. Maintenance fluids should then be supplemented with dextrose to make a 1.25–5% dextrose solution.

Glucocorticoid deficiency is responsible for the hypoglycemia, gastrointestinal signs, and general debility of patients in crisis, and may also contribute to hypotension. Supplementation should be instituted after the life-threatening issues (hypovolemia, hyperkalemia, and hypoglycemia) have been initially addressed. Dexamethasone sodium phosphate (0.25 mg/kg IV) is recommended, since it does not cross-react with the cortisol assay. Since it has approximately eight times the glucocorticoid activity of prednisone, this is equivalent to 2 mg/kg of prednisone, or 10 times the physiologic dose. Higher doses previously recommended (such as 2 mg/kg) are excessive and unnecessary. Hydrocortisone sodium succinate (0.5 mg/kg/h), cortisol acetate (1 mg/kg), and prednisolone sodium succinate (2 mg/kg) can also be used. However, since they cross-react with the cortisol assay, they should not be given until after the ACTH stimulation test.

Additional supportive therapy is provided as necessary. Dogs with gastrointestinal signs are given gastroprotectants, including proton pump inhibitors (omeprazole or pantoprazole, which can be given IV) and sucralfate. Due to potential bacterial translocation from the GI tract, dogs with significant GI signs may be given prophylactic antibiotics (such as ampicillin), but this is controversial. Packed red cell or whole blood transfusion is occasionally necessary in dogs with severe GI blood loss.

Frequent reassessment of patients is necessary following initial stabilization. Fluid rates should be adjusted to correct dehydration and azotemia. The ECG should be reassessed until arrhythmias resolve. Electrolyte concentrations should be rechecked following initial stabilization, and then every 6–12 hours until potassium and sodium concentrations normalize.

Intravenous fluids are continued until the dog is able to eat and maintain hydration on its own, and

mineralocorticoid supplementation (fludrocortisone or DOCP) is provided following definitive diagnosis of HOAC. Dexamethasone should be continued at a dose of 0.15–0.2 mg/kg/day until prednisone can be given orally. Prednisone is then started at 0.5 mg/kg BID. Following discharge of the patient, prednisone is usually tapered to approximately 0.5 mg/kg per day, and then decreased based on clinical signs, as discussed in chronic management.

Most patients in Addisonian crisis respond quickly to treatment (within hours), although more severely debilitated patients may take 2–3 days to demonstrate dramatic improvement. Dogs are usually discharged 3–5 days after initial presentation.

Chronic Management

Chronic therapy for hypoadrenocorticism consists of life-long glucocorticoid and mineralocorticoid supplementation to replace the missing cortisol and aldosterone.

Mineralocorticoids are given to correct hyperkalemia, hyponatremia, and hypochloremia. Either a monthly injection or a twice-daily pill can be used. Desoxycorticosterone pivalate is a long-acting, injectable mineralocorticoid. It is initially administered at a dose of 2.2 mg/kg, subcutaneously or intramuscularly, every 25 days. Electrolyte concentrations are then measured two weeks and 25 days following the first injection. The 14-day measurement helps determine whether the dose is sufficient, whereas the 25-day recheck confirms that the interval is acceptable. If hyperkalemia and/or hyponatremia are present, the dose (14-day recheck) is increased by 10–15%, or the interval is decreased by two days (25-day recheck). The author usually increases the dosing interval by 2–3 days each month, measuring the electrolytes before each injection to ensure that they are within reference range, until the interval reaches 30–31 days, for owner convenience. Most dogs also do not require the entire 2.2 U/kg, and since DOCP is expensive, the dose can be decreased by approximately 10% per month, measuring electrolytes immediately prior to each injection to ensure that the electrolyte concentrations are still acceptable. The author usually starts with 1.5 mg/kg and rarely decreases below 1 mg/kg/month. Clients *must* understand that using lower doses leaves room for less error and requires tight adherence to the dosing schedule. Owners must be warned not to prolong the dosing interval to save money without veterinary advice; this often results in Addisonian crisis, which is significantly more expensive to treat than a single injection of DOCP.

Following stabilization of DOCP dose, electrolytes should be measured every 3–6 months. Dogs receiving DOCP injections must also receive a glucocorticoid, as DOCP has no glucocorticoid activity.

Side-effects of DOCP are uncommon, but polyuria/polydipsia (PU/PD) has been reported. This is usually due to concurrent prednisone administration. However, PU/PD is occasionally reported to be worse immediately following DOCP injection, and to improve throughout the month. In these cases, prolonging the dose interval or decreasing the dose, while monitoring electrolytes, may result in improvement.

Fludrocortisone is a shorter-acting oral mineralocorticoid that is available in 0.1 mg pills. The starting dose is 0.01 mg/kg twice daily. Electrolytes are measured in one-week increments until they are within the reference range. If hyponatremia and/or hyperkalemia are present, the dose is increased by 0.05–0.1 mg/day. If hypernatremia and/or hypokalemia are present, the dose is decreased. Once the dose has normalized, electrolyte concentrations are rechecked every 3–6 months. The dose often increases during the first 1–2 years of therapy. Since fludrocortisone has some glucocorticoid activity, only approximately 50% of dogs need additional glucocorticoids long term. However, all dogs are started on concurrent prednisone therapy at initial diagnosis, which is then tapered as necessary.

Polyuria, polydipsia, polyphagia, and panting are the most commonly reported side-effects of fludrocortisone therapy. Most of these are due to the glucocorticoid properties of fludrocortisone, and resolve when the patient is switched to DOCP.

DOCP is available in two veterinary-approved products (Zycortal®, Dechra; Percorten-V®, Elanco). Fludrocortisone is available through human pharmacies.

Glucocorticoids are used to control the nonspecific and gastrointestinal signs associated with hypoadrenocorticism, and prednisone is most frequently used. All dogs receiving DOCP need glucocorticoid supplementation, and about 50% of dogs taking fludrocortisone will need additional glucocorticoid supplementation long term. The physiologic dose of prednisone is 0.1–0.25 mg/kg/day, although many dogs (particularly larger breeds) do well on 0.05 mg/kg/day or less. The dose is tapered to effect, based on the clinical signs. If the dog has any gastrointestinal signs or continues to display vague clinical signs, the dose is increased. If PU/PD, polyphagia, or panting occur, the dose needs to be decreased. Remember that the dose is adjusted based on clinical signs, and that an ACTH stimulation test is never required to monitor patients with primary hypoadrenocorticism.

During times of stress, the prednisone dose is usually increased by 2–4 times (two times is usually sufficient).

"Stressful" situations include physiologic and emotional stress, such as when a dog goes to the veterinary clinic for electrolyte rechecks, when new visitors are in the household, when the dog goes hunting (if applicable), and when the dog has a concurrent illness. The increased dose is usually started the morning before the stress begins, and continued for a day or two following the end of the stressful event. Astute clients are usually able to identify when their dog needs additional prednisone, and adjust the dose appropriately. However, some clients need frequent reminders, particularly when they present for electrolyte evaluation.

Prognosis

With appropriate treatment and monitoring, the prognosis for dogs with naturally occurring hypoadrenocorticism is excellent. Dogs enjoy a good quality of life, and may participate in normal activities, as long as they are provided with additional prednisone as needed. Consistent medication and patient monitoring must be stressed to owners, as poor medication compliance or prolonging the treatment interval for DOCP, without veterinary approval, may lead to Addisonian crisis.

Atypical Hypoadrenocorticism

Etiology/Pathophysiology

Atypical hypoadrenocorticism refers to hypoadrenocorticism with clinical signs attributable to cortisol deficiency only; electrolyte concentrations are within reference range. At this time, the etiology is unknown. Individual cases may result from different etiologies. In some cases, partial immune-mediated destruction of the adrenal cortex occurs, sparing the zona glomerulosa and aldosterone synthesis. Occasionally, this is an early manifestation of "typical" hypoadrenocorticism, and the glomerulosa is eventually destroyed, leading to concurrent electrolyte abnormalities. In other cases, dogs may actually be aldosterone deficient but able to compensate and maintain normal electrolyte concentrations. The compensatory mechanisms are unclear, but aldosterone deficiency has been documented in patients with normal electrolyte concentrations.

Secondary hypoadrenocorticism, due to ACTH deficiency, results in signs of cortisol deficiency without electrolyte abnormalities, as well. However, secondary HOAC can be identified by low to nonexistent ACTH concentrations. Dogs with atypical HOAC have normally functioning pituitary glands, and usually increased ACTH concentrations.

Epidemiology

Atypical hypoadrenocorticism is an uncommon form of hypoadrenocorticism. However, due to its vague clinical signs and lack of electrolyte abnormalities on serum biochemistry, it is likely underdiagnosed.

Signalment

The signalment for atypical HOAC is similar to that of typical HOAC. Young to middle-aged dogs are predisposed, as are poodles, West Highland white terriers, Great Danes, and NSDTRs. However, any breed of any age may be affected.

History and Clinical Signs

Historical findings and clinical signs associated with atypical HOAC are similar to those in typical HOAC. Addisonian crisis does not usually occur with atypical HOAC, partially because hyperkalemia and hyponatremia are not present. Nonspecific signs such as weight loss, lethargy, and anorexia predominate, while gastrointestinal signs such as vomiting and diarrhea are also common. Atypical HOAC should always be considered in dogs with chronic GI signs, especially if they are more common when the dog is stressed (such as "stress colitis"). Seizures secondary to hypoglycemia and megaesophagus are uncommon, but atypical HOAC should remain on the rule-out list for dogs with megaesophagus and hypoglycemia, even if they have normal electrolyte concentrations. PU/PD may also be reported in dogs with atypical HOAC.

Diagnosis

Dogs with atypical HOAC may have many of the same clinicopathologic abnormalities as dogs with typical HOAC, except for hyperkalemia, hyponatremia, and hypochloremia. Although mild to moderate azotemia is possible, it is less common and less severe than in typical HOAC. Anemia and hypoalbuminemia are more common in dogs with isolated cortisol deficiency, likely because typical Addisonians are more hemoconcentrated (hypovolemic) than atypical Addisonians. Hypocholesterolemia is also common, and hypoglycemia can also occur and result in seizures.

Definitive diagnosis of atypical hypoadrenocorticism relies upon the ACTH stimulation test, and is interpreted the same way as with typical hypoadrenocorticism. A more economical way to rule out atypical HOAC is to measure the baseline cortisol; patients with cortisol >2-3 µg/dL do not have the disease. However, if the baseline cortisol is <2 µg/dL, an ACTH stimulation test is necessary for diagnosis. Although atypical HOAC is uncommon, it is easily treated and has a good prognosis. Thus, testing is indicated in patients with unexplained GI signs, lethargy, and weight loss.

Patients with both atypical HOAC and secondary HOAC have similar clinical signs of isolated cortisol deficiency. Endogenous ACTH concentrations should be measured to differentiate between secondary and primary hypoadrenocorticism. High concentrations indicate that the patient has primary HOAC (due to lack of cortisol's negative feedback on the pituitary), whereas low to unmeasurable concentrations are consistent with secondary HOAC. If secondary HOAC is diagnosed, imaging of the brain is recommended, to rule out a pituitary/hypothalamic lesion; however, a distinct anatomic lesion may not be identified.

Therapy

Therapy for atypical HOAC consists of glucocorticoid replacement, usually with prednisone, given at 0.1–0.25 mg/kg/day. Some patients do well on even lower dosages, particularly big dogs. The author has used dosages as low as 0.03 mg/kg/day. The goal is to administer enough prednisone to control the clinical signs of HOAC, while not causing steroid side-effects. Additional prednisone (2–4 times the normal dose) is recommended during times of stress.

Approximately 10% of dogs with atypical hypoadrenocorticism develop signs of mineralocorticoid deficiency (electrolyte abnormalities) weeks to months after the initial diagnosis (usually within one year). It is impossible to predict which dogs will develop electrolyte abnormalities, so reevaluation of the electrolytes is recommended at one and three months following initial diagnosis, and then every six months thereafter.

Prognosis

Prognosis for atypical hypoadrenocorticism is excellent, provided that the owners continue to administer medication as recommended. Almost all patients die of disease unrelated to hypoadrenocorticism.

Hypoadrenocorticism in Cats

Etiology/Pathophysiology

Hypoadrenocorticism is rare in cats. Most cases are idiopathic, but suspected to be due to immune-mediated destruction of the adrenal cortex. Neoplastic infiltration and abdominal trauma have also been reported to cause HOAC in cats. Concurrent glucocorticoid (cortisol) and mineralocorticoid (aldosterone) deficiency occurs in most cats, and isolated glucocorticoid deficiency ("atypical" hypoadrenocorticism) is rare. Secondary iatrogenic hypoadrenocorticism can result from glucocorticoid or progestogen (megesterol acetate) administration, but this is uncommon. In cases of secondary iatrogenic HOAC, the administered glucocorticoid or progestogen causes decreased ACTH production from the pituitary gland. Decreased ACTH production results in atrophy of the zonae fasciculata and reticularis, leading to decreased cortisol production. Since ACTH is not required for the synthesis of aldosterone from the zona glomerulosa, electrolyte abnormalities do not occur.

Epidemiology

Hypoadrenocorticism is rare in cats, with fewer than 50 cases reported in the literature.

Signalment

Unlike in dogs, there are no sex, age, or breed predispositions. Affected cats range in age from 1.5 to 14 years. The majority of reported cases have been domestic short- or long-haired cats, but two British shorthair cats have also been reported.

History and Clinical Signs

Clinical signs and historical findings are similar to those described in dogs. The signs may be chronic (months) or acute (several days), and may wax and wane. Owners may note improvement following treatment with fluids and/or glucocorticoids. The most commonly reported signs include lethargy, inappetence, and weight loss. Vomiting, PU/PD, and constipation can also occur. In contrast to dogs, diarrhea has not been reported.

Physical examination usually reveals depression, weakness, dehydration, and hypothermia. About half of the cats present in hypovolemic shock, characterized by prolonged capillary refill time and weak femoral pulse. Collapse, ataxia, bradycardia, and abdominal pain are less common.

Diagnosis

Clinicopathologic findings in cats with HOAC are similar to those in dogs with HOAC. Hyponatremia and hyperkalemia are almost always present, although one may occur without the other. Most cats are also hypochloremic, azotemic, and hyperphosphatemic. Although the azotemia is usually prerenal, most Addisonian cats have a urine specific gravity <1.030. Hypercalcemia, hypoglycemia, and acidemia are less common than in Addisonian dogs, but can be severe. Alanine aminotransferase, alkaline phosphatase, and bilirubin may be mildly increased. Complete blood count may reveal mild anemia and lymphocytosis; alternatively, lack of a stress leukogram (neutrophilia

and lymphopenia) in a stressed cat should raise suspicion for HOAC.

Diagnostic imaging is not necessary to diagnose HOAC, but is often performed as part of the diagnostic work-up prior to suspicion for HOAC. Thoracic radiographs may reveal pulmonary hypoperfusion or microcardia due to dehydration; abdominal imaging is usually unremarkable. The ECG may reveal bradycardia, but the other classic ECG abnormalities (spiked T-wave, decreased R-wave, and absent P-wave) are less consistent in hyperkalemic cats, though the reason for this is unclear.

Definitive diagnosis of HOAC in cats relies upon an ACTH stimulation test. A serum sample is taken prior to administering 5 µg/kg cosyntropin (or tetracosactrin), which is given intravenously. A poststimulation sample is collected one hour later. The diagnosis of HOAC is consistent with a poststimulation cortisol concentration of <2 µg/kg.

Measurement of endogenous ACTH concentrations can help determine whether an Addisonian cat with normal electrolyte concentrations has primary or secondary HOAC. High concentrations are consistent with primary disease. Low concentrations are expected in cats with secondary disease.

Therapy

Treatment of feline HOAC is similar to treatment of canine HOAC. Intravenous crystalloid fluids (0.9% NaCl, LRS or Plasma-Lyte A) should be administered to cats in Addisonian crisis. One-third of a shock dose (40–60 mL/kg) is given, and then the patient is reassessed. Dexamethasone (0.15 mg/kg BID) is given intravenously until oral prednisolone is tolerated. Prednisolone is started at 1 mg/kg/day, and slowly tapered to 0.1–0.2 mg/kg/day following discharge. Two to four times the dose should be given when the cat experiences stress (going to the veterinarian, visitors in the house, concurrent illness).

Mineralocorticoid supplementation can be provided using either desoxycorticosterone pivalate (DOCP, 2.2 mg/kg every 25 days) or fludrocortisone (0.05–0.1 mg/cat, SID–BID). Dosage adjustments are made based on electrolyte concentrations, as described for dogs.

Prognosis

Cats in Addisonian crisis tend to respond to treatment more slowly than dogs, and may require 3–5 days for significant improvement. Long-term prognosis for cats with hypoadrenocorticism is good, provided that the owners continue to administer medication and monitor as directed.

Hyperaldosteronism in Cats

Etiology/Pathophysiology

Primary hyperaldosteronism (PHA) results from excessive aldosterone production by the zona glomerulosa of the adrenal cortex, and usually leads to clinical signs related to hypokalemia and/or systemic hypertension. Unilateral adrenocortical tumors are the most common cause; carcinomas are more common than adenomas. Bilateral adenomas occur rarely. Idiopathic adrenal hyperplasia ("non-tumorous hyperaldosteronism"), characterized by bilateral micronodular hyperplasia of the zona glomerulosa, is reported less frequently than the tumorous forms. However, since definitive diagnosis requires histopathologic confirmation, and these cats are treated medically instead of surgically, idiopathic adrenal hyperplasia is likely underdiagnosed.

Aldosterone is the most important endogenous mineralocorticoid in dogs and cats. It primarily acts on the principal cells of the distal tubules and collecting ducts in the kidney, stimulating sodium and water reabsorption (thus expanding the vascular volume), and promoting potassium and acid excretion.

Aldosterone is regulated by the renin-angiotensin-aldosterone system (RAAS). Decreased renal perfusion pressure and decreased delivery of sodium to the distal tubules stimulate the release of renin from juxtaglomerular cells. Renin cleaves angiotensinogen, produced by the liver, into angiotensin I. Angiotensin I is then converted to angiotensin II by angiotensin converting enzyme. Angiotensin II then stimulates aldosterone synthesis via the activity of aldosterone synthase. Hyperkalemia also has a direct stimulatory effect on aldosterone secretion, with ACTH contributing to a lesser degree.

Secondary hyperaldosteronism ("hyperreninemic hyperaldosteronism") results from increased renin produced in response to reduced arterial blood volume, such as occurs with congestive heart failure, renal failure, and liver failure. Primary hyperaldosteronism, however, is due to autonomous secretion of aldosterone from the zona glomerulosa, and is associated with low plasma renin activity. It is sometimes referred to as "hyporeninemic hyperaldosteronism" for this reason.

In addition to expected consequences of hyperaldosteronism, such as hypokalemia and hypertension, some cats with PHA develop progressive renal disease. There is evidence that aldosterone itself mediates vascular fibrosis and inflammation, resulting in glomerular sclerosis, hyaline arteriolar sclerosis, tubular atrophy, and interstitial fibrosis. Thus, in azotemic patients with

hypokalemia and/or hypertension, determining whether hyperaldosteronism is primary (PHA) or secondary (hyperreninemic hyperaldosteronism) can be a diagnostic challenge.

Epidemiology

Primary hyperaldosteronism is rare. However, because several of the diagnostic findings associated with PHA are also associated with chronic kidney disease, PHA is likely underdiagnosed.

Signalment

Middle-aged to older cats are predisposed (median age 13 years; range 5–20 years), but there does not appear to be a sex or breed predisposition.

History and Clinical Signs

The most common clinical signs are associated with hypokalemia and systemic arterial hypertension; polyuria, polydipsia, weight loss, and a palpable abdominal mass may also be noted (Box 11.1). Hypokalemic myopathy can be acute or chronic in onset and clinical signs can be mild or severe. Affected cats often have cervical ventroflexion, a plantigrade stance, difficulty jumping, and/or severe weakness. Forelimb stiffness followed by acute collapse and dysphagia have also been reported. Whereas most cats with PHA caused by adrenocortical tumors present for hypokalemic myopathy, fewer of the cats with idiopathic adrenal hyperplasia display this clinical feature.

Ocular changes due to hypertension are more common with idiopathic adrenal hyperplasia, and may include retinal detachment and sub- and intraretinal and intravitreal hemorrhages. Cats with these lesions usually present for acute-onset blindness, hyphema, and/or mydriasis (Figure 11.1). Subclinical retinal lesions are often identified in cats with myopathy, as well.

Box 11.1 Clinical findings in cats with hyperaldosteronism

Due to hypokalemia:
- Cervical ventroflexion
- Plantigrade stance
- Difficulty jumping
- Weakness

Due to hypertension (systolic BP >180 mmHg):
- Ocular changes
- Acute blindness
- Hyphema
- Mydriasis

Polyuria/polydipsia



Figure 11.1 A 13-year-old male neutered domestic shorthair presented for acute blindness due to severe hypertension (>250 mmHg, as measured by Doppler). Note the mydriasis with complete bullous retinal detachment and retinal hemorrhages. *Source:* Photo courtesy of Martin Coster, DVM, MS, DACVO.

Diagnosis

The diagnostic evaluation of a cat for PHA includes blood pressure measurement, complete blood count, serum biochemistry, urinalysis, imaging, and specific hormone testing. Cats with idiopathic adrenal hyperplasia are more likely to be hypertensive, with a median systolic blood pressure of 210 mmHg (range, 185–270 mmHg) in one study. Median systolic BP in cats with neoplasia was 185 mmHg (range, 160–250 mmHg) in another study. Hypertension is often difficult to control in cats with PHA, and PHA should be suspected in cats with refractory hypertension.

The CBC does not usually reveal any significant abnormalities in patients with PHA. Moderate to severe hypokalemia is often evident on the serum biochemistry profile, although not all cats with PHA are hypokalemic. Significant signs of hypokalemic myopathy are not usually obvious until potassium concentrations decrease to less than 2.5 mmol/L, but this is variable. Creatine kinase is markedly increased in cases of hypokalemic myopathy. Hypernatremia is uncommon, likely because of dilution from volume expansion.

Some cats with PHA are also mildly to moderately azotemic, and often develop progressive renal disease as a consequence of PHA. This is more common in cats with idiopathic adrenal hyperplasia. Determining whether hyperaldosteronism is a consequence of chronic kidney disease, or vice versa, can be difficult and relies on measurement of plasma renin activity, which is not readily available in the US. Interestingly, phosphorus concentration is often at the lower end of the reference range and does not become increased with progressive azotemia in cats with PHA. The reason for this is unclear but may be

related to hypersecretion of parathyroid hormone. Hypercalcemia is also present in some of these cats. Urine specific gravity is variable at the time of PHA diagnosis, ranging from 1.010 to 1.040 (mean 1.029).

Concurrent diseases reported in cats with PHA include hyperthyroidism, diabetes mellitus, and hyperprogesteronism. Thus, additional testing is prudent if a patient with suspected PHA has clinical signs that cannot be explained.

Since PHA caused by adrenocortical tumors and adrenal hyperplasia has different treatment recommendations, abdominal and thoracic imaging is recommended. Thoracic radiographs can help identify pulmonary metastases. Abdominal ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) can be used to visualize the adrenal glands and potential extension of a tumor into the caudal vena cava. Reported ranges for unilateral adrenocortical tumors range from 1–3.5 × 1–2.5 cm on US. The contralateral adrenal may not be seen, or may appear normal. CT and/or MRI is often used preoperatively to assess invasion of the caudal vena cava. In cats with bilateral adrenal hyperplasia, adrenal glands may be thickened, partially mineralized, or normal upon US examination. Unfortunately, imaging is not always definitive. Pulmonary metastases and caval invasion may be missed, bilateral disease may be present when unilateral disease is suspected, and an identified adrenal mass may be nonfunctional or producing something other than aldosterone, such as progesterone, cortisol, or catecholamines.

The gold standard for diagnosis of PHA is the aldosterone:plasma renin activity ratio, since aldosterone concentration should be increased with concurrent decrease in plasma renin activity (PRA), resulting in an increased ratio. However, measurement of PRA is difficult and inconsistently commercially available, limiting the utility of the ratio.

The plasma aldosterone concentration (PAC) is the most widely available test for confirmation of hyperaldosteronism. It is increased in all reported cases of PHA due to adrenocortical carcinomas or adenomas, but may only be mildly increased or within reference range in cats with adrenocortical hyperplasia. Additionally, an increased PAC does not differentiate between primary and secondary hyperaldosteronism. Measurement of the PAC:PRA ratio is useful in cases in which PAC is within reference range, and when clinical information does not differentiate between primary and secondary hyperaldosteronism (e.g., adrenal glands are of normal size and/or azotemia is present).

Adrenocorticotropic hormone stimulation testing is not usually necessary for the diagnosis of PHA. However, suppression testing is used to diagnose PHA in people. In a small study in cats, an oral fludrocortisone suppression test helped to differentiate some cases of PHA from other causes of arterial hypertension. Fludrocortisone was administered (0.05 mg/kg q12h) for four days, and urine was collected to measure the urine aldosterone to creatinine ratio (UACR) prior to the first dose, and the morning after the last evening dose of fludrocortisone. All of the non-PHA cats had >50% suppression of the UACR, while only 3/9 of the PHA cats had >50% suppression of the pretest UACR. This test has its limitations, including the availability of urine aldosterone measurement, but may be useful in PHA suspects with PAC within reference range.

Therapy

Initial treatment of PHA is aimed at controlling hypertension and hypokalemia and medical stabilization is recommended prior to adrenalectomy for adrenal tumors. Spironolactone is a competitive aldosterone receptor antagonist that helps control both hypertension and hypokalemia. The starting dose is 2 mg/kg q12h but this dose may be increased to 4 mg/kg q12h. Spironolactone has been reported to cause facial dermatitis in Maine Coon cats treated for hypertrophic cardiomyopathy, but this has not been reported in cats with PHA. Amlodipine, a calcium channel blocker, is given at 0.625–1.25 mg/cat q12–24h, to help control hypertension. Potassium gluconate is administered at a dose of 2–6 mEq PO q12h to alleviate hypokalemia. While adjusting medication doses, blood pressure and potassium concentration should be measured weekly. Myopathy is expected to resolve, although normokalemia may not be achieved. Hypertension usually resolves with appropriate therapy, but the vision loss is almost always permanent.

Patients with idiopathic adrenal hyperplasia should be treated medically. Following medical stabilization, adrenalectomy is ideal for patients with unilateral adrenocortical neoplasia. However, surgery is associated with a high mortality rate (30% in one study), particularly if the vena cava is affected. Additionally, some owners have financial limitations that prohibit surgery, and some cats have concurrent conditions or metastasis. If the owner elects not to pursue surgical therapy, medical management can be pursued long term.

The most common complication associated with adrenalectomy is hemorrhage; in one study, 4/10 cases experienced intraoperative or perioperative hemorrhage. One patient was stabilized with autotransfusion and another laparotomy, but the other three patients were euthanized following failed attempts at surgical hemostasis.

Postsurgical monitoring includes blood pressure and potassium monitoring, at least daily for 2–3 days. Amlodipine and spironolactone are discontinued postoperatively, and potassium supplementation is tapered until the potassium concentration normalizes.

Prognosis

Cats with unilateral adrenocortical neoplasia that survive the perioperative period have good long-term survival (up to 1803 days); patients with adenocarcinomas appear to have the same prognosis as cats with adenomas. Medically managed cats have reported survival times from several months to years. The prognosis for cats with adrenocortical hyperplasia is not well defined, but most cats eventually succumb to chronic kidney disease.

Further Reading

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12

Diabetes Mellitus in Dogs and Cats

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Etiology/Pathophysiology

Glucose is the primary source of energy in the body. Blood glucose concentrations are tightly controlled by a feedback system of endocrine hormones. Insulin is produced by the pancreatic beta-cells in response to increased blood glucose, and promotes storage of glucose, fatty acids, and amino acids as glycogen, fat, and protein. Insulin promotes uptake of glucose into most body cells for use, promotes storage of glucose as glycogen in liver and muscle, and inhibits gluconeogenesis. Cortisol, glucagon, epinephrine, and growth hormone oppose the actions of insulin, promoting catabolism of stored carbohydrate into glucose, stored triglycerides into free fatty acids and ketone bodies, and stored protein into amino acids. Because they oppose insulin's effects, these four hormones are called "counterregulatory hormones" (Table 12.1).

Diabetes mellitus is a disease characterized by hyperglycemia and associated clinical signs. It is classified into four broad types in human and veterinary medicine.

- Type 1 diabetes is a result of immune-mediated beta-cell destruction, usually leading to an absolute insulin deficiency. The majority of neutered diabetic dogs have type 1 diabetes, but this form appears to be very rare in cats. The etiology of type 1 diabetes in dogs is multifactorial, and likely involves genetic factors and poorly understood environmental factors, which trigger beta-cell injury and inflammation. In type 1 diabetes, following nonspecific beta-cell injury, autoimmunity then propagates continued destruction of beta-cells, preventing regeneration after injury. Factors which trigger the gastrointestinal immune system are implicated in human type 1 diabetes, and in dogs, pancreatitis is a potential triggering factor. As in humans, there is a seasonal influence, with the incidence peaking in winter. Environmental factors such as chronic insulin resistance secondary to glucocorticoid administration or obesity, and diseases which antagonize insulin's actions would be expected to hasten onset of clinical signs when superimposed on a reduced capacity to secrete insulin as a result of immune-mediated beta-cell destruction.
- Type 2 diabetes is characterized by insulin resistance with concomitant beta-cell dysfunction. In developed countries, the majority of feline diabetics are type 2. Insulin resistance is multifactorial and associated with genetic factors, obesity, physical inactivity, male gender, and glucocorticoid steroids. Beta-cell destruction is initiated and propagated by a variety of factors, not yet fully understood, that lead to a decline in insulin secretory capacity. When the increased demand to produce insulin as a result of insulin resistance is superimposed on beta-cell dysfunction, chronic hyperglycemia ensues. Chronic hyperglycemia is toxic to beta-cells and in turn causes injury and death of the beta-cells, reducing insulin production even further.
- "Other specific types of diabetes" includes most other forms in companion animals, including drug-induced diabetes (usually steroid use), endocrinopathies that antagonize insulin action (acromegaly, hyperadrenocorticism), or exocrine pancreatic disease. Chronic pancreatitis is the most common cause of canine diabetes in this category, accounting for approximately 30% of cases. Approximately 25–30% of poorly controlled diabetic cats have acromegaly.
- Gestational diabetes is not a significant cause of diabetes in companion animals in the US, as most companion animals are desexed. Pregnancy and diestrus are associated with increased progesterone concentrations, which uniquely in the bitch stimulate the mammary glands to produce growth hormone. Both hormones oppose insulin's glucose lowering effects, leading to periodic insulin resistance in intact female dogs, and diestrus-associated diabetes. Concurrent obesity would be expected to exacerbate this insulin resistance.

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Table 12.1 Effects of insulin and counterregulatory hormones on carbohydrate metabolism

Hormone	Effect on carbohydrates
Cortisol	Increases blood glucose • ↓ Glucose uptake by cells • ↑ Gluconeogenesis • ↑ Glycogenolysis • Inhibits insulin
Glucagon	Increases blood glucose • ↑ Gluconeogenesis • ↑ Glycogenolysis • Inhibits insulin
Epinephrine	Increases blood glucose • ↑ Gluconeogenesis • ↑ Glycogenolysis
Growth hormone	Increases blood glucose • ↓ Glucose uptake by cells • ↑ Gluconeogenesis
Insulin	Decreases blood glucose • ↑ Glucose uptake by all cells except liver, brain, red blood cells • ↑ Glycogen formation • ↓ Gluconeogenesis, glycogenolysis

Epidemiology

Diabetes mellitus is the most common disorder of the endocrine pancreas in dogs and cats. The incidence in dogs is approximately 0.13%, and the incidence in cats is approximately 0.5%, depending on the study population, and is influenced by geographical location and type of veterinary practice (referral or primary accession).

Signalment

Diabetes mellitus is a disease of middle-aged to older companion animals, with peak prevalence of 7–12 years of age in dogs and 10–13 years in cats. Intact female dogs and male cats are predisposed. Various breeds of cat and dog are overrepresented, and predisposed breeds vary with geographic area. For example, in the USA, dog breeds at increased risk include miniature schnauzer, Samoyed, and miniature poodle, whereas in the UK, in addition to miniature schnauzer and Samoyed, breeds more commonly seen include Tibetan, cairn, border and Yorkshire terriers and Labrador retrievers. In cats, Burmese are overrepresented in Australia, New Zealand and the UK, and in the USA, Maine Coon, domestic longhair, Russian blue and Siamese. Norwegian forest cats and Burmese are at increased risk in Scandinavia.

History and Clinical Signs

Diabetes is characterized by hyperglycemia resulting from insufficient insulin production or function. Hyperglycemia causes the hallmark clinical signs of polyuria, polydipsia, polyphagia, and weight loss that distinguish diabetes. Some dogs and up to 50% of cats present with decreased appetite. Other clinical signs include hepatomegaly, lethargy, cataract formation (dogs), and diabetic neuropathy (mainly cats). Signs are usually slowly progressive over weeks to months.

Polyuria and Polydipsia

Relative or absolute insulin deficiency in diabetes causes reduced blood glucose uptake by liver, muscle, and adipose tissues, and unchecked glucose production in the liver, which result in hyperglycemia. In the glomerulus of the kidney, nearly all the blood glucose is passively filtered into the ultrafiltrate. In the proximal tubule of the kidney, receptors are capable of resorbing only a fixed amount of glucose from the ultrafiltrate. This fixed amount is called the renal threshold, and is approximately 200 mg/dL in dogs and 250–290 mg/dL in cats. When the amount of glucose in the blood exceeds this renal threshold, glucose remains in the ultrafiltrate, acting as an osmotic diuretic and causing polyuria and compensatory polydipsia.

Polyphagia

Animals with uncomplicated diabetes mellitus may have an increased appetite. This is governed by central mechanisms, including increased hunger triggered by nutrient loss (predominantly glucose), and lack of insulin-mediated uptake of glucose into cells of the satiety center, which normally inhibits hunger.

Weight Change

Obesity is a common co-morbidity in middle-aged and senior diabetic dogs and cats. It reduces insulin sensitivity, and when superimposed on beta-cell loss from any cause, will hasten onset of hyperglycemia and clinical signs. However, untreated diabetes mellitus leads to weight loss, due to malassimilation of nutrients absorbed from the gut, and urinary loss of glucose and amino acids. Dogs in which pancreatitis is either a complicating co-morbidity or a cause of their diabetes may later progress to exocrine pancreatic insufficiency (EPI), which exacerbates weight loss, and may be first evident as increased frequency of defecation.

Hepatomegaly

Insulin promotes storage of lipid in adipose tissue. Relative or absolute lack of insulin promotes lipid catabolism into fatty acids, which are transported to the liver. The liver uses this excess of fatty acids to produce and store triglycerides (lipids), leading to hepatic lipidosis and hepatomegaly. In the diabetic liver, excess fatty acids are also used for gluconeogenesis, which worsens hyperglycemia, and are converted into ketone bodies, which cause ketoacidosis.

Cataracts

The pathogenesis of cataracts in diabetics is multifactorial and incompletely understood. The enzyme aldose reductase catalyzes the conversion of glucose to sorbitol, and the enzyme sorbitol dehydrogenase catalyzes the conversion of sorbitol to fructose. In the eye, the formation of sorbitol occurs more rapidly than its degradation into fructose. In the diabetic eye, a large amount of sorbitol is produced and acts as an osmotic agent within the lens fibers, drawing water into the lens, leading to lens swelling, lens fiber collapse, and ultimately cataract formation.

Lens-induced uveitis is common in diabetic dogs due to the rapid onset of the cataracts. Lens-induced uveitis occurs when the lens becomes swollen and the stretched lens capsule allows leakage of cataract lens proteins into the anterior and posterior chambers. This, in turn, causes iris and ciliary body vasculitis, resulting in serum protein leakage into the aqueous humor and prostaglandin release from the iris, which continue the uveitis.

Diabetic cataracts are found in 80% of diabetic dogs within 16 months (Figure 12.1). Diabetic cats are rarely clinical for cataracts, though recent studies suggest that mild diabetes-associated lens opacity is more common than previously thought. Topical administration of

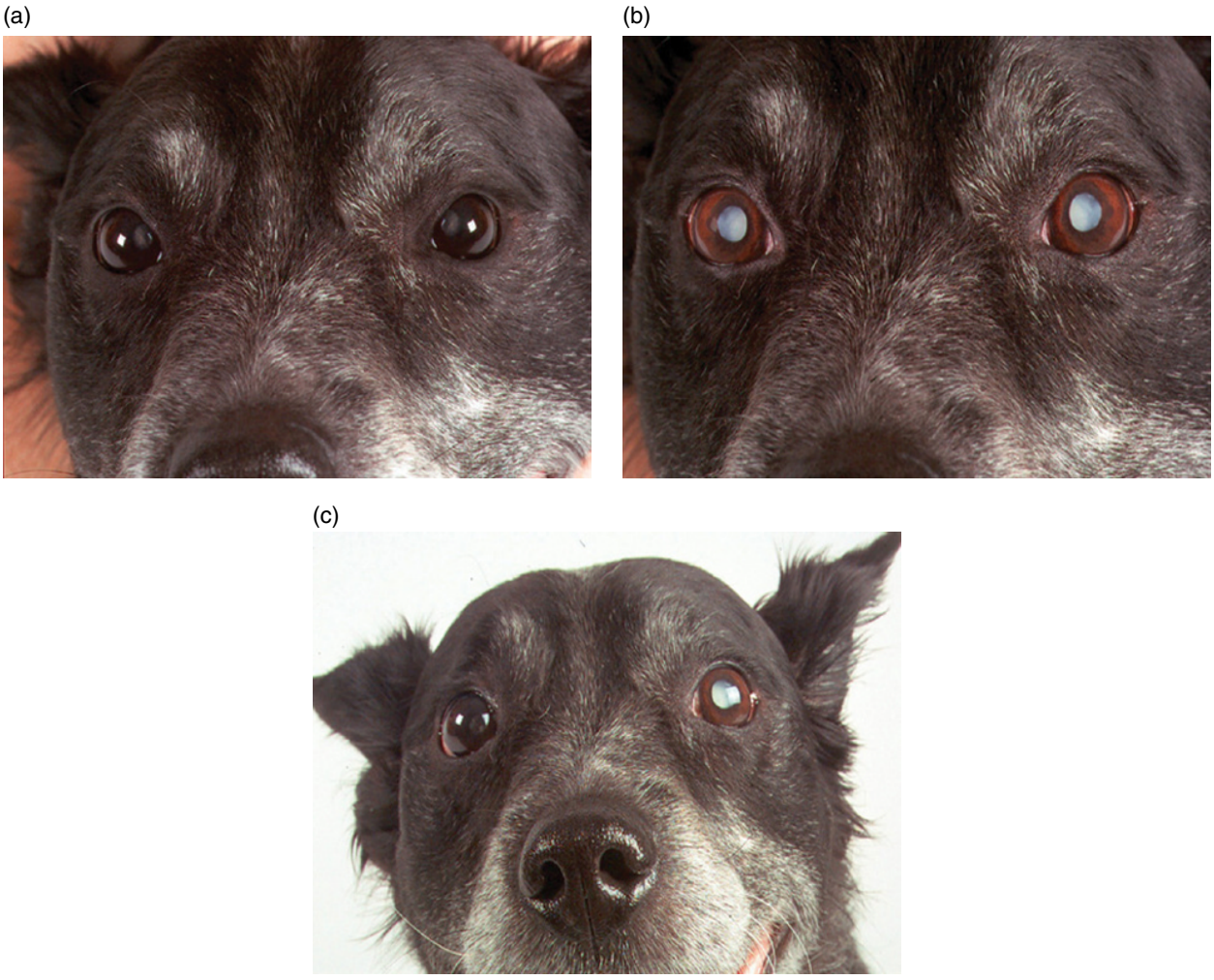


Figure 12.1 Diabetic cataracts in a dog. (a) An 11-year-old cross-bred dog photographed shortly after diagnosis of diabetes mellitus. (b) The same dog three months later. Diabetic cataracts had developed rapidly and the owners reported sudden vision loss. (c) The same dog following phacoemulsification surgery to remove the cataract from the right eye. *Source:* Fleeman and Rand 2000. Reproduced with permission.



Figure 12.2 Cat with plantigrade stance. *Source:* Rand 2013. Reproduced with permission of John Wiley & Sons.

aldose reductase inhibitors three times daily retards progression of ocular changes.

Diabetic Neuropathy

The majority of diabetic dogs, cats, and people have microscopic evidence of nerve injury, including demyelination, remyelination, and axonal degeneration. However, less than 50% of cats with diabetes mellitus have clinical neuropathy with hindlimb paraparesis, a plantigrade stance, and decreased ability to jump, as well as reduced reflexes and proprioceptive deficits (Figure 12.2). Weakness and muscle wasting are present in 50% of diabetic cats. Clinical diabetic neuropathy is rarely recognized in dogs.

Diagnosis of Diabetes Mellitus

Diagnosis of diabetes mellitus is based on demonstration of persistently increased blood glucose concentration, and is typically associated with glucosuria and classic clinical signs of polyuria and polydipsia. In dogs, blood glucose concentrations above the renal threshold of 200 mg/dL (11 mmol/L) are considered diabetic. In humans and cats, blood glucose concentrations persistently above normal but below that considered diabetic (>117 to < 180 mg/dL; >6.5 to <10 mmol/L) are associated with increased risk of developing diabetes and considered prediabetic in cats. Persistent hyperglycemia of ≥180 mg/dL (10 mmol/L) should be considered diabetic, but it will only be accompanied by clinical signs once it exceeds the renal threshold of 250–290 mg/dL (14–16 mmol/L). Stress hyperglycemia and postprandial hyperglycemia may complicate diagnosis of diabetic hyperglycemia in cats.

The presence of elevated plasma fructosamine (approximately >400 µmol/L; reference range varies by laboratory) or glycated hemoglobin (A1c) (reference range depends on assay used) in symptomatic pets with hyperglycemia and glucosuria helps confirm the diagnosis of diabetes mellitus. However, fructosamine is not consistently increased above the reference range in cats until blood glucose is approximately >300 mg/dL (>17 mmol/L), making it unsuitable for differentiating stress hyperglycemia from diabetes when blood glucose is 300 mg/dL (17 mmol/L) or less. In contrast, unpublished data suggest the new Baycom A1c is more sensitive at distinguishing transient hyperglycemia secondary to stress from persistent hyperglycemia of diabetes or prediabetes. Fructosamine is formed when blood glucose irreversibly binds plasma proteins (mainly albumin). Fructosamine concentration is roughly proportional to the average blood glucose concentration over the preceding 7–14 days, which is the half-life of albumin in dogs and cats. Therefore, while a single blood glucose measurement reflects blood glucose at one moment in time, fructosamine is used as an indicator of blood glucose over a longer period of time and is used to document persistent hyperglycemia. Similarly, glycated hemoglobin is formed when blood glucose irreversibly binds hemoglobin (especially hemoglobin A1), and its concentration reflects the average blood glucose concentration over approximately 70 days (erythrocyte lifespan).

A new test (Baycom A1c) validated for cats is available, and may be useful for differentiating cats with blood glucose in the normal range from those with a persistent mild hyperglycemia, for example prediabetic cats with glucose concentrations of 130–180 mg/dL (7.2–9.9 mmol/L) or cats with subclinical diabetes (>180 mg/dL up to the renal threshold of 250–290 mg/dL; >10 mmmo/L to 14–16 mmol/L).

In cats, stress hyperglycemia may be confused with diabetic hyperglycemia on initial presentation. Stress hyperglycemia is usually (but not always) lower than diabetic hyperglycemia, with median blood glucose in stressed cats around 305 mg/dL (16.9 mmol/L) with a wide range (126–505 mg/dL; 7–28.1 mmol/L). Median blood glucose in newly diagnosed diabetic cats is around 475 mg/dL (26.4 mmol/L) with a wide range of 180–1100 mg/dL (10–61. mmol/L) that overlaps with the range of stress hyperglycemia. Diabetic hyperglycemia and glucosuria will be persistent over time, and will always be accompanied by typical clinical signs if blood glucose is above the renal threshold. In contrast, stress hyperglycemia typically resolves in 3–4 hours but may take 24 hours in a very few cats. Therefore, in most cats, an easy way to rule out persistent hyperglycemia of diabetes or prediabetes, is to test a repeat sample from the ear after the cat has been sitting quietly in a cage for 4 hours; in the majority of cats with stress hyperglycemia, blood glucose will be <117 mg/dL (6.5 mmol/L).

Fructosamine is most often normal in cats with stress hyperglycemia, but elevated in diabetic cats that have been markedly hyperglycemic (≥360 mg/dL; 20 mmol/L) for at least 3–5 days. However, a normal fructosamine concentration does not rule out prediabetes or diabetes associated with more moderate hyperglycemia, whereas Hb1c appears more sensitive. Home blood glucose monitoring with a meter calibrated for feline blood may also assist in identifying prediabetic cats with persistent mild elevation of glucose (>117–162 mg/dL; 6.5–9 mmol/L).

A typical work-up for dogs or cats with suspected diabetes mellitus will include a complete blood count, chemistry profile with electrolytes, urinalysis, and urine culture via sterile collection. Some veterinarians routinely use fructosamine or, less commonly, glycated hemoglobin to document persistent hyperglycemia. In dogs, if hypothyroidism or hyperadrenocorticism is suspected, it is best tested after diabetes is regulated, because of the effect of poorly regulated diabetes on interpretation of tests. In intact female dogs, measurement of serum progesterone may also be helpful; elevated progesterone levels in diestrus or pregnancy increase secretion of growth hormone, a counterregulatory hormone, leading to insulin resistance. In cats, a total T4 and feline leukemia virus/feline immunodeficiency virus (FeLV/FIV) test is warranted. Middle-aged to older cats with polyuria/polydipsia, polyphagia, and weight loss should be screened for diabetes mellitus and hyperthyroidism, as the diseases cause similar clinical signs, and may occur concurrently. For patients with atypical or additional clinical signs, consider a thyroid panel (total or free T4 and thyroid-stimulating hormone), insulin like growth factor (IGF-1), trypsinogen-like immunoreactivity (TLI), pancreatic lipase immunoassay (PLI), cobalamin and folate, adrenal function testing, thoracic and abdominal radiographs, and abdominal ultrasound as indicated based on the patient's history and clinical exam findings. Cats with diabetes and blood glucose above the renal threshold have weight loss, and cats with a stable weight or weight gain should be tested for acromegaly. If IGF-1 is in the normal range, but clinical signs are consistent with acromegaly, test again after 6 weeks of insulin therapy.

Therapy

Nearly all veterinary patients with diabetes mellitus are managed with a combination of insulin therapy, diet, and weight management.

Human and veterinary insulins are categorized both by onset and duration of action, and by protein source. Based on onset and duration of action, insulins are short acting, intermediate acting, and long acting. Short-acting insulins are generally used in hospital for intensive blood glucose control, while intermediate- and long-acting insulins are used both in hospital and at home for long-term, daily glycemic control. Based on protein source, insulins are human, human analog (synthetic insulin that is altered from the natural form but retains biological function), bovine, or porcine. Porcine and canine insulin have an identical amino acid sequence, while bovine and feline insulin differ by just one amino acid.

Traditionally, veterinarians have managed canine and feline diabetes with a variety of veterinary or human insulins (Table 12.2). Veterinary insulins include porcine lente (Vetsulin/Caninsulin®, Merck), and protamine zinc human recombinant insulin (ProZinc®, Boehringer Ingelheim Vetmedica). Human insulins or insulin analogs include human-origin lente (no longer available), neutral protamine Hagedorn (isophane, NPH, various manufacturers), glargine (Lantus®, Sanofi-Aventis), detemir (Levemir®, Novo Nordisk), glargine 300 U/mL (Toujeo, Sanofi-Aventis) and degludec (Tresiba®, Novo Nordisk). Premixed combinations of short-acting lispro (Eli Lilly) or aspart (Novo Nordisk) insulin with longer-acting protamine insulin are also available as intermediate-acting insulins (Humalog® Mix 75/25 and Novolog® 70/30, respectively).

The goals of treatment in canine diabetes include resolution of polyuria, polydipsia and abnormal body condition, while avoiding clinical hypoglycemia, diabetic ketoacidosis, urinary tract infections, and other complications through excellent glycemic control. In dogs, American Animal Hospital Association guidelines recommend the use of porcine lente, PZI, or NPH insulins, and a complete and balanced diet that lacks simple carbohydrates.

A stable routine for meals, snacks, and exercise is crucial for good glycemic control; frequent changes in type of food or amount fed should be avoided (Box 12.1). The best diet for diabetic dogs is yet to be determined. Diets recommended include high-fiber/restricted-fat diets, which as a consequence are high in carbohydrate (>45%), and diets with moderate fiber and restricted carbohydrate (<30% metabolizable energy [ME]), which as a consequence are higher in fat and protein. High-fiber diets may help to delay glucose absorption from the gastrointestinal tract and reduce postprandial hyperglycemia. A number of prescription canine diabetic diets are available with increased fiber, although most have carbohydrate levels >45% ME. If used with NPH insulin, these high-fiber diets may exacerbate postprandial hyperglycemia in some dogs, because peak gastrointestinal glucose absorption occurs after peak insulin action, and in these cases are better fed 1–2 hours after insulin administration. High-fiber/moderate-fat diets may cause

Table 12.2 Insulin types used in companion animal medicine and their characteristics

Brand name	Product	Manufacturer	Concentration	Origin	Size
Intermediate acting					
Humulin N	NPH	Eli Lilly	U-100	Human	10 mL vial 3 mL pen
Vetsulin/ Caninsulin	Lente	Merck	U-40	Porcine	10 mL vial 2. mL pen
Humalog Mix 75/25 and 50/50	Lispro (rapid acting) plus lispro protamine (intermediate)	Eli Lilly	U-100	Recombinant human	10 mL vial 3 mL pen
Novolog Mix 70/30; 50/50	Aspart (rapid acting) plus aspart protamine (intermediate)	Novo Nordisk	U-100	Recombinant human	10 mL vial 3 mL pen
Long acting					
ProZinc	PZI (protamine zinc)	Boehringer Ingelheim	U-40	Recombinant human	10 mL vial
Lantus	Glargine	Sanofi-Aventis	U-100	Recombinant human analog	10 mL vial 3 mL pen
Toujeo	Glargine	Sanofi-Aventis	U-300	Recombinant human analog	1.5 mL pen
Detemir	Levemir	Novo Nordisk	U-100	Recombinant human analogue	10 mL vial 3 mL pen
Tresiba	Degludec	Novo Nordisk	U-100, U-200	Recombinant human analog	10 mL vial 3 mL pen

Box 12.1 Dosing protocol for dogs on lente, NPH, glargine or detemir

- Starting dose is 0.5 U/kg administred BID for NPH, lente (Caninsulin/Vetsulin, Merck) and glargine (Lantus, Sanofi-Aventis) insulin in dogs. Note starting dose for dogs on detemir (Levemir, Novo Nordisk) is 0.125 µ/kg BID. Dogs are on average four times more sensitive to detemir than other insulin.
- Home blood glucose monitoring is recommended using a meter calibrated for dog blood. Continuous or flash glucose monitoring systems are also very useful for assessing duration of action and adjusting insulin dose, but they measure interstitial blood glucose and are not calibrated for dogs. Their accuracy for determining actual nadir blood glucose concentration is poor.
- In the intitial stabilization phase, reassess dogs weekly. Feed a prescription diet formulated for diabetic dogs and keep amount fed and type of diet constant on a daily basis. Low carbohydrate is best when using lente, glargine or determir. Adjust amount of energy fed to achieve and maintain ideal body weight. If excessive weight loss occurs with a diabetic diet, swap to a premium maintenance diet with low carbohydrate and moderate fiber content.
- Increase insulin dose when the nadir (lowest) glucose concentration is >145 mg/dL (8 mmol/L) and when the blood glucose measurements obtained just prior to the morning and evening insulin injection are both ≥180 mg/dL (10 mmol/L).
- Do not change insulin dose when the nadir is 90–145 mg/dL (5–8 mmol/L) and when the blood glucose measurements just prior to the morning and evening insulin injection are both ≥180 mg/dL (10 mmol/L).
- Decrease insulin dose either when the nadir is <90 mg/dL (5 mmol/L) or when at least one of the blood glucose measurements just prior to the morning and evening insulin injection is <180 mg/dL (10 mmol/L).
- Once the dog is well controlled, the target nadir glucose concentration can be lower, e.g., 70–110 mg/dL (4–6 mmol/L).
- Assessment of the dog's clinical signs determines the magnitude of the change in insulin dose. When clinical signs of uncontrolled diabetes (water drunk >70 mL/kg/day, ketonuria, or lethargy) are present, increase insulin dose by 20% rounded down to the nearest unit. When dog has shown no clinical signs during the preceding 2 weeks, insulin dose adjust by 1 unit. Similarly, when reducing dose, adjust down by 1 unit if no clinical signs, but by 20% if signs of hypoglycemia.
- The protocol for serial blood glucose evaluation comprises administration of the dog's usual meal and insulin dose in the morning and 12 hours later at night and blood glucose measurement with a portable glucose meter every 2 hours for 12 hours beginning immediately prior to the morning insulin injection and meal until immediately before the next insulin injection.

Results of serial blood glucose concentration testing determine whether the insulin dose should be increased, left unchanged, or decreased. Be conservative with dose increases because severe clinical hypoglycemia kills dogs.

- Dogs are considered to have stable glycemic control when the following criteria are all met over 2 months: (a) fluctuation of insulin dose by 1 unit or less, (b) water drunk <70 mL/kg/day, (c) stable body weight, and (d) absence of ketonuria. The period required to achieve stablization ranges from 3 to 10 months (median 7 months).
- If duration of action of NPH or lente insulin apprears to be substantially less than 12 hours and signs of poor control persist, try detemir if the dog is >5–10 kg (note lower dose with detemir). If insulin sensitivity is normal, dosing dogs weighing <5–10 kg can be problematic with detemir. If necessary, it can be diluted with saline or sterile water or a special diluting solution from the manufacturer. Alternatively, glargine 300 U/ml (Toujeo) appears to be useful in some poorly controlled dogs and is best combined with a low carbohydrate diet.

significant weight loss in some diabetic dogs, and thus are not suitable for most lean or underweight dogs. A variety of commercially available, nonprescription grain-free diets are available which are lower in carbohydrate and higher in protein and fat, but have not yet been used in clinical trials with diabetic dogs. Dietary fat restriction (<30% ME) should be considered for diabetic dogs with concurrent chronic pancreatitis or persistent hypertriglyceridemia. It is usually recommended that insulin be given within one hour of a meal and in most cases, for convenience, it is given at the time of insulin injection.

The primary goal of treatment in feline diabetes is to obtain remission; that is, maintenance of euglycemia without the need for insulin therapy or oral hypoglycemic drugs. Remission is possible in 80% or more of newly diagnosed feline diabetics if managed to achieve normal or near normal blood glucose concentrations soon after diagnosis. Probability of remission is increased when a low-carbohydrate (<15% ME), high-protein diet (Hills® m/d, Purina® DM, or others) is used in combination with long-acting insulins such as glargine or detemir administered twice daily. Lower remission rates are reported using PZI or porcine lente insulin or when a moderate-carbohydrate diet is fed. Rapid institution of excellent glycemic control, ideally in conjunction with home monitoring, contributes to remission, while institution of tight control six months or more after diagnosis is associated with significantly lower rates of remission (84% versus 34%) (Box 12.2). Because remission often occurs within 4–8 weeks of therapy if cats are managed optimally, weight loss is not a major factor in achieving remission but it is critically important for maintaining remission. Eating does not need to be coordinated with insulin administration, especially if a low-carbohydrate diet and long-acting insulin are used. Type and amount of food and snacks should be consistent each day, and snacks must be low carbohydrate.

Exogenous Insulin Resistance

Insulin resistance means decreased sensitivity to endogenous or exogenous insulin. Endogenous insulin resistance is a major factor in the pathogenesis of type 2 diabetes in cats, when superimposed on reduced beta-cell function. Insulin resistance should be investigated in dogs or cats when insulin therapy does not have the expected effect – animals are consistently hyperglycemic despite insulin doses of greater than 1–1.5 units of insulin per kg body weight *per dose* (not per day).

Insulin resistance may incorrectly be diagnosed when insulin is stored, handled or administered improperly. It can also be misdiagnosed when duration of insulin action is too short to maintain good glycemic control and results in marked hyperglycemia prior to each insulin injection, despite increasing dose. Hyperglycemia following a hypoglycemic episode is often attributed to a rebound phenomenon associated with secretion of counterregulatory hormones, termed a Somogyi phenomenon. However, evidence for this pathogenesis as a cause of hyperglycemia following hypoglycemia is lacking in veterinary and human medicine. This pattern of hypoglycemia followed by marked hyperglycemia is a relatively rare occurrence in cats treated with glargine or detemir (1.5% of blood glucose curves), and inadequate duration of insulin action should be suspected rather than attributing the hyperglycemia to a rebound effect and associated insulin resistance. Persistent hyperglycemia also causes insulin resistance which likely explains why insulin dose, after an initial increase over 1–2 months in newly diagnosed animals, typically decreases over a similar period in both dogs and cats which remain insulin dependent.

Acromegaly is a syndrome of excess growth hormone production, which typically causes profound endogenous insulin resistance. It is rare in dogs, and caused by mammary tissue oversecretion. It is relatively common in cats, with at least 25–30% of poorly controlled diabetic

Box 12.2 Home blood glucose monitoring protocol for glargine or detemir using a preinsulin blood glucose concentration measured using a glucometer calibrated for feline blood, used in a feline-only practice for the last 8 years

Newly diagnosed diabetics (<2 months insulin therapy)

Blood glucose concentration >235 mg/dL (>13 mmol/L)	Increase the dose by 0.5 IU
Blood glucose concentration 126–235 mg/dL (7–13 mmol/L)	Keep the dose the same
Blood glucose concentration 72–<126 mg/dL (4–<7 mmol/L)	Decrease the dose by 0.5 IU
Blood glucose concentration <72 mg/dL (<4 mmol/L)	Do not give insulin and call the clinic to discuss

Longer-term diabetics (>2 months insulin therapy)

Blood glucose concentration >450 mg/dL (>25 mmol/L)	Increase the dose by 1 IU
Blood glucose concentration 270–450 mg/dL (15–25 mmol/L)	Increase the dose by 0.5 IU
Blood glucose concentration 108–<270 mg/dL (7–<15 mmol/L)	Keep the dose the same
Blood glucose concentration 90–<126 mg/dL (5–<7 mmol/L)	Decrease the dose by 0.5 IU
Blood glucose concentration <90 mg/dL (<5 mmmo/L)	Do not give insulin and call clinic to discuss, check for remission depending on dose

If using a glucometer calibrated for human blood, decrease target glucose concentration by 20% (approximately 18 mg/dL; 1 mmol/L).
Source: Adapted from Rand 2017.

cats subsequently shown to have acromegaly, and is caused by pituitary oversecretion. Cats that have poor glycemic control despite adequate or increased insulin doses should have insulin-like growth factor (IGF) measured and, if possible, brain imaging. Occasionally, diabetic cats with acromegaly are not insulin resistant at the time of diagnosis, but this is atypical. Hyperadrenocorticism causes clinically significant endogenous insulin resistance and is more common in dogs than cats. Approximately 1 in 20 dogs with hyperadrenocorticism develops diabetes.

Clinically significant insulin resistance occurs when concurrent disease causes upregulation of glucocorticoids, epinephrine, glucagon, and other counterregulatory hormones. Any concurrent infection or inflammatory disease, endocrine or cardiac disease, or neoplasia can contribute to insulin resistance. In dogs, common concurrent diseases that can contribute to insulin resistance include hyperadrenocorticism, acute pancreatitis, urinary tract infection, neoplasia, hypothyroidism, kidney disease, severe obesity, and oral infection. In cats, common concurrent diseases include pancreatitis, hepatic lipidosis, cholangiohepatitis, urinary tract infection, kidney disease, hyperthyroidism, acromegaly, inflammatory bowel disease, obesity, oral infection, and heart disease.

Diabetic Ketoacidosis

Diabetic ketoacidosis is a form of decompensated diabetes mellitus in which cells use free fatty acids as an energy source, because they cannot access glucose due to absolute or relative insulin deficiency. In the presence of elevated glucagon and other counterregulatory hormones, free fatty acids are broken down into ketoacids. As ketoacids and glucose accumulate in the blood, metabolic disturbances occur, which can be profound and life-threatening, and include dehydration, hypovolemia, elevated anion gap, metabolic acidosis, electrolyte disturbances, azotemia, elevated liver enzymes, hyperlactatemia, and clinical signs of vomiting and anorexia. Treatment involves rehydration and the use of short- and long-acting insulins to reduce ketone production and establish euglycemia.

Hyperosmolar hyperglycemic state is another syndrome of decompensated diabetes mellitus. It is characterized by profound hyperglycemia greater than 600 mg/dL (33.3 mmol/L) and hyperosmolality >320 mOsm/kg, with a normal pH and no or mild ketonemia or ketonuria. It is less common than diabetic ketoacidosis. In the classic form, animals are not ketotic or acidotic, but mixed forms occur with severe hyperosmolality, compounded by ketoacidosis.

Prognosis

Improved diets, insulin types, and the availability of home monitoring have led to improvements in canine and feline diabetes management in recent years. Most important of these is diabetic remission, thought to be attainable in 80% or more of newly diagnosed feline diabetics if managed to achieve normal or near normal blood glucose concentrations. Current data on prognosis that incorporates recent improvements in management are lacking. Older data suggest that in diabetic animals managed with

insulin therapy, median survival time from diagnosis is 2–3 years for dogs and 1.5 years for cats. Prognosis is likely better for cats that undergo diabetic remission.

Approximately 25–30% of cats relapse and require insulin to control blood glucose, and this increases with duration of remission. A small proportion of cats (approximately 22%) achieve a second remission, but most remain insulin dependent. Factors predisposing to diabetes such as obesity and corticosteroid administration are likely also important factors associated with relapse.

Intermittent home blood glucose is recommended for cats in remission to detect deteriorating glycemic status. Cats with impaired fasting glucose (>117 mg/dL and <180 mg/dL; >6.5 mmol/L and <10 mmol/L) or impaired glucose tolerance are at increased risk of relapse. Diabetic cats in remission with fasting blood glucose >135–162 mg/dL (>7.5–9 mmol/L) when measured after overnight hospitalization or at home, and blood glucose >250 mg/dL (>14 mmol/L) three hours after a glucose tolerance test (using 1 g/kg glucose IV) have an 86% probability of relapsing within nine months. In contrast, no cat with normal fasting glucose and normal glucose tolerance became diabetic again during the follow-up period (17–37 months). A low-carbohydrate diet should continue to be fed during remission.

Conclusion

Diabetes mellitus is a common endocrinopathy in middle-aged and older dogs and cats. The disease results from insulin deficiency. Most dogs have type 1 diabetes mellitus from immune-mediated pancreatic destruction, and most cats have type 2 diabetes mellitus from a combination of beta-cell failure and insulin resistance associated with obesity, inactivity, breed, and other factors.

Diagnosis is made by the demonstration of persistent hyperglycemia and glucosuria along with typical clinical signs of polyuria, polydipsia, and others.

Treatment is with exogenous insulin administration and an appropriate diet, and involves frequent blood glucose monitoring (ideally, home blood glucose monitoring), appropriate dose adjustment, and a stable daily schedule, together with elimination of factors that promote insulin resistance. In cats, diets that are low in carbohydrate assist with glycemic control. Complications include diabetic ketoacidosis, cataracts (dogs), muscle wasting, plantigrade stance (cats), and urinary tract infections. The treatment goal for diabetic dogs is to resolve clinical signs and achieve ideal body condition while avoiding complications and blood glucose extremes. The primary treatment goal for diabetic cats is diabetic remission and maintenance of euglycemia without the need for insulin therapy. Diabetic remission is achievable in 80% or more of newly diagnosed diabetic cats managed to achieve normal or near normal blood glucose. For cats that remain insulin dependent, goals of therapy are resolution of clinical signs while avoiding life-threatening hypoglycemia. Cats that remain poorly controlled with insulin doses above 1U/kg BID should be tested for acromegaly.

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13

Hypoglycemia in Patients without Diabetes Mellitus: Evaluation and Management

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Hypoglycemia is defined as a blood glucose concentration of <60 mg/dL (3.3 mmol/L). Because of the effectiveness of defense mechanisms against falling glucose concentrations, hypoglycemia is an uncommon clinical event in nondiabetic adult dogs and cats, although two exceptions are xylitol toxicity and babesiosis caused by *Babesia canis rossi* in the dog. However, hypoglycemia does occur with regularity in neonates, toy and miniature breed dogs less than 6 months of age without portosystemic vascular anomalies (PSVA), and young dogs with PSVA. In addition, hypoglycemia is a very common complication in insulin-treated diabetic dogs and cats; the incidence of owner-reported "occasional" hypoglycemic episodes ranges from 35% to 40%. Although animals with diabetes are not spared the risk for the same hypoglycemic disorders as those without diabetes, the vast majority of their hypoglycemic episodes are the result of diabetes treatment. Furthermore, because the pathophysiology of hypoglycemia in diabetes is distinct, and the diagnostic and management approaches are different for pets without diabetes, this chapter will only address the evaluation and management of hypoglycemia in patients without diabetes mellitus. In addition, insulin-secreting pancreatic endocrine tumors, more commonly known as insulinomas, will be covered in Chapter XX.

Maintenance of Normal Glucose Concentrations in Healthy Dogs and Cats

Cell function and metabolism are dependent on energy sources delivered via the circulation. There are two major sources of energy: meals (ingested carbohydrates, proteins, and fat) and glucose that is produced by the liver. The liver initially produces glucose by the breakdown of stored glycogen (glycogenolysis). As glycogen stores are depleted, glucose levels are augmented by gluconeogenesis. The whole process of gluconeogenesis is quite complex and is dependent on certain substrates such as amino acids and free fatty acids mobilized from muscle and adipose tissue. In addition, a normally functioning endocrine system is also necessary to maintain glucose homeostasis and prevent hypoglycemia. Insulin is the dominant glucose-lowering hormone. It suppresses endogenous glucose production and stimulates glucose utilization. The glucose-raising or counterregulatory hormones include epinephrine, glucagon, growth hormone (GH), and cortisol. These increase hepatic glucose production by stimulating glycogenolysis and gluconeogenesis and also inhibit glucose utilization by tissues.

Because the brain cannot synthesize glucose, store glycogen, or use physiologic circulating concentrations of alternative fuels effectively, maintenance of brain function, and ultimately survival, requires a continuous supply of glucose from the circulation. That, in turn, requires maintenance of the plasma glucose concentration within the physiological range because blood-to-brain glucose transport is a direct function of the arterial plasma glucose concentration. Glucose counterregulatory mechanisms effectively prevent or rapidly correct hypoglycemia. These critical physiologic defenses include a decrease in insulin secretion as glucose levels decline within the physiologic range; an increase in glucagon secretion; or, in its absence, an increase in epinephrine secretion, both occurring as glucose levels decline just below the physiologic range. In addition, increased cortisol and GH secretion are involved in the defense against prolonged hypoglycemia. If these defense mechanisms fail, blood glucose levels will continue to fall, and as a result, insulin secretion is virtually completely suppressed at glucose levels <60 mg/mL.

In essence, hypoglycemia develops when the sum of glucose utilization from the circulation (largely by the

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brain but also by the renal medulla, red blood cells, and insulin-sensitive tissues, such as muscle) exceeds the sum of glucose delivery into the circulation (from ingested carbohydrates and hepatic and renal glucose production).

Clinical Signs of Hypoglycemia

Clinical hypoglycemia is a blood glucose level low enough to cause symptoms, including impairment of brain function. For example, values below 50 mg/dL (2.8 mmol/L) are often accompanied by symptoms, but values below the lower end of the normal reference range may not be. Hence clinical hypoglycemia, which is also referred to as "the hypoglycemic syndrome," is not defined by hypoglycemia alone, but according to Whipple's triad – hypoglycemia accompanied by symptoms that are relieved by the administration of glucose or by feeding.

Symptoms of hypoglycemia are categorized as neuroglycopenic (lack of glucose supply to the brain) or autonomic (largely the result of the sympathoadrenal discharge triggered by hypoglycemia). The neuroglycopenic signs range from lethargy, weakness, ataxia, and unusual behavior to seizures and coma. Clinical signs resulting from stimulation of the sympathoadrenal system include restlessness, muscle tremors, and hunger. Clinical manifestations are dependent on the duration and severity of hypoglycemia. For example, in healthy people, symptoms of hypoglycemia develop at a mean plasma glucose concentration of 55 mg/dL. However, people with recurring fasting hypoglycemia appear to tolerate low blood glucose levels (e.g., <40 mg/dL) for prolonged periods without exhibiting clinical signs. This adaptive process to chronic severe hypoglycemia also occurs in animals.

Etiology/Pathophysiology

Identification of randomly obtained or a fasting blood glucose concentration below 60 mg/dL is cause for concern in dogs or cats. Although this finding is not always diagnostic of organic disease, normal dogs and cats have consistently been shown not to have blood glucose concentrations decline below this level. Therefore, once artifactual hypoglycemia has been ruled out as a possible cause, organic disease is a likely cause of persistent hypoglycemia. Failure in any one of the key steps in the production or conservation of glucose may result in hypoglycemia and clinical signs of hypoglycemia. The many causes of hypoglycemia and a list of differential diagnoses are given using the acronym DAMN IT scheme for diagnosis (Box 13.1).

Box 13.1 DAMN IT diagnosis mnemonic

D	=	Degenerative or Developmental
A	=	Anomalous or Autoimmune
M	=	Metabolic, Mechanical, or Mental
N	=	Nutritional or Neoplastic
I	=	Inflammatory, Infectious, Ischemic, Immune-mediated, Inherited, Iatrogenic, or Idiopathic
T	=	Traumatic or Toxic

Artifactual Hypoglycemia

Artifactual hypoglycemia, also called pseudohypoglycemia, is not a clinical syndrome but rather a result of artifactually low blood glucose concentration *in vitro*, mainly in the presence of leukocytosis, polycythemia, or both. In dogs, it has been reported that the glucose concentration in whole blood kept at room temperature can decrease by as much as 10 mg/dL/h. Presumably, this decrease in glucose concentration is due to continuing utilization of glucose by cells present in the blood. Therefore, whole blood obtained for glucose determination should be centrifuged within an hour after collection, separated and refrigerated or frozen to minimize artifactual lowering of blood glucose concentration. In addition, the practice of measuring glucose in whole blood immediately after collection using portable hand-held glucometers specifically designed and manufactured for measuring human blood glucose, while quick and convenient, is less accurate than measurements by an accredited veterinary laboratory. Because dogs, cats, and humans have different ratios of glucose between the plasma and red blood cells, if a portable hand-held glucometer is used to determine the blood glucose, it is recommended to use the AlphaTRAK® glucometer (Abbott Animal Health) which is calibrated specifically for dogs and cats.

Another cause of artifactual hypoglycemia is laboratory error. Incorrect values can occur with any assay and therefore, it is always wise to confirm a finding of hypoglycemia by evaluating another blood sample before more sophisticated or extensive studies are performed.

Other less common causes of pseudohypoglycemia are seen with the following conditions.

- Leukemias (e.g., chronic lymphocytic leukemia) and benign forms of leukocytosis (e.g., leukemoid reactions).
- Chronic hemolytic anemia accompanied by a high (>3%) nucleated red blood cell count.

- Polycythemia vera: an 87% decrease in blood glucose levels over four hours has been reported.
- Hypovolemic shock: poor capillary circulation leads to increased glucose transit time, promoting increased glucose extraction by the tissue. Capillary blood sampling from the ear or paw pads is low compared to central venous glucose levels which are normal.

Congenital Hepatic Disease: Portosystemic Vascular Shunts, Microvascular Dysplasia, and Glycogen Storage Disease

The most common congenital cause of hepatic-induced hypoglycemia is portosytemic vascular anomalies (PSVA). PSVA is really an "umbrella term" which includes dogs with extrahepatic shunting (PSVA-E) or intrahepatic shunting (PSVA-I). In addition, many small-breed dogs with PSVA have concurrent microvascular dysplasia (MVD). The prevalence of hypoglycemia in dogs with PSVA varies from 5% to 10%. The hypoglycemia associated with PSVA is presumably caused by chronic hepatic hypoperfusion which leads to insufficient glycogen stores and inadequate hepatocellular function to support gluconeogenesis.

Signalment

There is no gender predilection while the average age at presentation is 1.5 years for PSVA-E and 1.0 year for PSVA-I, although dogs can be as young as 1 month or as old as 12 years. Significant difference in body weight between PSVA-E and PSVA-I correlates with the long-recognized propensity for PSVA-E to occur in small-breed dogs and PSVA-I to occur in large-breed dogs. Breed prevalence for PSVA-E implicates high risk in the Yorkshire terrier and several other small breeds including shih tzu, Maltese, pug, miniature schnauzer, West Highland white terriers, bichon frise, miniature and toy poodles, Havanese, cairn terriers, silky terriers, and mixtures of these breeds. The most prevalent breed with PSVA-I is the Labrador retriever, followed by mixed-breed dogs and Siberian huskies.

History

Historical features of PSVA include pediatric hypoglycemia, small body stature (runt of the litter), episodic inappetence, vomiting, salivation, polyuria and polydipsia, and signs associated with ammonium biurate urolithiasis (hematuria, stranguria, and pollakiuria). Neurobehavioral signs of hepatic encephalopathy may be unapparent or may include ataxia, obsessive circling, and head pressing.

Laboratory Findings

In a cohort of 610 dogs with PSVA at Cornell University, no dog with a portosystemic shunt was undetected when tested with paired serum bile acids. Therefore, the most reliable tests for detection of a portosystemic shunt are paired fasting and postprandial bile acid (100% detection), 80% demonstrate low protein C activity (this test reflects the severity of shunting), >60% show microcytosis, low total protein and cholesterol, and a urine specific gravity <1.025, and biurate crystalluria occurs in approximately 33% and 22% of PSVA-E and PSVA-I respectively. It is important to remember that usually, biopsy alone cannot differentiate PSVA and MVD and that MVD alone is not associated with signs of illness (e.g., clinical hypoglycemia).

Other Diagnostics

Imaging studies are needed to differentiate PSVA-E from PSVA-I and MVD and are important for surgical and medical treatments. These include transsplenic microbubble studies, transsplenic and colorectal technetium-99m scintigraphy. However, the gold standard of imaging studies is contrast multisector CT imaging and three-dimensional image reconstruction, which provides optimal comprehensive information for diagnosis and surgical planning for PSVA.

Treatment

It is inarguable that optimal therapy for symptomatic PSVA is shunt attenuation. However, it is important to remember that all symptomatic PSVA dogs will benefit from medical management, yet all dogs do not require all forms of therapy. For example, a wide spectrum of PSVA patients at Cornell University have been managed medically with survival outcome and survival duration no different than for shunt ligation.

Glycogen Storage Diseases

Glycogen storage diseases (GSD) are rare congenital hepatic disorders in which hypoglycemia results from the inability to convert glycogen to glucose because of the absolute or relative deficiency of the enzymes necessary for the breakdown of glycogen stores in the liver. Type III GSD (Cori disease), a deficiency of amylo-1,6-glucosidase, was documented in puppies with massive hepatomegaly caused by glycogen accumulation, failure to thrive, and muscle weakness. Type I GSD (von Gierke disease) has been documented in the Maltese breed. This uncommon disorder is a deficiency of glucose-6-phosphatase caused by a defect in the glucose-6-phosphatase gene. Affected puppies develop progressive hepatomegaly characterized by diffuse hepatocellular vacuolization, tremors, weakness, and neurologic signs when hypoglycemic. Biochemical abnormalities include fasting hypoglycemia, hypercholesterolemia, hypertriglyceridemia, and elevated uric acid levels. Confirmatory

tests include histologic evaluation of liver biopsies and specific enzyme assays that are rarely performed in veterinary medicine. And lastly, GSD type IV has been documented in a family of Norwegian forest cats. It leads to death as a result of perinatal hypoglycemic collapse or late juvenile-onset neuromuscular degeneration.

Idiopathic Causes of Liver-Associated Hypoglycemia in Young Animals: Neonatal and Juvenile Hypoglycemia

Neonatal Hypoglycemia

The blood glucose concentration in the healthy neonate falls during the first few hours after birth because of the loss of continuous transplacental infusion of glucose. Thereafter, the neonate is dependent on glycogenolysis and gluconeogenesis to maintain euglycemia between feedings. Limited glycogen stores, small muscle mass, and lack of adipose tissue as alternative energy sources place the neonate at risk for hypoglycemia. That said, the ill neonate should always be evaluated for hypoglycemia, especially if sepsis, toxic milk syndrome, or starvation is suspected or hypothermia is noted. Orally administered glucose or frequent bottle feeding can help correct or prevent hypoglycemia.

Juvenile Hypoglycemia

Hypoglycemia of toy and miniature breed dogs younger than 6 months of age is common. Deficiency of gluconeogenic precursors such as the amino acid alanine or an age-related transient malfunction or deficiency of enzymes responsible for gluconeogenesis is implicated in this syndrome. Insufficient food supply of any cause such as starvation or gastrointestinal disturbances may cause hypoglycemia within 24 hours of fasting. In addition, underlying conditions such as PSVA that cause anorexia or impaired liver function may contribute to the precipitation of this syndrome. Many of these puppies have a history of being recently purchased along with a recent change in environment and diet. Presenting signs may include weakness, depression, vomiting and diarrhea with or without intestinal parasites, ataxia, stupor, and seizures. Similar forms of juvenile hypoglycemia have not been well documented in kittens.

Treatment and Prognosis

Intravenous administration of a 20% or 50% dextrose solution (0.8 mL to 0.2 mL per 100 g body weight respectively) is indicated if there are neurologic signs. If the pup can take the glucose solution orally, this is administered at regular intervals until appetite returns. The small amounts of food are given at two-hour intervals. If tube feeding is needed, oral rehydration is guided by electrolyte measurements. Clinical improvement occurs rapidly following glucose administration. The prognosis is good if hypoglycemia is corrected before brain damage occurs. The risk of developing hypoglycemia decreases with increasing age and body weight.

Nonislet Cell Tumor-Induced Hypoglycemia

Hypoglycemia can be a manifestation of neoplastic disease. Tumors related to the occurrence of hypoglycemia can, as a general rule, be divided into three groups. First, tumors can produce excess insulin such as pancreatic insulinomas or ectopic insulin-producing tumors. Second, hypoglycemia can be caused by tumor-related factors such as destruction of the liver by massive tumor infiltration. And lastly, there is now convincing evidence that secretion of insulin-like growth factor (IGF)-2 and incompletely processed IGFs (e.g., pro-IGF-2 or "big"-IGF-2) causes hypoglycemia in humans. This mechanism has also been documented in a few cases of hypoglycemia in dogs. Nonislet cell tumor-induced hypoglycemia (NICTH) can arise in virtually every benign and malignant tumor. However, it mainly occurs in patients with solid tumors of mesenchymal (e.g., leiomyosarcoma, fibrosarcoma) and epithelial origin (e.g., hepatoma, hepatocellular carcinoma), but rarely in patients with tumors of hematopoietic or neuroendocrine origin. The most frequent nonpancreatic tumors associated with hypoglycemia are leiomyoma, leiomyosarcoma, hepatoma, hepatocellular carcinoma, and tumors with extensive hepatic metastasis.

Pathophysiology

Understanding the cause of hypoglycemia with NICTH involves a brief review of the IGF system. The IGF system is composed of two IGF ligands (IGF-1 and IGF-2) and two IGF receptors: the IGF-1 receptor (IGF1R) and IGF-2 receptor (IGF2R). Both IGF-1 and IGF-2 are structurally and functionally related to insulin but the glucose-lowering effect of IGFs is 10 times lower than that of insulin, although in healthy human subjects the serum concentration of IGFs is about 1000 times higher than insulin. The crucial event in the development of NICTH seems to be overexpression of the IGF-2 gene by the tumor. NICTH is characterized by recurrent fasting hypoglycemia and is associated with the secretion of precursors of IGF-2 ("big"-IGF-2) by the tumor.

Diagnosis

Dogs with hypoglycemia caused by NICTH are usually brought to the veterinarian with clinical signs of hypoglycemia, or hypoglycemia may be noted on a biochemical profile in an asymptomatic patient during a wellness exam. The diagnosis of a nonislet cell tumor requires a

thorough physical examination, thoracic and abdominal radiographs, abdominal ultrasonography, and histopathologic examination of the tumor, which is often located in the abdominal cavity.

Treatment

The long-term therapeutic strategies in NICTH involve complete removal of the tumor or reduction of the tumor mass. In order to treat hypoglycemia, a short-term beneficial effect is best achieved with (continuous) parenteral administration of glucose and dietary guidelines. Glucocorticoids, at least in humans, seem to be the most effective form of medical therapy in terms of long-term relief from hypoglycemia by stimulating glyconeogenesis and suppressing, although not in all cases, the production of "big"-IGF-2. In addition, moderate to high doses of glucocorticoids may cause shrinkage of the tumor.

Hypoadrenocorticism

Incidence

Hypoadrenocorticism should always be on the rule-out list for hypoglycemia. Of 506 dogs diagnosed with hypoadrenocorticism at UC Davis Veterinary Medical Teaching Hospital, 116 (25%) were hypoglycemic at the time of diagnosis. Interestingly, however, clinical signs attributable to hypoglycemia appear to be uncommon. In this cohort of cases, hypoglycemic seizures and other clinical signs that may have been caused by hypoglycemia, such as ataxia and disorientation, were observed in only 30 dogs (6%).

Pathophysiology and Treatment

With glucocorticoid deficiency, glucose production by the liver (i.e., gluconeogenesis) is decreased and the sensitivity of insulin receptors in peripheral tissues is increased. In tandem, these factors predispose the animal with adrenal insufficiency to hypoglycemia. That said, the blood glucose concentration should always be measured in a dog suspected or known to have hypoadrenocorticism. A 2.5–5% dextrose infusion, usually added to lactated Ringer's or normal saline solution, should be administered as soon as hypoglycemia is documented in addition to glucocorticoid replacement therapy. If the pretreatment serum sodium and potassium concentrations are normal, mineralocorticoid replacement is not necessary over the short term, and may never be indicated in some dogs with adrenal insufficiency (atypical hypoadrenocorticism). These dogs, despite low serum aldosterone concentrations, are able to maintain normal serum sodium and potassium levels for reasons that are unclear.

Critical Illness and Hypoglycemia: Renal Failure, Acquired Liver Disease, Sepsis, and Virulent Babesiosis

Renal Failure

Renal failure is associated with hypoglycemia in critically ill diabetic and nondiabetic human patients, but the impact of renal failure on the blood glucose concentration is unpredictable in dogs and cats. In most cases, the blood glucose concentration is normal. However, hyperglycemia may develop as a result of uremic-induced carbohydrate intolerance and insulin resistance in a dog or cat with impaired insulin secretion; this phenomenon has been referred to as "pseudodiabetes." Alternatively, renal failure may induce hypoglycemia.

Several mechanisms for the development of hypoglycemia during renal insufficiency have been proposed. These include reduced renal gluconeogenesis and decreased caloric intake related to inappetence. Normally, renal gluconeogenesis may supply as much as 45% of new glucose during prolonged starvation. Additional defects in glucose homeostasis occur in renal insufficiency, including an increased insulin half-life related to decreased renal degradation or excretion of insulin, impaired hepatic glycogenolysis and gluconeogenesis, inadequate glucose counterregulatory responses, or a combination of these factors. It should be emphasized that hypoglycemia is rarely the cause of death in the critically ill patient with renal failure and is considered more a marker for multisystem failure than a cause of mortality.

Acquired Hepatic Dysfunction

Hypoglycemia has been associated with a wide spectrum of liver diseases in people. These disorders include everything from type 1 glycogen storage disease, cirrhosis, viral hepatitis, procainamide-induced hepatitis, cholecystitis, and metastatic infiltration to fulminant liver failure after cardiac arrest. In dogs and cats, hypoglycemia often results from severe destruction of the liver from bacterial infection, hepatotoxins, neoplasia, and chronic fibrosis/cirrhosis with the development of acquired portosystemic shunts. The underlying cause of hypoglycemia results from inadequate amounts of functional liver tissue for optimal gluconeogenesis and glycogen storage to maintain normal blood glucose levels.

The diagnosis of acquired liver dysfunction is usually quite straightforward. Common CBC, serum biochemical profile and urinalysis abnormalities may include microcytosis, low serum albumin, BUN and cholesterol concentrations, elevated serum bilirubin levels, elevated paired serum bile acid concentrations, ammonium biurate crystals in the urine, radiographic evidence of abnormal liver size, and/or ultrasonographic changes consistent with abnormal echotexture or liver size. A liver biopsy is

necessary to determine the exact cause of the liver disorder and may help guide specific treatment options such as the selective use of antibiotics, glucocorticoids, copper chelation, ciclosporin, lactulose, and dietary therapy.

Sepsis-Induced Hypoglycemia

Systemic illness caused by microbial (usually bacteria) invasion of normally sterile parts of the body is referred to as sepsis. Sepsis plus organ dysfunction or hypoperfusion is termed severe sepsis. And severe sepsis accompanied by hypotension is termed septic shock.

Impaired glucose homeostasis has been well documented in patients with sepsis. Hyperglycemia is the most common blood glucose abnormality seen early in the course of bacterial sepsis. In preterminal sepsis, profound hypoglycemia may occur because of hyperinsulinemia, increased tissue uptake of glucose, and the failure of hepatic glucose production. It is postulated that sepsis-related hypoglycemia is a manifestation of nonspecific inflammatory responses mediated by high levels of cytokines, including tumor necrosis factor and interleukin-6.

The signs and symptoms of sepsis are highly variable. They are influenced by the virulence and "bioburden' (the amount) of the organism, the portal of entry (e.g., skin, gut, urinary tract) and host susceptibility (the young and very old and patients with weakened immune systems are most at risk). Patients with sepsis can present with a fever or hypothermia and CBC findings may show a leukocytosis with a left shift or leukopenia. Common causes of sepsis-induced hypoglycemia include parvovirus infection, prostatic and liver abscesses, pyothorax, pyometra, hemorrhagic gastroenteritis, and gram-negative bacteremia. The diagnosis of sepsis-induced hypoglycemia is often one of suspicion or identification of an infection based on history, physical examination and CBC findings, and other diagnostics such as bacterial cultures, radiography and ultrasonography, and resolution of hypoglycemia after initiation of antibiotic therapy.

Virulent Babesiosis

Hypoglycemia has been identified as a life-threatening metabolic complication in almost 20% of severely ill dogs suffering from babesiosis caused by *Babesia canis rossi*. This highly virulent subspecies of *Babesia canis* is endemic only to South Africa. Clinical signs include pale mucous membranes, depression, tachycardia, tachypnea, anorexia, weakness, splenomegaly, and fever. The clinical signs are attributed to tissue hypoxia resulting from anemia and a concomitant systemic inflammatory response syndrome caused by marked cytokine release. The severe form of the disease is characterized by hemolytic anemia and severe acid–base derangements, with secondary multiple organ failure and complications such as acute renal failure, hepatopathy with marked icterus, hypoglycemia, acute respiratory distress syndrome, cerebral pathology, and additional immune-mediated erythrocyte destruction. Mortality is around 12%. A feature of the disease is that, in contrast to babesiosis in other domestic species, pups and immature dogs are also severely affected. Only one case of *Babesia canis rossi* has been reported in a dog in the United States and that was a dog imported from South Africa.

Several contributing factors have been implicated as causes of the hypoglycemia. These include increased peripheral requirement for glucose during febrile and critical illness, obligatory demands of the parasites that use glucose as their major fuel, hyperinsulinemia, failure of hepatic gluconeogenesis and glycogenolysis, and increased glucose consumption by anaerobic glycolysis because of tissue hypoxia.

Blood glucose concentration should ideally be measured in all dogs requiring inpatient treatment for babesiosis, but is mandatory in collapsed dogs, puppies and dogs with severe anemia, vomiting, or icterus. Many dogs have probably been misdiagnosed with cerebral babesiosis in the past, and hypoglycemia should be suspected in any dog with coma or other neurologic signs. Response to treatment with selected antibabesial compounds such as imidocarb dipropionate, atovaquone, azithromycin, clindamycin, and doxycycline is variable, and intravenous dextrose does not reliably improve glycemic status or survival.

Persistent Hyperinsulinemic Hypoglycemic Syndrome

In humans, persistent hyperinsulinemic hypoglycemia of infancy (PHHI) represents the most common cause of hyperinsulinism in neonates and children; currently, many authors prefer the term congenital hyperinsulinism (CHI). Severe recurrent hypoglycemia associated with an inappropriate elevation of serum insulin defines CHI. This disturbance of the normal relationship between glucose concentration and insulin secretion is caused by a variety of genetic mutations. If left untreated, CHI can lead to brain damage or death secondary to severe hypoglycemia. Although it was initially thought to affect only infants and children, numerous cases have been reported in adults of all ages but at a much lower incidence. CHI is often poorly responsive or unresponsive to medical management, necessitating 95% or near-total pancreatectomy.

Recently, a persistent hyperinsulinemic hypoglycemic syndrome, not associated with sepsis or insulinoma, was diagnosed in two dogs. Both dogs were less than 12 months of age. The clinical signs in these dogs were similar; hypoglycemic-induced seizures unresponsive to

intravenous glucose administration and anticonvulsant therapy. The owners of these dogs chose euthanasia because of poor response to therapy and poor prognosis. Blood was cultured from one dog using a special enrichment PCR media to rule in or rule out an infection caused by a fastidious bacteria; *Bartonella hensalae* was amplified and sequenced from this dog's blood. In the other dog, *Bartonella kohlerae* was amplified and sequenced retrospectively from paraffin-embedded tissue. Despite isolating *Bartonella* spp. from both dogs, it is unclear whether *B. hensalae* and *B. kohlerae* contributed to the pathogenesis of this unusual and rare hypoglycemic syndrome. That said, persistent hyperinsulinemic hypoglycemic syndrome should be suspected in any young dog with hypoglycemia refractory to intravenous glucose. Moreover, until more is known about the cause of this syndrome, testing and treating for *Bartonella* should be a diagnostic and therapeutic consideration.

Xylitol Toxicity

Xylitol exposure, even in small amounts, can cause hypoglycemia and severe liver damage in dogs. Xylitol is a 5-carbon sugar alcohol that is used primarily as an artificial sweetener that has less than two-thirds of the calories of most sugars. The two major sources of xylitol exposure are food and dental or medical products. Initially, exposure to xylitol in dogs was from "sugar-free" chewing gums. However, with demands from human diabetic patients, particularly because of the popularity of Atkins-like "low-carb" diets, many foods now contain xylitol. A large number of low-carbohydrate foods, including breads, candies, gums, and deserts, have xylitol as the sweetener of choice. Xylitol has a wide margin of safety in mammals with the exception of dogs. Oral exposures as low as 0.1 mg/kg have induced hypoglycemia in the dog, and levels of 0.5 mg/kg have resulted in hepatotoxicity in some dogs. For example, one piece of Trident gum contains 0.22 g of xylitol and the popular breath mint Ice Breakers contains 1 g of xylitol per piece and therefore, nine pieces of Trident or two Ice Breaker pieces could potentially cause xylitol toxicity in a 20 kg dog. The literature reports no cases of xylitol toxicity in cats.

Prevalence

Recently, there has been a rapid increase in the number of products containing xylitol. According to the ASPCA Animal Poison Control Center (APCC), the number of reported xylitol exposures in dogs has been increasing steadily and exponentially over the past few years. In 2007, theAPCC began to log xylitol cases. That year, the center received 1764 calls about xylitol. In 2012, the figure was 3184. The number of products containing xylitol has been steadily rising over the last few years, with a resultant surge in xylitol cases reported to the APCC.

Clinical Signs and Laboratory Abnormalities

In laboratory experiments, xylitol directly stimulates insulin synthesis and secretion within 30 minutes after ingestion. However, in clinical cases, the onset of clinical signs varies based on the form of xylitol used in the product ingested. The powder used in candies and mints is absorbed quickly and signs can be seen in 30 minutes. Gum must be chewed to release the xylitol. If the gum is swallowed whole it leaches into the stomach, and the onset of clinical signs can be delayed 8–18 hours. Vomiting is often the first symptom. Clinical signs can include ataxia, depression, dilated pupils, and seizures (related to hypoglycemia), and lethargy, inappetence, vomiting, and diarrhea (related to liver failure). Laboratory abnormalities initially include hyperinsulinemia, hypoglycemia, hypophosphatemia, hypokalemia, and increased AST and ALT concentrations. Dogs that do not exhibit hypoglycemia immediately after ingestion of xylitol may still develop acute liver failure. These dogs may develop severe signs 24–72 hours later.

Diagnosis

The diagnosis of xylitol toxicity is made by history of exposure, clinical signs, and serum biochemical abnormalities consistent with xylitol poisoning. Because the serum half-life of xylitol is about two minutes and there is rapid progression of the toxic effect, testing for xylitol in the blood is not realistic.

Treatment and Monitoring

Blood glucose levels should be determined initially and monitored at least every four hours for 24 hours or longer, as indicated. Liver enzyme levels and prothrombin time/partial thromboplastin time (PT/PTT) should be monitored every 24 hours for 48–72 hours. It is not uncommon to have a transient elevation in ALT (300–800) very quickly after ingestion. Electrolyte status and packed cell volume (PCV) should also be monitored regularly.

- There is no antidote for xylitol toxicity.
- Induce emesis if the xylitol ingestion is recent.
- Use of activated charcoal is of limited efficacy with xylitol because it is not effective at binding xylitol.
- IV fluid support: important to restore or maintain hydration, treat hypoglycemia, and prevent or treat disseminated intravascular coagulation (DIC). Patients with normal blood glucose levels should receive a 2.5% dextrose solution.
- Hypoglycemia caused by xylitol toxicity is usually responsive to IV dextrose solutions. Refractory cases

may be treated with glucagon or dexamethasone. Feeding small frequent meals may be beneficial in helping to manage hypoglycemia.
- Use antiemetics and gastrointestinal protectants as needed.
- Avoid drugs that are metabolized by the liver.
- Antibiotics may be indicated in acute liver failure cases to treat concurrent infection (clavamox or amoxicillin, ampicillin, cephalexin, or cefadroxil with metronidazole).

Duration of Treatment and Prognosis

The length of treatment depends on the severity of clinical signs**.** Treatment for cases without liver involvement may last 1–3 days. Treatment should continue until glucose levels are normal. Treatment of cases with liver involvement may last weeks. The prognosis for patients that only develop hypoglycemia is good. Prognosis for patients who develop liver failure is guarded and depends on the severity of the disease. Typically, there are no lingering medical issues once liver problems have been successfully resolved.

Diagnostic Approach to Disorders Associated with Hypoglycemia

After confirming the finding of hypoglycemia, the history (including exposure to insulin, sulfonylureas, or xylitol), signalment, physical exam findings, and a careful review of available laboratory data guide the evaluation. This information will either provide clues to the cause of hypoglycemia or exclude hypoglycemia caused by acknowledged drugs or toxins, critical illnesses, hormone deficiencies, or a nonislet cell tumor. A test of adrenocortical function is reasonable although hypoadrenocorticism is not commonly found as a cause of hypoglycemia in dogs in the absence of other clinical clues. Nonislet cell tumor hypoglycemia is often associated with a large, clinically apparent mesenchymal tumor (e.g., leiomyoma and leiomyosarcoma) as well as epithelial tumors that are associated with the liver (e.g., hepatoma or hepatocellular carcinoma).

As part of the signalment, age of the animal can be quite useful in narrowing down the long list of rule-outs for hypoglycemia. For example, hypoglycemia in a puppy or kitten is often idiopathic in origin or related to starvation, PSVA, or sepsis. In young adult dogs, hypoglycemia is usually caused by hepatic insufficiency, hypoadrenocorticism, or sepsis. And in older dogs, hepatic insufficiency, insulinoma (see Chapter XX), nonislet cell tumor-induced hypoglycemia, hypoadrenocorticism, and sepsis are the most common causes of hypoglycemia.

The results of routine and specialized tests can also be quite helpful diagnostically. For example, dogs with adrenal insufficiency without the classic electrolyte changes of hyperkalemia and hyponatremia often have hypoalbuminemia, hypocholesterolemia and a resting cortisol <2 µg/dL, although an ACTH response test is required for a definitive diagnosis. Paired fasting and postprandial serum bile acids are diagnostic for virtually all dogs with a portosystemic shunt, and CBC findings which include a neutrophilic leukocytosis with a left shift in a hypoglycemic febrile dog or cat are highly suggestive of sepsis.

When the cause of the hypoglycemic disorder is not evident in a seemingly well adult dog, serum glucose and insulin concentrations should be measured during an episode of spontaneous hypoglycemia to rule out an insulinoma. The key pathophysiologic feature of endogenous hyperinsulinism (e.g., an insulinoma) is the failure of insulin secretion to fall to very low rates as blood glucose concentrations fall to hypoglycemic levels.

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14

Canine Autoimmune Polyglandular Syndromes

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Many endocrine disorders, such as lymphocytic thyroiditis, hypoadrenocorticism, and type 1 diabetes mellitus, have an autoimmune basis. When endocrine immune disorders occur in the same individual, they are known as autoimmune polyglandular syndromes (APS). These syndromes (APS) can be further divided into APS type 1 (diabetes mellitus, ectodermal mucositis, etc.), APS type 2 (hypoadrenocorticism, hypothyroidism, etc.), and APS type 3 (liver cirrhosis plus endocrinopathies). The combination of hypoadrenocorticism and hypothyroidism is called Schmidt syndrome after the pathologist who described concurrence of these two diseases in human beings. Autoimmune polyglandular syndrome type 2 is the only one that has been described in dogs.

Etiology and Pathophysiology

Polyendocrine gland failure or autoimmune polyglandular syndrome, the most common form of which is APS type 2, has been well documented in humans. Autoimmune polyglandular syndrome type 2 is defined as the occurrence of two or more of the following disorders in the same individual: adrenal insufficiency, primary hypothyroidism, type 1 diabetes mellitus (DM), primary hypogonadism (premature ovarian failure, immune-mediated orchitis), myasthenia gravis, megaesophagus, immune-mediated hemolytic anemia (IMHA), immune-mediated thrombocytopenia (ITP), hypoparathyroidism, hypopituitarism, and celiac disease.

Circulating organ-specific autoantibodies are commonly present in APS type 2. Environmental factors combined with an HLA-associated genetic predisposition are thought to trigger the process. Cell-mediated immune abnormalities in the type 2 syndrome include defects and alterations of cell surface markers, but the most consistent abnormality is a functional defect leading to a decrease in suppressor T cell activity. Approximately 45% of all human patients with idiopathic (autoimmune) adrenal insufficiency will develop one or more additional endocrinopathies (usually hypothyroidism).

The genetics of APS has been studied extensively in human beings. APS 2 is inherited as an autosomal dominant trait in humans associated with the presence of human leukocyte antigens (HLA). In families where this syndrome has been documented in several individuals, the inheritance of major histocompatibility loci haplotype correlates most strongly with the disease. Many individuals with this haplotype have circulating organ-specific autoantibodies directed against cytochrome P450 without clinical signs of disease. Recently, one study found that a higher proportion of dogs with hypoadrenocorticism were P450scc autoantibody positive when compared to hospital controls (24% vs 1%). Lymphocytic and plasmacytic destruction of the affected endocrine glands may be documented histologically.

Hypoadrenocorticism is the most common initial endocrinopathy observed in polyendocrine gland failure in dogs and is usually followed by the development of hypothyroidism. However, type 1 diabetes combined with immune-mediated thyroid disease (Hashimoto thyroiditis) is also a common combination of immune endocrinopathies in humans and has been described in dogs. Studies show that 45–50% of humans with adrenal insufficiency associated with polyendocrine gland failure (onset 20–30 years) develop a second endocrinopathy. The most common second endocrinopathy, primary hypothyroidism, develops 10–20 years after the first endocrinopathy.

In a retrospective of 225 cases of canine hypoadrenocorticism, 4% of the dogs (n = 9) also suffered from hypothyroidism, two dogs had concurrent IDDM and hypoadrenocorticism, and one had concurrent hypoadrenocorticism, hypothyroidism, IDDM, and hypoparathyroidism. Another retrospective of 45 dogs with

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adrenal insufficiency reported four with concurrent hypothyroidism, one dog with concurrent IDDM and one dog with concurrent primary gonadal hypoplasia. A single case of type 2 APS has been described in a middle-aged female dog presenting in a hypothyroid crisis; treatment of the hypothyroid state resulted in precipitation of the hypoadrenocorticism. The presence of serum autoantibodies to thyroid and adrenal tissue was observed in this dog as evidence of APS type 2.

History and Clinical Signs

Most of the dogs in reported studies were diagnosed with hypoadrenocorticism initially and the mean age of onset of the disease was in young adulthood. Dogs are usually diagnosed with a second endocrinopathy approximately one year after the first endocrinopathy.

A familial tendency was observed in one study where two dogs were mother and daughter and one dog had a sibling with hypoadrenocorticism. Hypoadrenocorticism is inherited in several breeds, including standard poodles, West Highland white terriers, Nova Scotia duck tolling retrievers, Portuguese water dogs, and Leonbergers; however, there may be different DLA haplotypes depending on breed. There is a distinct breed predisposition for primary hypothyroidism with golden retrievers, Doberman pinschers, Irish setters, miniature schnauzers, dachshunds, cocker spaniels, and beagles. Diabetes mellitus (type 1a), which has an autoimmune basis, is seen with increased frequency in Samoyeds, Tibetan terriers, Australian terriers, keeshonds and several other breeds. In fact, one study showed that the DLA-DRB1*009/DQA1*/DQB1*008 haplotype was associated with DM in certain breeds (Samoyed, Tibetan, and cairn terriers) and that the DLA-DQA1*001 allele is also associated with hypothyroidism in dogs, suggesting a common susceptibility allele for canine immune-mediated endocrinopathies.

A decreasing insulin requirement is often the earliest sign of adrenal insufficiency in a patient with type 1 diabetes mellitus secondary to APS in human beings. In contrast, dogs with concurrent hypothyroidism and IDDM often have increasing insulin requirements; hypothyroidism may cause insulin resistance resulting from lipid abnormalities or other factors.

The most common presenting complaints for hypoadrenocorticism as the initial diagnosis include lethargy, collapse, vomiting, weight loss, weakness, ataxia, anorexia, bradycardia, megaesophagus, and diarrhea. Clinicopathologic features include hyponatremia, hypercholesterolemia, hyperkalemia, hypochloremia, azotemia, hypocalcemia, and hypercalcemia.

In dogs diagnosed with hypoadrenocorticism as the initial endocrinopathy, thyroid evaluation is often performed because of continued lethargy despite adequate mineralocorticoid replacement therapy, persistent hyponatremia, hypercholesterolemia, dermatologic disease, bradycardia, obesity, and heat-seeking behavior. In cases of combined DM and hypothyroidism, diabetes mellitus insulin resistance is usually the reason for thyroid testing.

Diagnosis and Prognosis

In two studies, dogs with concurrent diabetes and hypothyroidism showed significantly lower serum sodium concentration and had significantly higher fasting serum cholesterol compared with nonhypothyroid diabetic dogs; similarly, dogs with hypoadrenocorticism combined with hypothyroidism exhibited significantly lower sodium and higher serum cholesterol than dogs with hypoadrenocorticism alone. These two chemistry abnormalities are highly suggestive of hypothyroidism in a dog with otherwise well-regulated hypoadrenocorticism or in a poorly regulated diabetic dog. Severe hyponatremia (<120 meq/L) is a sign of Schmidt syndrome in humans. Thyroid testing should be performed in diabetics dogs that exhibit poor glucose regulation, persistent hyponatremia and hypercholesterolemia, obesity or weight gain, lethargy, dermatologic disease, and regurgitation.

Resting serum cortisol concentration is often subnormal (<2 µg/dL) in dogs that suffer from APS 2 that manifests as hypoadrenocorticism and all will show inadequate response to adrenocorticotropic hormone (ACTH) stimulation. Endogenous ACTH levels should be increased due to primary adrenal insufficiency and loss of negative feedback to the pituitary gland. One reported case of Schmidt syndrome (APS 2) had evidence of lymphocytic adenohypophysitis in addition to adrenalitis and thyroid gland atrophy; immune-mediated pituitary disorders have been reported in humans as well. Mean basal thyroxine (T4) and free T4 levels are usually low to low normal and endogenous thyroid-stimulating hormone (TSH) is usually elevated in dogs with multiple endocrinopathies resulting from APS.

Therapy

Treatment of multiple endocrinopathies consists of specific hormone replacement. For dogs with hypoadrenocorticism, treatment with fludrocortisone (0.018 mg/kg PO q24h) or deoxycorticosterone pivalate (DOCP) (1 mg/kg IM monthly) should be initiated first, followed by levothyroxine therapy (22 µg/kg once or twice daily PO). One should be aware that aggressive levothyroxine therapy might precipitate a life-threatening adrenal crisis

in a patient with APS so starting once daily would be suggested. When the hypothyroid and hypoadrenal states occur concurrently, the rate of clearance of cortisol and cholesterol is reduced due to low serum thyroxine concentrations. When thyroid supplementation is initiated, cortisol clearance increases suddenly without a compensatory increase in cortisol synthesis because of destruction of adrenal tissue. As a result, thyroid therapy may precipitate an adrenal crisis. Hence, one should assess adrenal function prior to initiation of levothyroxine therapy in animals with suspected multiple endocrinopathies. In dogs with diabetes mellitus and hypothyroidism, one must balance the insulin dose with the levothyroxine therapy. A reduction of 25% of the insulin dose is recommended when starting levothyroxine at 22 µg/kg BID. In dogs with hypoadrenocorticism and diabetes mellitus, the insulin dose will need to be gradually increased as supplementation with glucocorticoids (0.22 mg/kg PO q24h) and DOCP will cause insulin resistance.

Conclusion

In summary, multiple endocrine deficiencies occur with a low incidence in dogs with hypoadrenocorticism, hypothyroidism, IDDM, and perhaps hypoparathyroidism. This syndrome appears to be similar to APS 2 of human beings. Veterinarians should be aware of some of the features, such as persistent hyponatremia and hypercholesterolemia, which may indicate the presence of multiple endocrinopathies in the same individual. Dogs with hypoadrenocorticism that exhibit inadequate response to therapy, persistent hypercholesterolemia and hyponatremia despite normalization of serum potassium, dermatologic disease, and/or bradycardia should be evaluated for thyroid function. Diabetic dogs that exhibit inadequate glycemic control associated with persistent hyponatremia, hypercholesterolemia (>500 mg/dL), obesity and dermatologic disease should also be tested for hypothyroidism.

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Section 3

Cardiovascular Disease

15

Approach to the Patient with Suspected Cardiovascular Disease

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Suspicion of cardiac disease in dogs and cats may arise due to information obtained from owner complaints and/or physical findings. Unfortunately, most of the common clinical signs of heart disease are not specific for heart disease. Likewise, heart disease may occur concurrently with other disease, making it unclear whether the clinical signs are due to cardiac disease or something else. The approach to the patient with suspected cardiovascular disease is therefore to obtain as much information as possible in order to make a correct diagnosis.

Signalment

Signalment information is the first step in the clinical work-up of a patient with suspected heart disease as some diseases are more commonly seen in specific types of animals. However, this type of data is only supportive in nature, and does not provide sufficient evidence for a definite diagnosis. The signalment data should include information concerning age, species, breed, sex, and geographic location.

Age

Age can provide valuable information in a patient with suspected cardiac disease; congenital heart disease, which is defined as a heart defect present at birth, is more likely in young pets. However, congenital heart disease may remain undiscovered in middle-aged or old dogs and cats not previously examined by a veterinarian. Acquired heart disease, defined as a heart condition developing after birth, is most frequently found in middle-aged and old dogs and cats, although its presence in a younger individual cannot be excluded. For both dogs and cats, presence of cardiac neoplasia is more common in older individuals. Extracardiac disease may affect the heart by causing myocyte damage in dogs and cats of any age.

Species and Breed

Some specific heart diseases, both congenital and acquired, are more commonly identified in individuals of certain breeds compared to others (see separate disease chapters), which supports a genetic background for these disorders.

Sex

Very little is known concerning the effect of sex on the prevalence of congenital heart disease in dogs and cats. In most studies, no sex predilection has been reported. However, sex appears to affect the prevalence of the most common forms of acquired heart disease in dogs (myxomatous mitral valve disease [MMVD] and dilated cardiomyopathy [DCM]) and cats (cardiomyopathy). Males appear affected at an earlier age in both cats and dogs, which leads to a slightly higher proportion of affected individuals at a given age and a higher cause-specific mortality. The reason for this influence of sex is unknown.

Geographic Location

Information concerning the geographic origin of the pet is important because the prevalence of certain congenital and acquired heart diseases differs between continents, countries, and even within countries. Again, this likely reflects different gene pools within breeds, but it underlines the importance of interpreting results of disease prevalence with caution. It is also important to obtain information about where the animal has lived geographically because some diseases, for example parasitic diseases (e.g., dirofilarosis), are prevalent in certain areas but nonexistent in others.

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Case History and Owner Complaints

A thorough medical history provides important information and is an integral part of the cardiovascular examination. The questions may vary depending on the nature of the animal's health problem. Information obtained from the owner interview and findings at the physical examination are used to formulate a problem list, which can be used in the decision to pursue further clinical testing.

Dogs and cats with heart disease can present with clinical signs related to the heart condition but also, the pet can be completely free of signs of disease and the only reason for the cardiac examination is an incidental finding of a heart murmur or arrhythmia. Common owner complaints for a pet with heart disease include increased respiratory rate (tachypnea), difficulty of breathing and changed respiratory pattern (dyspnea), coughing (unusual in cats), abdominal distension (ascites), fainting (syncope), tongue and mucous membrane cyanosis, weight loss, and weakness and exercise intolerance. These signs of heart disease can be grouped into four main categories:

- respiratory abnormalities caused by left-sided congestive heart failure (CHF)
- exercise intolerance, weakness, wasting, and syncope caused by low cardiac output
- abdominal distension caused by right-sided CHF
- cyanosis caused by reduced oxygenation of peripheral blood.

Unfortunately, none of these signs is specific for heart disease, and may be caused by a wide variety of disorders.

Dyspnea, Tachypnea, and Cough

The most common sequela of heart disease in dogs and cats is left-sided CHF. The increased pulmonary venous pressure leads to pulmonary congestion and edema formation, causing respiratory signs such as dyspnea, tachypnea, and cough (unusual in cats). Dyspnea may appear in many different forms in pets with heart disease. In working dogs, an experienced owner might note a changed respiratory character during and/or after work at an earlier stage of disease. However, many dogs and cats do not exercise in this intense manner, which means that owners do not observe changed respiration until it is apparent at rest (at a comparably advanced stage).

In general, the respiratory rate gradually increases followed by a worsening of dyspnea, but the respiratory signs may develop at different rates in different diseases and individuals. Accordingly, it is useful to have the owner monitoring the respiratory rate at home in an animal at risk for developing CHF. Dogs and cats without decompensated CHF have in general a sleeping/resting respiratory rate of <30/min. As a general rule, long-standing (weeks or months) respiratory signs that have not worsened over time speak against CHF. Respiratory signs, with or without cough, while lying down or asleep, a phenomenon called nocturnal dyspnea/coughing, are common early signs of left-sided CHF. The severity of dyspnea can range from mild, with only minimal changes in breathing pattern and respiratory rate, to severe life-threatening dyspnea, when the pet is unwilling to lie down (orthopnea), usually with respiratory rates >50/min. The owner often describes changed breathing sounds in animals with severe pulmonary edema. Cats with left-sided CHF frequently develop pleural effusion alone or in addition to pulmonary edema, and these cats can exhibit a paradoxical breathing pattern.

Dogs presenting with left-sided decompensated CHF may present with cough. Cough is not commonly associated with CHF in cats, and owner complaints of coughing in cats should raise the suspicion of other respiratory disease. In dogs, there is also a problem distinguishing cough caused by other diseases, such as small bronchial disease and tracheal collapse, from cough associated with pronounced cardiomegaly with or without CHF. There is no definitive way of distinguishing cardiac from noncardiac cough in dogs. A noncardiac cough is more frequently nonproductive, loud and "honky," whereas cough caused by left-sided CHF can be softer and may have a more productive "wet" character, in particular in large dogs with DCM where co-existing respiratory disease is less common.

Exercise Intolerance, Weakness, Wasting, and Syncope

Variable degrees of weakness and exercise intolerance often develop in dogs and cats with heart disease. However, exercise intolerance can be difficult to assess in cats. Weakness and exercise intolerance can occur as a consequence of a reduced cardiac output resulting in reduced peripheral perfusion with reduced oxygen and nutrient delivery to skeletal muscles.

Weakness, exercise intolerance, and syncopal events can develop due to pulmonary hypertension or cardiac arrhythmia, intermittent or sustained, in dogs and cats with heart disease. Pets with sustained bradycardia or tachycardia are often weak even at rest and exhibit significant exercise intolerance. In cases of intermittent arrhythmia, the owner often describes a rapid change in the dog's behavior, consciousness, or postural tone. Defecation and urination can accompany these events. Even though syncope can occur in dogs and cats with heart disease, it is not specific for heart disease or heart failure, which underlines the importance of obtaining an accurate and detailed case history.

In dogs with CHF and a chronic reduction of peripheral perfusion, a loss of body weight may be apparent. Sequential measurements of body weight over time can be useful to identify subtle weight loss. However, identification of weight loss may be problematic if loss of muscle mass is masked by concurrent fluid retention.

Abdominal Distension

Abdominal distension can be caused by a wide variety of diseases, both cardiac and noncardiac in origin. In heart disease, abdominal distension is the result of right-sided CHF leading to congestion of abdominal organs (such as the liver) and transudation of fluid into the abdominal cavity. This usually occurs slowly, and remains unnoticed by the owner until quite advanced stages. In other conditions, such as pericardial effusion, the ascites may develop more rapidly.

Cyanosis

Cyanosis is defined as a blue to blue-gray discoloration of the mucous membranes as the result of increased concentration of deoxygenated hemoglobin. It can be evident on physical examination and also described by the owner. Discoloration of the tongue and mucous membranes is a common complaint of owners suspecting heart disease in their pet, but can be difficult to identify or replicate at the clinic. Additionally, cyanosis can be difficult to identify because of pigmentation of the skin and mucous membranes. Cyanosis in veterinary patients is usually associated with severe left-sided CHF or congenital heart disease. In case of severe left-sided CHF, other significant signs of disease always accompany the cyanosis. In some cases of congenital heart disease leading to right-to-left shunting of blood, some animals can have reduced exercise capacity, pelvic limb weakness and frequently have to sit down during play or exercise. Depending on the degree of shunting, some of these animals can be cyanotic at rest but the cyanosis becomes more apparent with physical exercise.

Physical Examination

A thorough physical examination is the foundation for the clinical work-up in dogs and cats with suspected heart disease. The examination includes general inspection and observation (e.g., attitude, body condition, mobility, degree of anxiety, and respiratory pattern), and a thorough physical examination to identify abnormalities in other organ systems. The cardiovascular examination includes evaluation of the peripheral circulation (mucous membranes), systemic veins (jugular veins), peripheral arterial pulses, the precordium (left and right chest wall over the heart), palpation of abdomen to identify ascites, and auscultation of heart and lungs.

Mucous Membranes

The mucous membrane color and capillary refill time are used to evaluate peripheral perfusion. The mucous membranes of the oral cavity are usually used for this purpose, but also ocular and caudal (vaginal or preputial) membranes can be examined. Preferably findings of caudal membranes should be compared with findings in the oral cavity. Findings of bluish discoloration are suggestive of cyanosis (see earlier), darkish red is suggestive of erythrocytosis, and pale membranes are suggestive of anemia and/or decreased perfusion. Capillary refill time (CRT) is conducted to evaluate peripheral perfusion. While commonly performed, CRT is a comparably insensitive method to detect abnormal perfusion.

Systemic Veins

The jugular veins should be inspected in cases with suspected heart disease, and clipping or wetting of the fur may be required to visualize these vessels. Distension or pulsations of the jugular veins, while the animal is sitting with the neck moderately extended, are indicative of increased systemic venous pressure (right-sided CHF) or occlusion (most commonly neoplasia or thrombosis) of the vessel at the level between the right heart and the jugular vein. Because there is no valve between the right atrium and the systemic veins, changes in pressure in the right atrium are transmitted within the systemic veins, and can be caused by right atrial contractions at high systemic venous pressure or tricuspid regurgitation. Sometimes, the carotid arterial pulse is transmitted through the soft tissues, mimicking a venous pulsation (so-called false venous pulsations). Differentiation between true and false venous pulsations can be obtained by applying pressure to the jugular vein at a level slightly below the area of the pulsation. If the pulsation disappears, it is a sign of true venous pulsation; if it continues, it is a sign of false venous pulsation.

Peripheral Arterial Pulsations

The strength and quality of the femoral arterial pulses are subjectively assessed by simultaneous palpation of both femoral arteries in a standing animal. Sufficient pressure should be placed on the vessels to occlude them, so that pulsation is no longer palpable. The pressure is then slowly released until maximal pulsation is evident.

This subjective evaluation provides information on the pulse pressure (i.e. the difference between systemic arterial peak systolic and diastolic pressures) and potential presence of various heart diseases.

The quality of pulses in the two limbs should be compared, particularly in cats. Absent femoral arterial pulse in one or both limbs may be indicative of arterial thromboembolism. The femoral artery should be palpated simultaneously with cardiac auscultation to detect heartbeats that do not produce pulses. Arrhythmias can cause the heart to contract before it is properly filled with blood, producing variable pulses or pulse deficits.

Palpation of the Precordium

The precordium is evaluated by placing palms and fingers on each side of the thorax over the cardiac ostia (Figure 15.1). Normally, the cardiac contraction (precordial impulse) is best felt on the left side of the thorax over the apical area. Changes in cardiac size and shape, or space-occupying thoracic masses can cause a shift of the location of the precordial impulse. A weak impulse can be caused by obesity, hypovolemia, thoracic masses, pleural or pericardial effusion, or pneumothorax. Increased precordial impulse can be caused by hyperkinetic conditions such as stress or anemia or conditions characterized by cardiac volume overload and cardiomegaly, such as severe MMVD or DCM. Severe valvular regurgitation or stenosis can cause palpable "buzzing" vibrations called a *precordial thrill*. The intensity of the auscultated heart murmur is always greatest over the area of the thrill.

Evaluation of Fluid Accumulation

Right-sided CHF leads to accumulation of fluid in body cavities, most commonly in the abdomen. The abdomen should therefore be palpated for ballottement and the presence of fluid accumulation (ascites). Mild ascites is difficult to detect, whereas moderate to severe ascites is comparably easy to detect. Pleural effusion is more difficult to detect and thoracic radiography or centesis is often required to obtain a definite diagnosis. The limbs should also be inspected for the presence of peripheral edema, although this is an extremely unusual finding in dogs and cats with heart disease.

Auscultation

Cardiac auscultation is an important component of the physical examination in dogs and cats with suspected cardiac disease. An exact diagnosis can seldom be established based solely on cardiac auscultation, but optimal auscultation technique can substantially narrow down the list of differential diagnoses. Auscultation allows assessment of heart rate, rhythm, and presence of abnormal sounds, such as murmur, click, and additional heart sounds.

Auscultation should be performed in a quiet environment, and background noise should be minimized. The animal should preferably be standing on all four limbs during cardiac auscultation as abnormal sounds, which can easily be mistaken for heart murmurs, can arise in a recumbent animal due to rubbing of the heart against the chest wall. Furthermore, localization of the area of origin of different cardiac sounds is more easily achieved in a

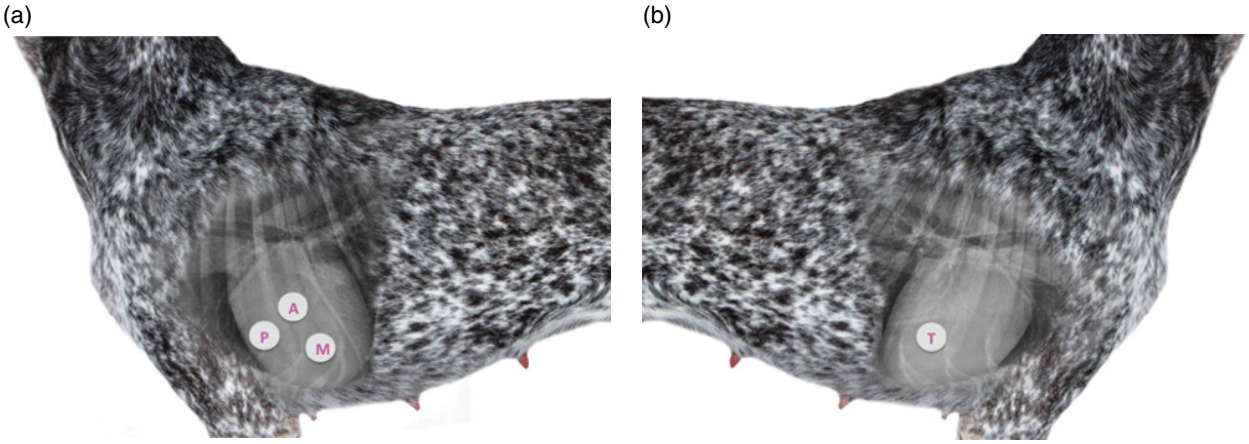


Figure 15.1 Principal areas of cardiac auscultation in dogs. The valve relationships are the same in cats, whereas intercostal space (ICS) guidelines differ slightly for cats and are, accordingly, mentioned in parentheses. Because of the small size of the feline heart, murmurs in cats are often described as sternal versus parasternal, basilar versus apical, and left versus right. (a) Left hemithorax: M = mitral valve area: 5th (cat: 5th–6th) ICS at the costochondral junction. A = aortic valve area: 4th ICS (cat: 2nd–3rd ICS) just above the costochondral junction. P = pulmonic valve area: 2nd–4th (cat: 2nd–3rd) ICS just above the sternum. (b) Right hemithorax: T = tricuspid valve area: 3rd–5th (cat: 4th–5th) ICS near the costochondral junction.

standing animal. The entire cardiac area should be auscultated thoroughly. The areas of auscultation of the heart are shown in Figure 15.1.

The areas of the ventral thorax adjacent to the sternum should always be auscultated in cats, as murmurs and gallop rhythms often are heard best at this location. If needed, the animal's mouth should be manually gently closed for brief periods of time as panting can generate referred sounds, which can be mistaken for murmurs. Evaluation of heart sounds and murmurs is often difficult in purring cats. The purring can be stopped by quickly occluding a nostril, by placing the cat in the proximity of a running tap, by holding cotton wool soaked in alcohol near the cat's nose, or by blowing short bursts of air into the face of the cat. Breathing sounds, especially in cats, can be mistaken for sounds originating from the heart, and differentiating heart sounds from breath sounds can be facilitated by watching the cat's breathing pattern while simultaneously ausculting the heart.

Heart Rate and Rhythm

Dogs in CHF are likely to be tachycardic, although the degree of tachycardia may be modest. Tachycardia in CHF patients results from parasympathetic withdrawal and increased sympathetic tone. Cats in decompensated CHF may present with normal, increased or decreased heart rate. Healthy dogs have either a regular heart rhythm or a respiratory sinus arrhythmia where the heart rate increases during inspiration and decreases during expiration due to changes in vagal tone. This phenomenon can be exaggerated, particularly in the presence of respiratory disease. Dogs presenting with respiratory sinus arrhythmia are unlikely to be in decompensated CHF with pulmonary edema. Healthy cats normally have a regular heart rhythm, and the finding of respiratory sinus arrhythmia in cats warrants further examination of potential respiratory disease. Other arrhythmias in dogs and cats, such as the detection of premature beats or long periods of asystole, can indicate presence of heart disease, and further diagnostic tests such as an electrocardiogram are then indicated.

Heart Sounds and Murmurs

Two heart sounds are normally audible in healthy dogs and cats. The first heart sound (S1), which is heard loudest at the heart apex, occurs concurrently with closure of the atrioventricular valves, whereas the second heart sound (S2), which is heard loudest at the heart base, occurs concurrently with closure of the semilunar valves. The intensity of heart sounds is influenced by many factors, such as auscultation technique, body condition, and presence of cardiac disease. Heart sound intensity can be decreased in animals affected by obesity, pericardial or pleural effusions, space-occupying lesions (such as thoracic masses), diaphragmatic hernias, shock, bradycardias, or severely affected myocardial function. The intensity of S2 is commonly dampened in dogs with severe MMVD. Heart sound intensity can be increased in animals with increased sympathetic tone, cardiac enlargement, or in those with narrow chest conformation. Intensity of heart sounds often varies from beat to beat in animals affected by cardiac arrhythmias, such as atrial fibrillation and ventricular tachycardia.

In dogs and cats, the presence of S3 and/or S4 signifies a gallop heart sound (tripling or quadrupling of the heart sounds, resembling the canter of a horse), and is generally an indication of myocardial disease in dogs and cats. The S3 (ventricular gallop) occurs early in diastole, and is associated with rapid ventricular filling during early diastole into a ventricle with decreased compliance, and is typically heard in dogs with conditions characterized by ventricular volume overload, such as DCM, MMVD or patent ductus arteriosus (PDA). The S4 (atrial gallop) occurs later in diastole, and is associated with vigorous atrial contractions in animals with conditions characterized by increased resistance to ventricular emptying or impaired ventricular compliance. This typically occurs in disorders with ventricular concentric hypertrophy, such as in cats with hypertrophic cardiomyopathy (HCM) or systemic hypertension. The S4 can also be present in dogs with third-degree atrioventricular (AV) block, dogs with ruptured chordae tendineae, or even in healthy cats due to decreasing ventricular compliance with age. The S3 and S4 can be superimposed in animals with tachycardia (most commonly in cats), resulting in one additional diastolic sound called a summation gallop.

Systolic clicks are transient, mid to late systolic sounds, which are higher in frequency than gallop sounds and are mainly heard in dogs with abnormal AV valve leaflet movement, such as mitral valve prolapse in dogs affected by mild MMVD. Clicks occurring in early systole can be associated with abnormal valve leaflet movement or great vessel dilation in dogs with aortic or pulmonic stenosis.

Murmurs are auditory vibrations caused by high-velocity and turbulent blood flow through the heart and vessels. Murmurs can be characterized by timing within the cardiac cycle, anatomic location, radiation area, intensity (loudness), frequency (pitch), and shape of vibration pattern (which is visualized by phonocardiography). Most cardiovascular diseases in dogs and cats result in systolic murmurs, which most commonly start immediately after the S1, but they can also start later in systole. Systolic murmurs can last for only a portion of the systole (early, mid or late systolic murmurs), throughout systole from the end of S1 to the beginning of S2

(holosystolic murmur), or, rarely, throughout systole from the beginning of S1 to the end of S2 (pansystolic murmur). Diastolic turbulent blood flow is rare in dogs and cats, and can be relatively difficult to detect. Diastolic murmurs most commonly start immediately after the S2. Continuous murmurs last throughout systole and diastole. The most common heart disease associated with a continuous murmur is PDA where the murmur commonly peaks in intensity at the time of the S2.

Point of maximum intensity (PMI) of a murmur is commonly the location over the thorax where the murmur is loudest, and can serve as a guide to the origin of the murmur. The PMI is associated with a particular valve region (i.e., pulmonic, aortic, mitral, tricuspid). The small size of the feline heart makes it difficult to distinguish the different valve areas on the thorax. Accordingly, localization of murmurs in cats is often described as sternal versus parasternal, base versus apex, and left versus right. The areas of auscultation of the heart in dogs are shown in Figure 15.1. The area of murmur radiation refers to how widely the murmur can be heard from the PMI, and generally increases with increasing turbulence.

Table 15.1 Classification of murmur intensity

	Grade	Description
Low-intensity murmurs	Grade 1	A very soft, barely audible murmur localized to a small area
	Grade 2	A soft murmur, heard immediately, localized to a small area
Moderate-intensity murmurs	Grade 3	A moderately loud murmur, evident at more than one location
	Grade 4	A loud murmur that radiates considerably to other areas, but without a consistent palpable precordial thrill (vibrations created by turbulence within the heart through the chest wall)
High-intensity murmurs	Grade 5	A loud murmur that radiates considerably to other areas, accompanied by a palpable precordial thrill
	Grade 6	Very loud murmur that radiates considerably to other areas, accompanied by a palpable precordial thrill, and is audible without the use of a stethoscope or when the stethoscope is slightly lifted off the thoracic wall

Murmurs are traditionally graded on a scale of 1–6. However, evidence exists that a four-grade scale can be used for some heart diseases without losing clinically important information (Table 15.1).

For some cardiac diseases, such as MMVD and aortic/pulmonic stenosis, grading of murmurs serves as a rough estimate of disease severity. However, a lack of agreement exists between severity of cardiac disease and murmur grade for other conditions, such as for ventricular septal defects, dilated or restrictive cardiomyopathy (DCM/RCM), and feline cardiomyopathies. Although the majority of dogs with heart disease have an audible murmur, it is important to remember that some cardiac diseases (such as pericardial diseases, cardiac neoplasia, DCM, atrial septal defects [ASD], right-to-left shunting PDA, and primary myocardial diseases in cats) do not necessarily produce blood flow turbulence and an audible murmur (Table 15.2).

Presence of a heart murmur does not always signal structural cardiac disease as murmurs in cats and dogs can also arise due to other physiologic processes. Physiologic murmurs tend to be fairly quiet (grade 1/6–3/6), and may vary in intensity with changes in heart rate. Mild dynamic right ventricular outflow tract obstruction is a common cause of murmurs in healthy cats in stressful situations such as examination at a veterinary hospital. Puppies and kittens may have "innocent" physiologic murmurs assumed to arise due to large stroke volumes relative to the size of their great vessels and/or due to physiologic anemia. These murmurs usually disappear before approximately 5 months of age. Murmurs may also be created in an anemic animal due to the combination of decreased blood viscosity and increased stroke volume. High-output diseases, such as chronic renal disease and hyperthyroidism, can also give rise to a systolic murmur due to increased velocity of the ejected blood. Finally, murmurs are common in fit dogs with athletic hearts, where the murmurs are caused by mild mitral/tricuspid valve insufficiency and/or a large stroke volume into the aorta.

Respiratory Auscultation

Normal respiratory sounds differ in frequency (pitch), intensity (loudness), and timing along different parts of the animal's upper and lower respiratory tract. Normal lung sounds are comparably soft sounds heard louder on inspiration than expiration, whereas normal sounds auscultated over the trachea are much louder and higher pitched and heard well on both inspiration and expiration. Based on location and sound characteristics, normal lung sounds are commonly termed vesicular, bronchial, or bronchovesicular, even though the term "vesicular" incorrectly implies that sounds are made in the vesicles (alveoli) of the lung.

Auscultation of the lungs of a cardiovascular patient may reveal abnormal sounds superimposed on normal

Table 15.2 Simplified table for presumptive diagnosis of murmur origin in common heart conditions

Point of maximal intensity	Timing	Associated heart conditions	Cause of murmur	Sound quality
Left heart base	Systolic	Physiologic or innocent murmurs	Turbulence in aorta/pulmonary artery	Soft or musical. Crescendo-decrescendo
		Aortic and pulmonic stenosis (tetralogy of Fallot)	Turbulence in aorta/pulmonary artery	Soft to harsh (depending on disease severity). Crescendo-decrescendo
		Atrial septal defect	Turbulence in pulmonary artery	If present, soft. Crescendo-decrescendo
	Diastolic	Aortic and pulmonic regurgitation	Turbulence in left or right ventricle	Soft, blowing (barely audible). Decrescendo
Left axillary region/left heart base	Continuous (systole and diastole)	Left to right shunting patent ductus arteriosus (PDA)	Turbulence in the main pulmonary artery	"Machinery" sound of varying intensity throughout the cardiac cycle. Crescendo-decrescendo in systole peaking at S2
Left heart apex	Systolic	Mitral regurgitation (secondary to myxomatous mitral valve disease, mitral dysplasia, etc.)	Turbulence in the left atrium	Soft (blowing), musical, or harsh, depending on disease severity. Decrescendo or plateau shaped
Right heart apex	Systolic	Tricuspid regurgitation (secondary to myxomatous tricuspid valve disease, tricuspid dysplasia, pulmonary hypertension, etc.)	Turbulence in the right atrium	Soft to harsh depending on disease severity. Decrescendo if mild in intensity, plateau shaped when moderate/severe in intensity
Right heart base (cranially near the sternum)	Systolic	Ventricular septal defects (left to right shunting)	Turbulence in the right ventricle/right ventricular outflow tract	Harsh and plateau shaped (occasionally varying conformation throughout systole)
Parasternal (cats)	Systolic	Left ventricular outflow tract obstruction with or without mitral regurgitation (commonly caused by hypertrophic cardiomyopathy)	Turbulence in the left ventricular outflow tract, sometimes accompanied by turbulence in the left atrium if systolic anterior motion (SAM) is present	Soft to harsh, crescendo-decrescendo
	Systolic	Dynamic right ventricular outflow tract obstruction (DRVOTO) (commonly stress-induced or caused by hemodynamic alterations)	Turbulence in the right ventricular outflow tract	Soft crescendo-decrescendo

lung sounds. Auscultation of dogs and cats presenting with pulmonary edema often reveals harsh lung sounds, or high-frequency crackles at the end of inspiration. Crackles are interrupted, nonmusical, crepitant sounds, which in general are associated with conditions in which some airways are closed. Crackles should not be considered pathognomic for pulmonary edema as primary respiratory disease can also produce crackles. Wheezes, which are high-frequency musical sounds of longer duration associated with narrowing of an airway, can also be heard in animals with pulmonary edema. Animals can present with interstitial pulmonary edema without any abnormal auscultatory sounds other than increased bronchovesicular sounds due to hyperpnea.

Attenuated or absent bronchovesicular sounds can be due to pleural effusion or shallow breathing. Animals with pleural space disease, such as pleural effusion in cats in decompensated CHF, often present with a paradoxical respiratory pattern with prominent abdominal wall movements. Thoracic auscultation in these animals may reveal dull lung sounds, muffled heart sounds, or an auscultable fluid line.

16

Imaging in Cardiovascular Disease

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The diagnosis of canine and feline heart diseases as well as that of heart failure is predominantly based on thoracic radiography associated with standard transthoracic echocardiography, also called conventional echocardiography. In the late 1980s, the miniaturization of transesophageal probes led to the use of transesophageal echocardiography especially for analyzing specific abnormalities or for monitoring surgical and interventional techniques. During the last decade, newer imaging modalities such as tissue Doppler imaging, strain and strain rate imaging, and speckle tracking echocardiography have been introduced in veterinary cardiology, allowing an accurate assessment of myocardial performance, deformation, and synchrony. The following chapter provides an overview of these imaging techniques and their application in clinical settings, with particular emphasis on the two most commonly used in practice: thoracic radiography and conventional echocardiography.

Cardiac Radiography

Although most radiographic findings are not specific and therefore do not lead to an accurate definitive diagnosis of a given heart disease, thoracic radiography remains a key complementary examination to detect heart enlargement, assess the presence or absence of congestive heart failure, and distinguish between respiratory and cardiovascular diseases.

Normal Thoracic Radiography

Heart and thoracic vessels should be systematically evaluated on at least two good-quality views taken during inspiration – the dorsoventral view and a lateral view. Ventrodorsal views may also be used, but dorsoventral views usually provide a better definition of caudal pulmonary vessels and of the hilar area than the ventrodorsal view, and therefore allow a better assessment of cardiogenic pulmonary edema, particularly in the canine species. Additionally, dorsoventral views are often better tolerated than ventrodorsal views in the case of dyspnea. Ventrodorsal views, which are most often associated with a more central position of the heart within the thorax, may sometimes be used to complement the dorsoventral view to detect small volumes of pleural effusion and to better assess specific lung lesions.

In both canine and feline species, the heart shape is most often relatively ovoid with a pointed ventral apex. Nevertheless, several noncardiac factors (Table 16.1) can influence heart size and shape, including respiratory phase, pericardial fat accumulation (Figure 16.1), age and, most of all, breed (see details below and Figure 16.2). All these are important to take into consideration, as they may be a source of misinterpretation of cardiomegaly.

Lateral Views

Either right or left lateral views may be performed. Nevertheless, as some variations may exist according to positioning of the patient, the same lateral projection should be used to ensure a reliable comparison of radiographic findings over time in sequential radiographs.

On lateral views, the heart, which is located between the third and sixth intercostal spaces, tends to "lie" more on the sternum in cats than in dogs, and in older cats (>7 years old) more than in younger cats (Figure 16.3). The maximum heart width (or maximum cranial–caudal diameter) is usually around two intercostal spaces in the cat and between 2.5 and 3.5 intercostal spaces in the dog, with breed variations (Figures 16.2 and 16.3). For example, the heart in "barrel-chested" dogs tends to be more globular, with a greater sternal

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Table 16.1 Main noncardiac-related factors able to induce cardiac silhouette changes on thoracic radiographs

Factors	Radiographic change
Age	
Young age (dog)	Heart tends to be larger relatively to the thoracic cavity size than that of adult dogs
Old age (cat)	Heart of cats >7 years old tends to have a more horizontal orientation on lateral views, with a prominent aortic arch on lateral, DV, and VD views
Breed	See Table 16.2, text, and Figure 16.2
Patient positioning	Chest rotation can increase the apparent heart base size and that of the left atrium
Respiration phase	
Expiration	The heart appears wider than in inspiration with increased sternal contact (therefore potentially mimicking right heart enlargement)
Body condition score	
Overweight	Pericardial and mediastinal fat accumulation can mimic cardiomegaly (Figure 16.1)
Cachexia	Cachexia can be associated with a small cardiac silhouette (microcardia)
Hypovolemia	Hypovolemia is associated with microcardia and small vessels (pulmonary vessels and caudal vena cava)
Lung, mediastinal, pleural and sternal diseases	
Lung parenchymal and mediastinal mass lesions	Such lesions can modify position and axis of the heart and can also obscure cardiac margins ("positive silhouette" sign). The cranial cardiac silhouette may also be masked by the thymus in puppies
Lung atelectasis	Atelectasis can cause a mediastinal shift and therefore can modify position and axis of the heart
Sternal deformations (congenital or acquired)	Such lesions can modify position and axis of the heart

DV, dorsoventral; VD, ventrodorsal.

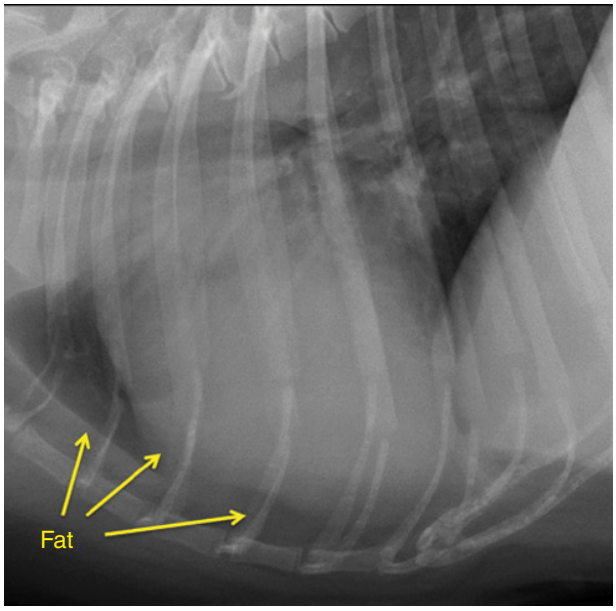


Figure 16.1 Lateral thoracic radiograph of an obese dog. The cardiac silhouette appears falsely enlarged owing to mediastinal and pericardial fat accumulation. Fat, which is characterized by slightly lower density than the heart, is clearly seen ventrally to the heart. *Source:* Medical Imaging Unit, ENVA.

contact than that of narrow- and deep-chested dogs, which appears elongated with a more vertical orientation (Figure 16.2).

Right heart chambers are approximately positioned cranially and left chambers caudally to the line drawn from the tracheal bifurcation to the apex (base–apex axis). Both atrial chambers are located dorsally and the ventricular chambers ventrally to the line drawn perpendicular to the base–apex axis and running along the ventral border of the caudal vena cava (Figure 16.4).

The vertebral heart score (VHS) may be used to objectively assess heart size, and to confirm and determine the severity of cardiomegaly in both cats and dogs (Figure 16.5). The mean ± SD canine VHS is 9.7 ± 0.5 vertebrae (range: 8.5–10.6). Nevertheless, VHS values are influenced by breed-dependent heart shape and size, thoracic conformation (long *versus* short thorax), and thoracic vertebrae abnormalities such as hemivertebrae. For example, abnormal thoracic vertebrae have recently been shown to be associated with a significant increase of VHS in the bulldog and Boston terrier. Such breed-dependent variations of VHS (Table 16.2) represent a limitation of the vertebral heart-size method in the dog. Nevertheless, the VHS system is easy to use and may be helpful to objectively compare heart size in sequential radiographs.

Feline VHS seems to be less subject to variations than canine VHS, with normal values of 7.5 ± 0.3 vertebrae.

Dorsoventral View

As in the lateral views, the normal canine cardiac shape varies widely among breeds, with a wider and more rounded cardiac silhouette in barrel-chested

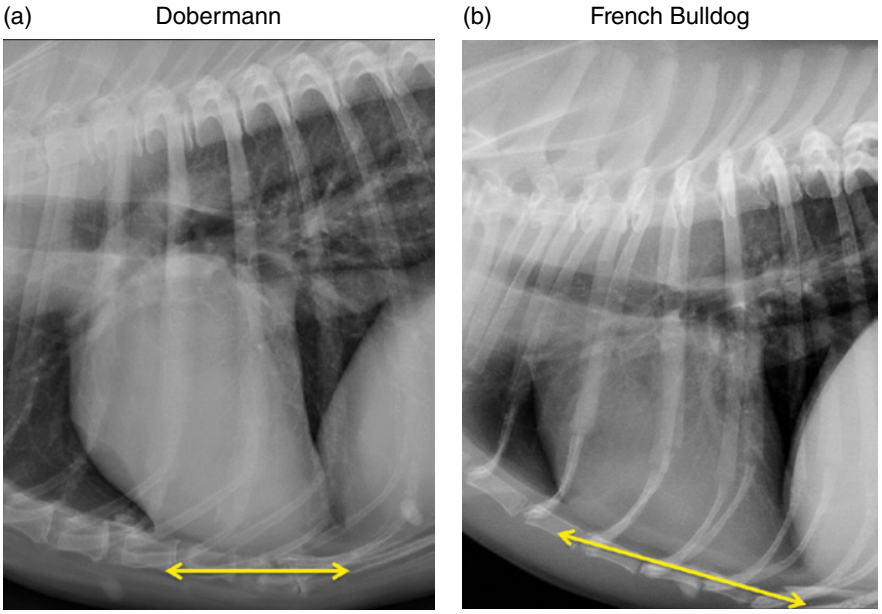


Figure 16.2 Lateral thoracic radiographs of two normal dogs from different breeds (a: Doberman; b: French bulldog). Both cardiac shape and size vary markedly between the two dogs. Note the elongated upright orientation of the Doberman's heart and the wider silhouette, with a greater sternal contact (*double arrows*) and a more horizontal orientation, of the bulldog's heart. *Source:* Medical Imaging Unit, ENVA.

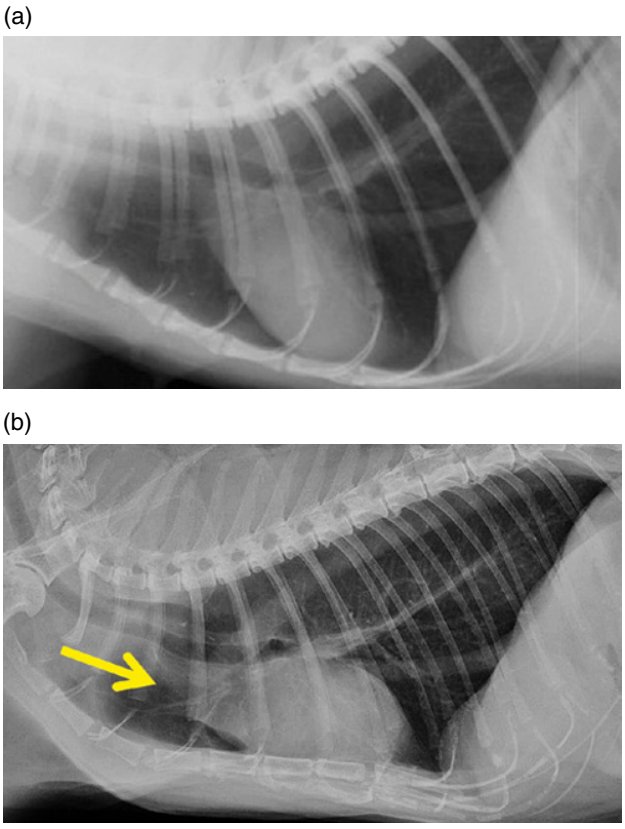


Figure 16.3 Lateral thoracic radiographs of two normal cats, one young adult cat (a) and one 15-year-old cat (b). Compared to the young adult cat, note the more horizontal orientation of the heart and the prominent aortic arch (*arrow*) in the aged cat. *Source:* Medical Imaging Unit, ENVA.

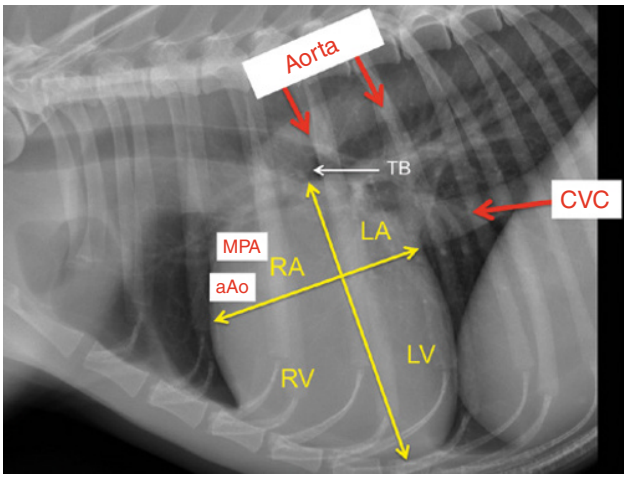


Figure 16.4 Lateral thoracic radiograph of a normal dog showing the approximate location of the four cardiac chambers, the tracheal bifurcation (TB) and the main thoracic vessels. aAo, ascending aorta; CVC, caudal vena cava; LA, left atrium; LV, left ventricle; MPA, main pulmonary artery; RA, right atrium; RV, right ventricle. *Source:* Medical Imaging Unit, ENVA.

dogs than in narrow-chested and deep-chested dogs. The maximum canine heart width is usually less than 65% of the thorax width at the same level. The maximum feline heart width is less than one half of the thorax width, with a prominent aortic arch in aged animals.

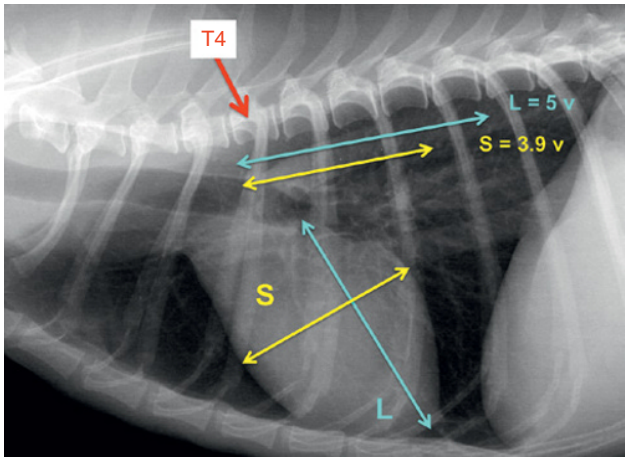


Figure 16.5 Calculation of the vertebral heart score (VHS) from a thoracic lateral radiograph in a normal mixed-breed dog. The cardiac long-axis dimension (L) represents the combined size of the left atrium and the left ventricle, and is measured from the cardiac apex to the base where it intersects the tracheal bifurcation. The cardiac short-axis dimension (S) is perpendicular to L, and is measured at the point of maximum cardiac width, which usually corresponds to the point at which the cardiac silhouette intersects the ventral border of the caudal vena cava (as shown here). S therefore includes left and right cardiac chambers in the region of the coronary groove. L and S cardiac dimensions are then transposed on the vertebral column and recorded as the corresponding number of vertebrae (v), as measured caudally from the cranial edge of the fourth thoracic vertebra (T4). These values are summed to calculate the VHS. As in the present case, L is equal to 5 v and S to 3.9 v, the VHS value is 8.9 v, which is within normal ranges (8.5–10.6 v according to Buchanan *et al*., *J Am Vet Med Assoc* 1995; **206**: 194–9). *Source:* Medical Imaging Unit, ENVA.

A clock face analogy can be used to approximately localize the normal cardiovascular structures responsible for the cardiac silhouette (Figure 16.6). This clock face analogy can help in identifying the origin of bulges and deformations of the cardiac silhouette associated with heart diseases.

The VHS can also be calculated on the dorsoventral view as follows: sum of cardiac long-axis (distance from cardiac apex to base) and short-axis dimensions (perpendicular to the long-axis measurement at the maximum cardiac width) assessed in vertebrae beginning with the cranial edge of the fourth vertebra on the lateral radiograph. The feline VHS on the dorsoventral view is 8.1 ± 0.45 vertebrae. Also in the cat, the maximum short-axis cardiac dimension on the dorsoventral view, compared with the thoracic spine beginning at the cranial edge of the fourth vertebra on the lateral chest radiograph, is usually less than four vertebrae.

Common Abnormal Cardiac Radiographic Patterns

Congenital and acquired heart diseases can be responsible for generalized or localized cardiac enlargement associated with changes in the intrathoracic blood vessels. The main cardiac causes responsible for left, right and global heart enlargement are presented in Table 16.3 and in Figures 16.7–16.12.

Left Heart Diseases (Figures 16.7–16.10)

Left Atrial Enlargement

On lateral views, left atrial enlargement is characterized by:

- straightening of the dorsocaudal part of the cardiac silhouette
- dorsal elevation of the caudal portion of the trachea and tracheal bifurcation (carina)
- separation of the normally superimposed caudal main bronchi owing to a disproportionate dorsal elevation of the latter (with a more dorsal position of the left bronchus as compared to the right).

On the dorsoventral view, left atrial enlargement is characterized by:

- bulging of the cardiac silhouette in the 2–3 o'clock position (Figures 16.7b and 16.9b) owing to the enlargement of the left auricular appendage (dog and cat) and the left atrium (cat)
- the presence of a round soft tissue opacity covering the caudal part of the cardiac silhouette, with lateral displacement of the mainstem bronchi in the case of marked left atrial dilation in the dog (Figures 16.7b and 16.8c).

Similar abnormal patterns are detected on the ventrodorsal view.

Left Ventricular Enlargement

On lateral views, left ventricular enlargement is characterized (Figures 16.7a, 16.7c, 16.8a, 16.10a) by:

- a "taller" heart with straightening of the caudal part of the cardiac silhouette
- dorsal elevation of the trachea, carina, and mainstem bronchi.

On the dorsoventral view, left ventricular enlargement is characterized by:

- elongation and enlargement at the 3–6 o'clock position of the cardiac silhouette (Figure 16.8c)
- broadening and rounding with a possible shift to the right of the cardiac apex.

Similar abnormal patterns are detected on the ventrodorsal view.

Table 16.2 Examples of vertebral heart score (VHS) values assessed on lateral thoracic radiographs in normal dogs. For calculation of VHS, see Figure 16.5. SD, standard deviation.

Animals	VHS value (mean ± SD vertebrae)	Comments	*References*
All breed dogs (n = 100)	**9.7 ± 0.5**		*1. Buchanan JW, et al. J Am Vet Med Assoc 1995;206:194–9*
Boston terrier (n = 19)	**11.7 ± 1.4**	VHS assessed on right lateral views – 74% of dogs had a VHS >2SD above the VHS of reference #1 (9.7 ± 0.5)	*2. Jepsen-Grant K, et al. Vet Radiol Ultrasound 2013;54:3–8*
Bulldog (n = 30)	**12.7 ± 1.7**	VHS assessed on right lateral views except for 1 dog – 93% of dogs had a VHS >2SD above the VHS of reference #1 (9.7 ± 0.5)	*2. Jepsen-Grant K, et al. Vet Radiol Ultrasound 2013;54:3–8*
Dachshund (n = 29)	**9.7 ± 0.5**	VHS assessed on right lateral views – 7% of dogs had a VHS >2SD above the VHS of reference #1 (9.7 ± 0.5)	*2. Jepsen-Grant K, et al. Vet Radiol Ultrasound 2013;54:3–8*
Lhasa apso (n = 18)	**9.6 ± 0.8**	VHS assessed on right lateral views – 6% of dogs had a VHS >2SD above the VHS of reference #1 (9.7 ± 0.5)	*2. Jepsen-Grant K, et al. Vet Radiol Ultrasound 2013;54:3–8*
Pomeranian (n = 18)	**10.5 ± 0.9**	VHS assessed on right lateral views except for 1 dog – 50% of dogs had a VHS >2SD above the VHS of reference #1 (9.7 ± 0.5)	*2. Jepsen-Grant K, et al. Vet Radiol Ultrasound 2013;54:3–8*
Pug (n = 30)	**10.7 ± 0.9**	VHS assessed on right lateral views – 43% of dogs had a VHS >2SD above the VHS of reference #1 (9.7 ± 0.5)	*2. Jepsen-Grant K, et al. Vet Radiol Ultrasound 2013;54:3–8*
Shih tzu (n = 30)	**9.5 ± 0.6**	VHS assessed on right lateral views – 0% of dogs had a VHS >2SD above the VHS of reference #1 (9.7 ± 0.5)	*2. Jepsen-Grant K, et al. Vet Radiol Ultrasound 2013;54:3–8*
Yorkshire terrier (n = 30)	**9.9 ± 0.6**	VHS assessed on right lateral views – 13% of dogs had a VHS >2SD above the VHS of reference #1 (9.7 ± 0.5)	*2. Jepsen-Grant K, et al. Vet Radiol Ultrasound 2013;54:3–8*
All breed dogs (n = 63) *Right lateral recumbency* *Left lateral recumbency*	**9.8 ± 0.6** **9.5 ± 0.8**	VHS was significantly larger in right than in left lateral recumbency	*3. Greco A, et al. Vet Radiol Ultrasound 2008;49:454–5*
Beagle (n = 19) *Right lateral recumbency* *Left lateral recumbency*	**10.5 ± 0.4** **10.2 ± 0.4**	VHS was significantly larger in right than in left lateral recumbency	*4. Kraetschmer S, et al. J Small Anim Pract 2008;49:240–3*
Boxer (n = 20)	**11.6 ± 0.8**	Right lateral thoracic radiographs	*5. Lamb CR, et al. Vet Record 2001;148:707–11*
Doberman (n = 20)	**10.0 ± 0.6**	Right lateral thoracic radiographs	*5. Lamb CR, et al. Vet Record 2001;148:707–11*
Cavalier King Charles (n = 20)	**10.6 ± 0.5**	Right lateral thoracic radiographs	*5. Lamb CR, et al. Vet Record 2001;148:707–11*
German Shepherd dog (n = 20)	**9.7 ± 0.7**	Right lateral thoracic radiographs	*5. Lamb CR, et al. Vet Record 2001;148:707–11*
Rottweiler (n = 38)	**9.8 ± 0.1**		*6. Marin L, et al. Vet Radiol Ultrasound 2007;48:332–4*
Greyhound (n = 42)	**10.5 ± 0.1**	VHS was significantly higher in greyhounds than in rottweilers	*6. Marin L, et al. Vet Radiol Ultrasound 2007;48:332–4*

Left-Sided Congestive Heart Failure

In the case of left-sided congestive heart failure, prominent pulmonary veins owing to venous congestion are seen, particularly in the hilar area (as they enter the left atrium) on lateral views. The pulmonary vein diameter appears greater than that of the corresponding arteries. This asymmetry is easiest to detect for cranial vessels on lateral views (where the pulmonary veins are ventral to the accompanying arteries), and for caudal vessels on the dorsoventral view (where the pulmonary veins are medial to the accompanying arteries).

Radiographic signs of left-sided congestive heart failure also include visualization of mild to severe interstitial, peribronchial to alveolar pulmonary opacity

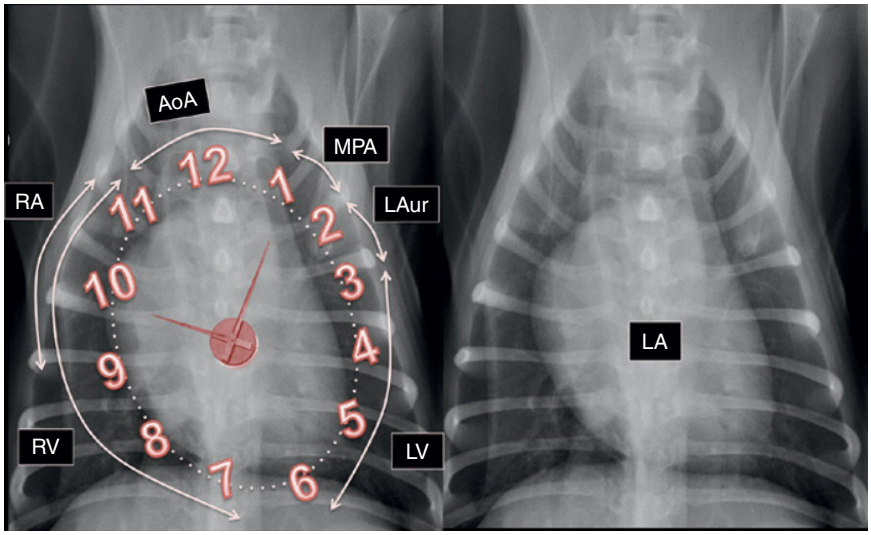


Figure 16.6 Clock face analogy (a) applied to the canine cardiac silhouette (b) on the dorsoventral view. The aortic arch (AoA) approximately extends from 11 o'clock to 1 o'clock, the main pulmonary artery (MPA) from 1 o'clock to 2 o'clock, the left ventricle (LV) from 3 o'clock to 6 o'clock, and the right ventricle (RV) from 6–7 o'clock to 11 o'clock (with a superimposition with the RA between 9 and 11 o'clock). In cats and dogs, enlargement of the left auricular appendage (Laur) contributes to a deformation of the cardiac silhouette between 2 and 3 o'clock. In the cat, the body of the left atrium (LA) also extends from 2 to 3 o'clock, whereas in the dog the LA is rather superimposed over the caudal part of the cardiac silhouette (b). *Source:* Medical Imaging Unit, ENVA.

(Figures 16.7c, 16.10a and 16.10b) due to pulmonary edema. Cardiogenic pulmonary edema is typically more pronounced in the dorsal perihilar area on lateral views in the dog, with a bilateral distribution on the dorsoventral view in both species. In some instances, it can be asymmetric in the dog, with the right lung fields more severely affected than the left. In the case of alveolar edema, the alveolar spaces are filled with fluid. The margins of the pulmonary vessels are therefore totally obscured and air bronchograms (corresponding to black air-filled bronchi surrounded by white radiopaque lung tissue) are detected.

Right Heart Diseases

Right Atrial Enlargement

On lateral views, right atrial enlargement is characterized by:

- enlargement of the dorsocranial part of the cardiac silhouette (Figure 16.11a)
- dorsal elevation of the trachea over the cranial portion of the heart (less commonly).

On the dorsoventral view, right atrial enlargement is characterized by bulging of the cardiac silhouette in the 9–11 o'clock position.

Right Ventricular Enlargement

On lateral views, right ventricular enlargement is characterized (Figures 16.7c and 16.11a) by:

- increased sternal contact, with widening and increased convexity of the cranioventral heart margins
- elevation of the apex from the sternum and, in the case of severe enlargement, dorsal elevation of the caudal vena cava as well.

On the dorsoventral view, right ventricular enlargement is characterized (Figure 16.11b) by:

- broadening and rounding of the cardiac silhouette at the 6–7 to 9–11 o'clock position with a reverse-D appearance
- a shift to the left of the cardiac apex in the case of severe enlargement.

Similar abnormal patterns are detected on the ventrodorsal view.

Right-Sided Congestive Heart Failure

Thoracic radiographic signs of right-sided congestive heart failure include visualization of right heart enlargement associated with widening of the caudal vena cava (whose normal diameter is usually approximately that of the descending thoracic aorta) and interlobar pleural fissures secondary to pleural effusion (with lung collapse and rounded pulmonary borders in severe cases).

Extrathoracic radiographic signs include hepatomegaly (extension of the liver caudally to the last rib with abnormally round margins and caudal displacement of the stomach) and ascites, which is characterized by abdominal distension and increased fluid opacity with loss of intraabdominal details.

Specific Radiographic Signs Associated with Heart Diseases

The main specific radiographic signs associated with heart diseases are presented in Table 16.3 and in Figures 16.7 to 16.12.

Table 16.3 Generalized or localized heart enlargement on thoracic radiographs: main cardiac causes, associated radiographic signs, differential diagnosis

Type of heart enlargement	Main causes	Potential associated radiographic signs	Differential diagnosis
Left heart enlargement			
Left atrial and/or ventricular enlargement	**Congenital heart diseases:** mitral dysplasia with mitral valve regurgitation, significant left-to-right shunting due to VSD and PDA, subaortic stenosis and/or aortic insufficiency **Acquired heart diseases:** hypertrophic and restrictive cardiomyopathy (cat), degenerative mitral valve disease (dog), mitral or aortic valve endocarditis, dilated cardiomyopathy, cardiomyopathy secondary to systemic arterial hypertension and hyperthyroidism (cat)	**Enlargement of the aortic arch** in the case of PDA, subaortic stenosis and systemic arterial hypertension **Increased pulmonary artery prominence and increased pulmonary vessels (veins and arteries)** in the case of VSD and PDA with significant left-to-right shunting **Increased pulmonary veins** in cases with **left-sided congestive heart failure** (see text)	Pulmonary mass and/or adenopathy in the hilar area (left atrial enlargement)
Isolated left atrial enlargement	**Congenital heart diseases:** mitral valve stenosis		
Right heart enlargement			
Right atrial and/or ventricular enlargement	**Congenital heart diseases:** tricuspid dysplasia with tricuspid regurgitation, significant left-to-right shunting due to ASD, pulmonic stenosis and/or pulmonic insufficiency (rare), tetralogy of Fallot **Acquired heart diseases:** degenerative tricuspid valve disease, arrhythmogenic right ventricular cardiomyopathy, pulmonary arterial hypertension (main causes: dirofilariosis, angiostrongylosis, respiratory diseases, pulmonary embolism, reversed-shunting congenital defects, etc.)	**Increased caudal vena cava** on lateral views in cases of **right-sided congestive heart failure** (see text) **Enlargement of the main pulmonary artery (post-stenotic dilation) with decreased pulmonary vasculature** in the case of pulmonic stenosis **Enlargement of the main pulmonary artery, abnormal pulmonary arteries (tortuous, larger than their accompanying veins)** in the case of pulmonary hypertension **Pulmonary infiltrates** in the case of dirofilariosis, pulmonary embolism, respiratory diseases, etc.	Tracheobronchial adenopathy and cranial mediastinal mass (including heart base tumor)
Isolated right atrial enlargement	**Congenital heart disease:** tricuspid stenosis **Acquired heart disease:** right atrial neoplasia (hemangiosarcoma)		
Generalized heart enlargement	Severe left and/or right heart diseases Pericardial effusion, peritoneal-pericardial hernia Intracardiac mass (tumor) "Athletic heart"	Globoid cardiac silhouette in the case of pericardial diseases, with gas-containing structures within the pericardial sac and loss of outline between the ventral diaphragmatic surface and the caudal ventral cardiac silhouette in the case of peritoneal-pericardial hernia	

ASD, atrial septal defect; DV, dorsoventral; PDA, patent ductus arteriosus; VD, ventrodorsal; VSD, ventricular septal defect.

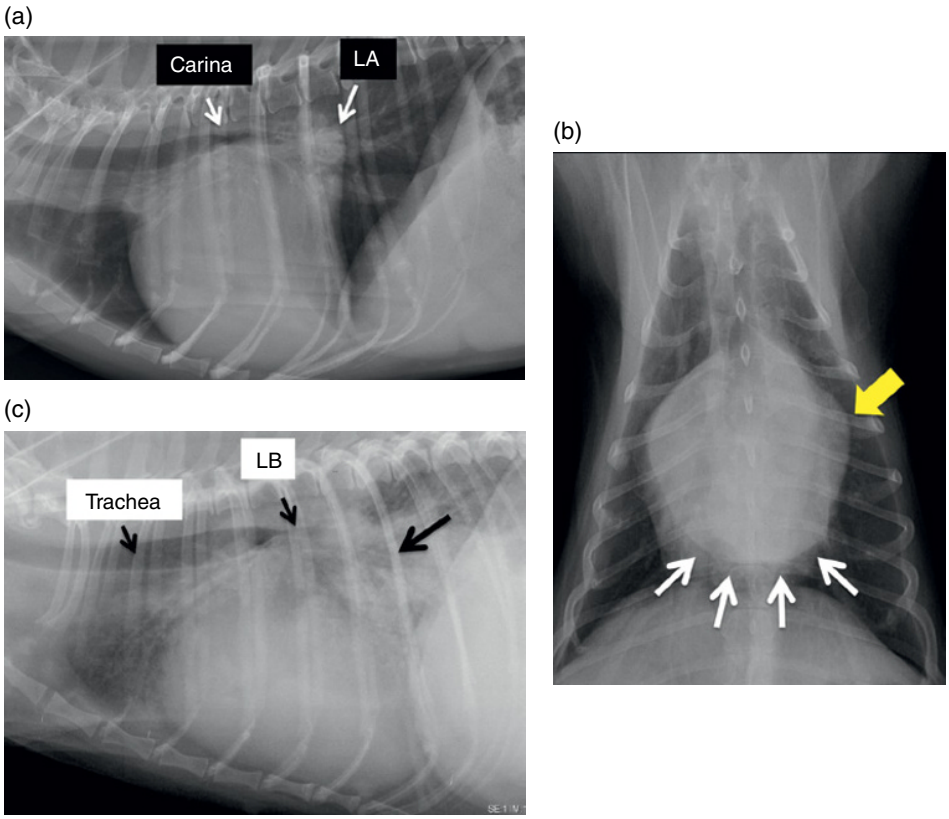


Figure 16.7 Thoracic radiographs of three different dogs with compensated (a,b) and decompensated (c) degenerative mitral valve disease. (a) A marked left atrial enlargement (LA) is seen on this lateral radiograph. Note the tracheal and carina dorsal elevation as well as the straightening of the caudal part of the cardiac silhouette, suggesting left ventricular dilation as well. (b) On this dorsoventral view, enlargement of the left auricular appendage produces a bulge (*large arrow*) at the 2–3 o'clock position. Additionally, the dilated LA body (*thin arrows*) creates a "mass effect" in the dorsocaudal region of the cardiac silhouette. (c) This lateral radiograph shows diffuse cardiogenic pulmonary edema that is more severe in the caudodorsal perihilar area (*arrow*). Left heart enlargement is responsible for dorsal elevation of the intrathoracic trachea, carina, and left main bronchus (LB). Note also the abnormal increased sternal contact of the heart, suggesting right ventricular enlargement (which was further confirmed to result from pulmonary arterial hypertension). *Source:* Medical Imaging Unit, ENVA.

Conventional Echocardiography

Over the last 30 years, standard transthoracic echocardiography has become a major imaging tool for the diagnosis, management, and follow-up of canine and feline heart diseases, allowing noninvasive assessment of heart morphology (ventricles, atria, cardiac valves, auricular appendages) and function, as well as examination of the anatomy of the proximal great vessels.

General Principles and Technique

Conventional echocardiography combines 2D and M-mode imaging. M-mode echocardiography provides one-dimensional views of the heart, while 2D echocardiography displays cross-sectional or 2D cardiac images (in transverse and longitudinal planes) moving in real time. M-mode echocardiograms display motion over time of the various tissue interfaces crossed by the linear M-mode ultrasound beam. Currently, the 2D mode is always used to guide accurate placement of the M-mode cursor, which appears as a vertical line on 2D echocardiograms. M-mode echocardiography has a much higher spatial and temporal resolution than 2D echocardiography, and therefore allows recording of the motion of subtle cardiac structures.

Transthoracic 2D and M-mode echocardiography can be performed on animals in lateral recumbency or in standing position, as the measurements obtained in both positions show similar variability. Some animals may not tolerate a recumbent position because of discomfort or dyspnea, making the standing position easier and more suitable. Placing the patient in lateral recumbency decreases lung interference but, on the other hand, may increase stress in nervous animals.

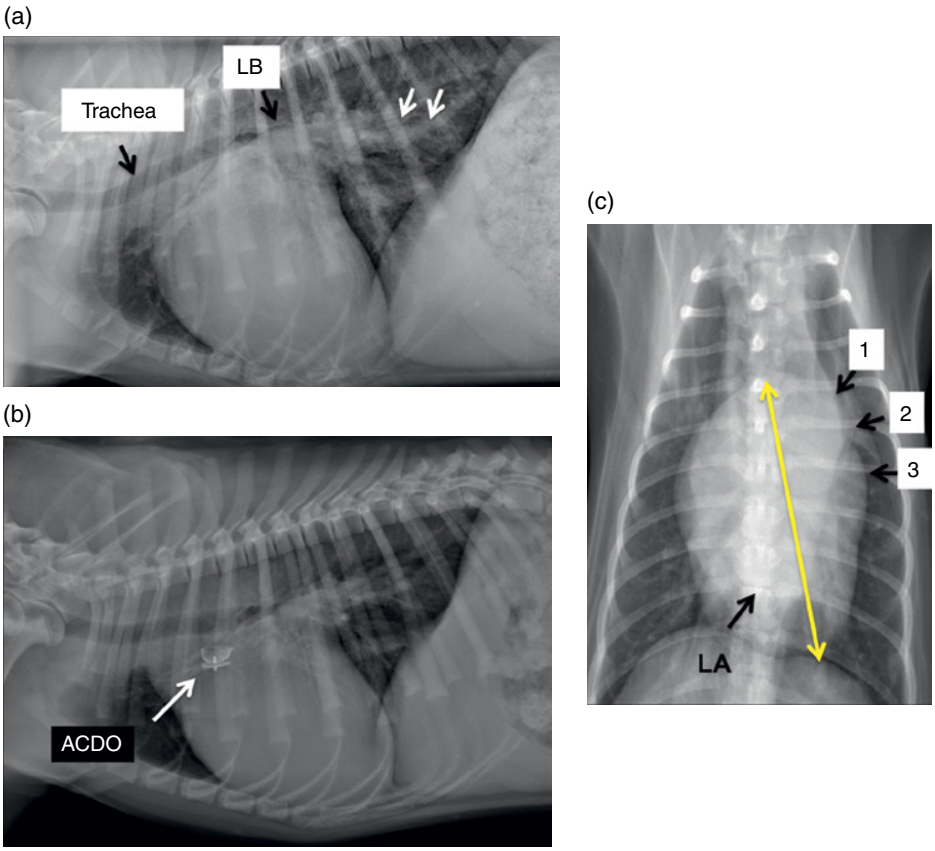


Figure 16.8 Thoracic radiographs of two dogs with patent ductus arteriosus (PDA). (a,b) Lateral radiographs of the same dog (German shepherd) respectively before and 24 hours after surgery (placement of an Amplatz canine duct occluder, ACDO). Note the marked generalized heart enlargement on (a), with dorsal elevation of the intrathoracic trachea, carina, and left main bronchus (LB), associated with vascular congestion (*arrows*) due to overcirculation of the lung field, and interstitial edema in caudal lungs. After ACDO placement (b), heart size (width and height) has decreased and vascular congestion disappeared. (c) Dorsoventral radiograph of a Cavalier King Charles spaniel with PDA before surgical closure. Note the elongated cardiac silhouette (*double arrow*), the heart base enlargement (including 1: descending aorta, 2: main pulmonary artery, 3: left auricular appendage), and the increased opacity caudally to the tracheal bifurcation, corresponding to the dilated left atrium (LA) superimposed over the caudal cardiac silhouette. *Source:* Medical Imaging Unit, ENVA.

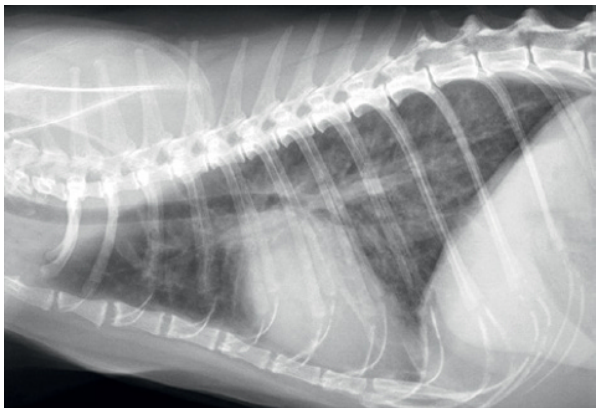
When patients are echoed in a recumbent position, a special scanning table with a cutout is needed, and images are obtained from beneath the table through the table hole. The standing position does not require a specific scanning table, as the animal is gently restrained against an assistant to keep its position stable. For both animal positions, the transducer is placed on the thoracic wall in an intercostal space over the precordial impulse area, close to the sternum, to obtain parasternal views. However, subcostal (or subxiphoid) views may sometimes be used for Doppler assessment of the aortic outflow (as they may provide a better Doppler beam alignment than parasternal views).

In most cases where manual restraint is sufficient, sedation is avoided as it can alter systolic function and may affect cardiac dimensions.

Most animals do not require clipping of hair over the area of contact on the thoracic wall (more than 90% of the patients at our unit are not clipped for conventional echocardiographic examinations or for advanced ultrasound techniques, such as tissue Doppler imaging). Acoustic gel helps to provide an optimal air-free contact between the probe and the thoracic wall.

High-frequency transducers are characterized by low penetrating power but high resolution. Conversely, low-frequency transducers are characterized by high penetrating power but low resolution. In canine and feline cardiology, transducer frequencies are usually between 2.5 and 12 MHz. Transducer frequencies are commonly adjusted during a single echocardiographic examination, depending on the location and size of the cardiovascular structures tested. As most commercially

(a)



(b)

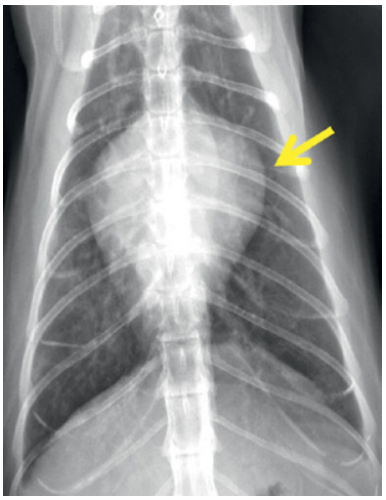


Figure 16.9 Thoracic radiographs of a cat with left-sided congestive heart failure secondary to hypertrophic cardiomyopathy. Note on the lateral view the mild convexity of the caudal heart border and the increased cranial–caudal diameter associated with mild but diffuse interstitial pulmonary edema (a). On the dorsoventral view (b), the dilated left atrium (*arrow*) associated with the pointed appearance of the left apex (owing to concentric left ventricular hypertrophy) creates a "Valentine-shaped" heart silhouette. *Source:* Medical Imaging Unit, ENVA.

available transducers have a wide frequency bandwidth, frequencies can be changed while using the same probe.

If possible, the ultrasound machine's ECG should be connected to the patient during the echocardiographic examination, in order to detect potential arrhythmias and study the correlation between electrical and mechanical events.

Standard 2D Echocardiographic Views and Measurements

A variety of standardized 2D transverse and sagittal echocardiographic views have been defined from the right and left parasternal positions. Transverse views, also called short-axis views, are obtained with the 2D ultrasound plane perpendicular to the long axis of the heart. Conversely, sagittal views, also called long-axis views, are obtained from short-axis views by rotating the transducer 90° counterclockwise, so that the 2D ultrasound plane becomes parallel to the long axis of the heart.

Main Parasternal Short-Axis Views

The three most commonly used 2D transverse echocardiographic views are the right parasternal transventricular short-axis view (Figure 16.13), the right parasternal transmitral short-axis view (Figure 16.14), and the right parasternal transaortic short-axis view (Figure 16.15).

The right parasternal transventricular short-axis view (Figure 16.13a) provides transverse visualization of the two ventricular cavities, and is therefore used to assess left (Figures 16.13b and 16.13c) and right (Figure 16.13d) ventricular changes in size and shape. This view is also commonly used to obtain M-mode echocardiograms at the ventricular level.

The right parasternal transmitral short-axis view (Figure 16.14) allows visualization of the mitral valve leaflets within the left ventricular cavity, and is therefore commonly used to obtain M-mode echocardiograms at the mitral valve level.

The right parasternal transaortic short-axis view (Figure 16.15a) provides transverse visualization of the heart base, with the ascending aorta visible as a circle in the middle of the sector image. This view is commonly used to calculate the left atrium/aorta ratio, and to therefore allow detection of left atrial dilation (Figure 16.15b, Tables 16.4 and 16.5). This view is also used to evaluate the right ventricular outflow tract as well as the pulmonary cusps (Figure 16.15c). A slight rotation of the transducer provides a short-axis view of the heart base optimized for the pulmonary arteries, which is useful for observing heartworms or blood clots within the pulmonary arteries (Figure 16.15d) and for detecting indirect signs of pulmonary arterial hypertension (Figure 16.15e). A similar view can be obtained from the left parasternal position.

Main Parasternal Long-Axis Views

Two 2D sagittal echocardiographic views can be obtained from the right side of the thorax – the right parasternal long-axis four- and five-chamber views (Figures 16.16 and 16.17, respectively). The right parasternal long-axis four-chamber view provides clear visualization of the atrial septum and the atrioventricular valves, and is therefore useful for the diagnosis of

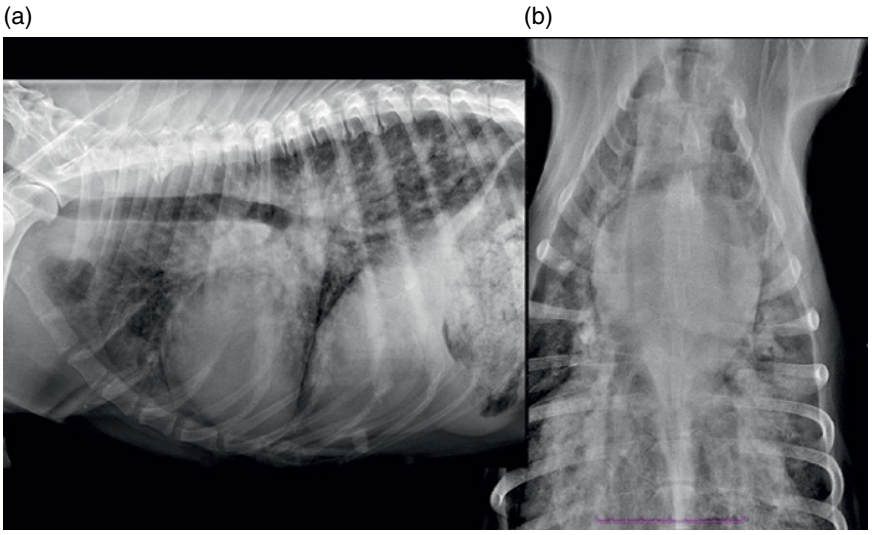


Figure 16.10 Thoracic radiographs of a Doberman with acute left-sided congestive heart failure secondary to dilated cardiomyopathy. Note the tracheal and carina dorsal elevation as well as the straightening of the caudal part of the cardiac silhouette, suggesting left heart enlargement on the lateral view (a). Diffuse patchy interstitial and alveolar opacities consistent with cardiogenic pulmonary edema are also present. They are symmetrically distributed in the right and left lung fields on the dorsoventral view (b). *Source:* Medical Imaging Unit, ENVA.

atrial septal defects (Figure 16.16b) and mitral valve lesions (Figure 16.16c).

The right parasternal long-axis five-chamber view is commonly used to examine the left ventricular outflow tract, the mitral valve leaflets, and the junction between the interventricular septum and the anterior aortic wall in order to respectively diagnose left ventricular outflow tract obstruction (Figure 16.17b), mitral valve lesions (Figure 16.17c), and ventricular septal defects (Figure 16.17d).

Long-axis four- and five-chamber views can also be obtained from the left parasternal position (2D left apical or caudal four- and five-chamber views; Figure 16.18).

The left apical four-chamber view provides good visualization of the ventricular inflow tracts and is therefore used to assess mitral and tricuspid diastolic inflows. It may also be used to calculate end-diastolic and end-systolic left ventricular volumes (Box 16.1).

The end-diastolic left ventricular length can also be measured from the left apical four-chamber view and the index of sphericity can then be calculated (this index is defined as the end-diastolic left ventricular length / left ventricular diameter assessed by M-mode at end-diastole; normal values are usually >1.65). The main use of the left apical five-chamber view is for the Doppler assessment of systolic aortic outflow.

Standard M-Mode Views and Measurements

The two most commonly used M-mode echocardiograms are obtained at the ventricular level and the mitral valve level (Figure 16.19). The M-mode echocardiogram obtained at the ventricular level is used to measure left ventricular end-diastolic and end-systolic diameters, left ventricular free wall thickness and interventricular septal thickness at end-diastole and at end-systole (which correspond to the onset of qRs and end of T-wave, respectively, on concomitant ECG tracing), in order to detect and quantify left ventricular alterations (Figure 16.20a and 16.20b). The left ventricular fractional shortening can then be calculated to indirectly assess the transverse systolic myocardial function (Figure 16.19a; see also Tables 16.4 and 16.5). The M-mode echocardiogram obtained at the ventricular level can also be used to measure right ventricular dimensions (end-diastolic diameter and end-systolic myocardial wall thickness).

E point to septal separation (up to 5–8 mm in the dog, depending on the size of the animal) can be measured from M-mode echocardiograms obtained at the mitral valve level. This distance increases in the case of severely reduced systolic left ventricular function. The same M-mode view may be used to detect systolic anterior motion of the mitral valve, which is commonly associated with obstructive forms of feline hypertrophic cardiomyopathy (Figure 16.20c).

Conventional Doppler Echocardiography

Conventional Doppler echocardiography allows detection and analysis of blood flows within the cardiovascular system. The conventional Doppler examination consists of locating blood flows within the cardiac chambers and vessels, as well as assessing their direction, velocity, and duration. This technique is also used to differentiate normal laminar flows from abnormal nonlaminar (or turbulent) flows. Additionally, flow volumes and pressure

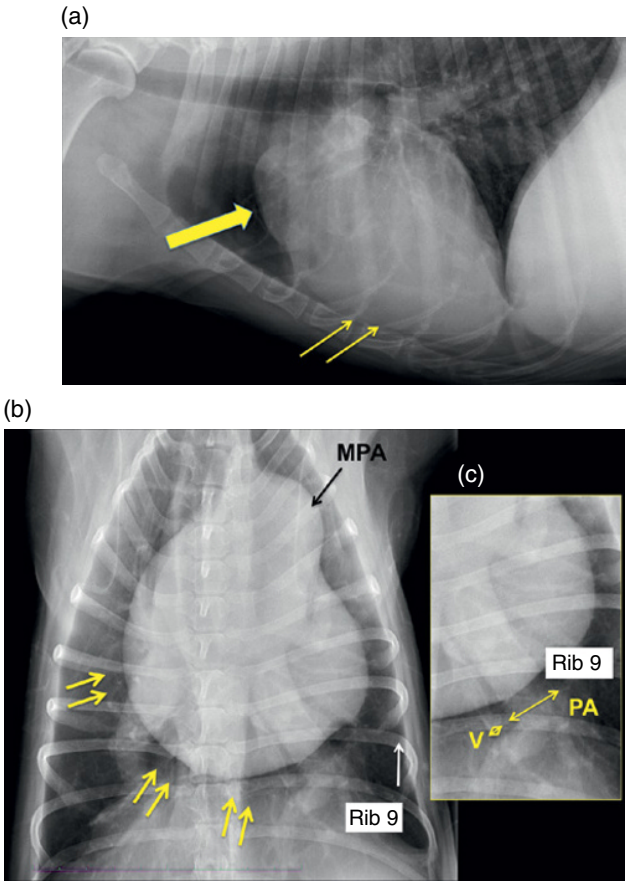


Figure 16.11 Thoracic radiographs of two dogs with marked right heart enlargement resulting from severe pulmonic stenosis (a) and pulmonary arterial hypertension secondary to a large reversed ventricular septal defect (b,c). (a) Note on this lateral view the increased sternal contact of the cranial cardiac margin (*small arrows*) consistent with right ventricular enlargement, as well as protrusion of the dorsal cranial margin of the cardiac silhouette (*large arrow*) owing to both right atrial dilation and enlargement of the main pulmonary artery. The pulmonary vasculature is also slightly diminished. (b) On this dorsoventral view, right ventricular enlargement is characterized by a rounded right heart border bulging to the right (approximately between 6 and 9 o'clock; *arrows*) and a leftward shift of the cardiac apex, leading to a reverse-D appearance. Note also the marked prominence of the main pulmonary artery (MPA) between 1 and 2 o'clock and the enlarged peripheral pulmonary arteries (PA), compared with the pulmonary veins (V, see details on (c)), which indicates pulmonary arterial hypertension. Width of peripheral pulmonary arteries should be similar to that of the corresponding pulmonary veins and should not be larger than the ninth rib diameter at the crossing point between the two. *Source:* Medical Imaging Unit, ENVA.

gradients across valves or between cardiac chambers can be estimated from velocity Doppler data using specific equations. Conventional Doppler echocardiography complements 2D and M-mode echocardiography by providing accurate cardiovascular hemodynamic information, and has now supplanted invasive techniques such as cardiac catheterization for the diagnosis of most human and animal heart diseases. Advanced ultrasound imaging techniques beyond the scope of this chapter are summarized in Box 16.2.

Basic Principles

Conventional Doppler echocardiography is based on the Doppler principle, discovered by Christian Doppler in the 19th century, which states that a moving structure (e.g., blood cells) reflects the incident ultrasound beam back to the transducer with a higher or lower frequency than the original transmitted frequency depending on whether the structure is, respectively, moving toward or away from the transducer. This difference between transmitted and received frequencies, also called the Doppler shift or frequency shift, is directly related to the velocity of the reflecting moving structures, which can thus be deduced from the frequency shift analysis.

The recorded frequency shift (and therefore the calculated flow velocity) also depends on the cosine of the intercept angle (θ) between the ultrasound beam and blood flow path. Therefore, whichever Doppler mode is used, the incident ultrasound beam must be perfectly parallel to the blood flow path ($\theta = 0°$), otherwise the blood flow velocity will not be assessed correctly, that is, it will be underestimated as compared to the actual velocity.

As frequency shift values are usually within the hearing range of the human ear, an audible signal can be simultaneously associated with spectral Doppler tracings of flow velocities. Listening to this Doppler audio signal is particularly useful in practice to help in aligning the ultrasound beam parallel to blood flow: the louder the audible signal, the higher the Doppler shift, the smaller the intercept angle θ, the better the alignment between blood flow and the ultrasound beam.

Standard Doppler Modes

Standard Doppler echocardiography includes different complementary modes, spectral Doppler modes and color-flow Doppler mode (see examples on Figures 16.21–16.23). Each mode has specific advantages and limitations, of which the observer must be perfectly aware in order to avoid misinterpretation of the recorded Doppler signals.

Spectral Modes: Pulsed-Wave and Continuous-Wave Doppler Modes

The two main spectral Doppler modes are pulsed-wave (PW) and continuous-wave (CW) Doppler modes.

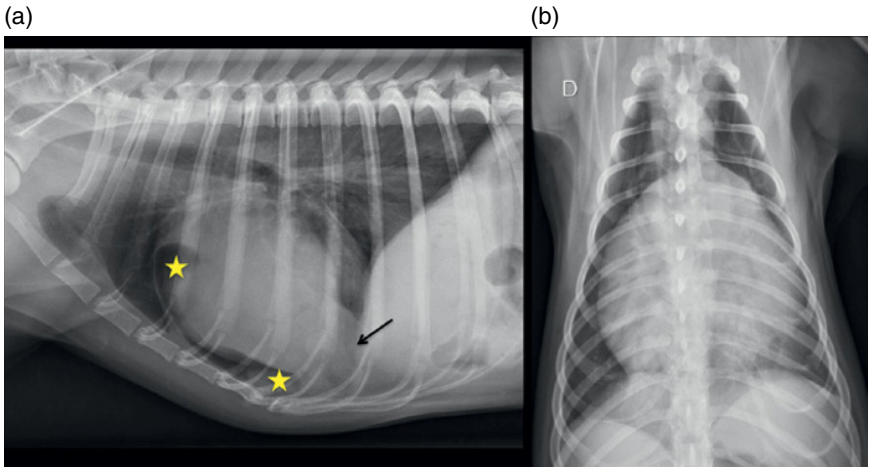


Figure 16.12 Lateral (a) and ventrodorsal (b) thoracic radiographs of a dog with a peritoneal-pericardial diaphragmatic hernia. Note the marked enlargement and the globoid shape of the heart on both views, overlap of the diaphragmatic and caudal heart borders (*arrow*), associated with a small liver and gas-filled intestinal loops (*stars*), that are superimposed on the cardiac silhouette because of their pericardial location. *Source:* Medical Imaging Unit, ENVA.

With these spectral Doppler modes, blood flow velocities (expressed in m/s) are displayed over time in a region of interest, that is, either all along a linear axis (or cursor line) for the CW Doppler mode or in a specific site, also called a sample gate or sample volume, for the PW Doppler mode. The position of the CW Doppler cursor as well as the location and size of the PW sample volume are carefully selected by the observer on 2D echocardiographic views. Whichever spectral Doppler mode is selected, the velocity profiles are displayed as positive (i.e., above the baseline) or negative (i.e., below the baseline), when blood cells respectively move toward or away from the transducer.

The CW mode uses two transducer elements, one continuously emitting and the other continuously receiving ultrasound waves. Because this emission–reception process is continuous, there is no loss of blood flow information and therefore no maximum limit for velocity measurements. Velocities higher than 8 m/s can thus be measured. Conversely, the PW mode uses only one transducer element which discontinuously emits short bursts of ultrasound waves at a given frequency (pulse repetition frequency, PRF = number of pulses per second), and receives reflected ones only at a given time and for a limited duration. This pulsed emission–reception process explains why the main limitation of the PW Doppler mode is its inability to measure high velocities: there is a maximum value for PW velocity recording, also called the Nyquist limit. When blood flow velocities exceed the Nyquist limit, an aliasing artifact occurs, characterized by a reversal of the velocities (Figure 16.24). The maximum velocity that can be recorded without aliasing is usually around 1.5–2.5 m/s. Its value depends on both the transducer frequency and the sample gate depth: the lower the transducer frequency and the lower the sample gate depth, the higher the maximal velocity that can be recorded.

Nevertheless, the advantage of the PW Doppler mode is that blood flows can be analyzed at very specific locations, whereas with the CW Doppler mode it is impossible to determine the accurate location of recorded blood flow velocities on the line of interrogation.

Color Flow Doppler Mode

The color flow Doppler mode provides a color-coded map of the velocity and direction of blood flows, which is superimposed in real time on black-and-white 2D-mode images. Blood flow velocities towards the transducer are coded in red whereas those away from the transducer are coded in blue (Blue Away, Red Toward or "BART"), with lighter colors for higher velocities. Many ultrasound systems also use variance color maps, adding green to the above-mentioned colors when the tested flow is turbulent.

As color flow imaging provides numerous color sites of flow information, it may be considered as a form of PW Doppler mode with numerous sample gates located on many scan lines. It therefore suffers from the same limitation, the aliasing artifact, which occurs when blood flow velocities exceed the Nyquist limit. This artifact is characterized by a color reversal (blue instead of red, red instead of blue). The maximum value for color-coded velocity without aliasing is dependent on blood flow depth and transducer frequency, as with the PW Doppler mode.

Normal Transvalvular Flows

General Characteristics

Transvalvular flows include two arterial flows (pulmonary and aortic flows) and two atrioventricular flows (mitral and tricuspid flows). These four flows are typically laminar, which means that all blood cells are moving in the same

direction and at approximately the same velocity throughout the entire cardiac cycle. Normal PW Doppler transvalvular flow profiles therefore appear as hollow (Figures 16.21c, 16.21d, 16.22b, 16.22c, 16.23c), because the blood flow velocities in the selected sample gate are very similar. Conversely, normal CW Doppler flow profiles appear as completely filled because of the various velocities recorded all along the CW scan line (Figure 16.21b).

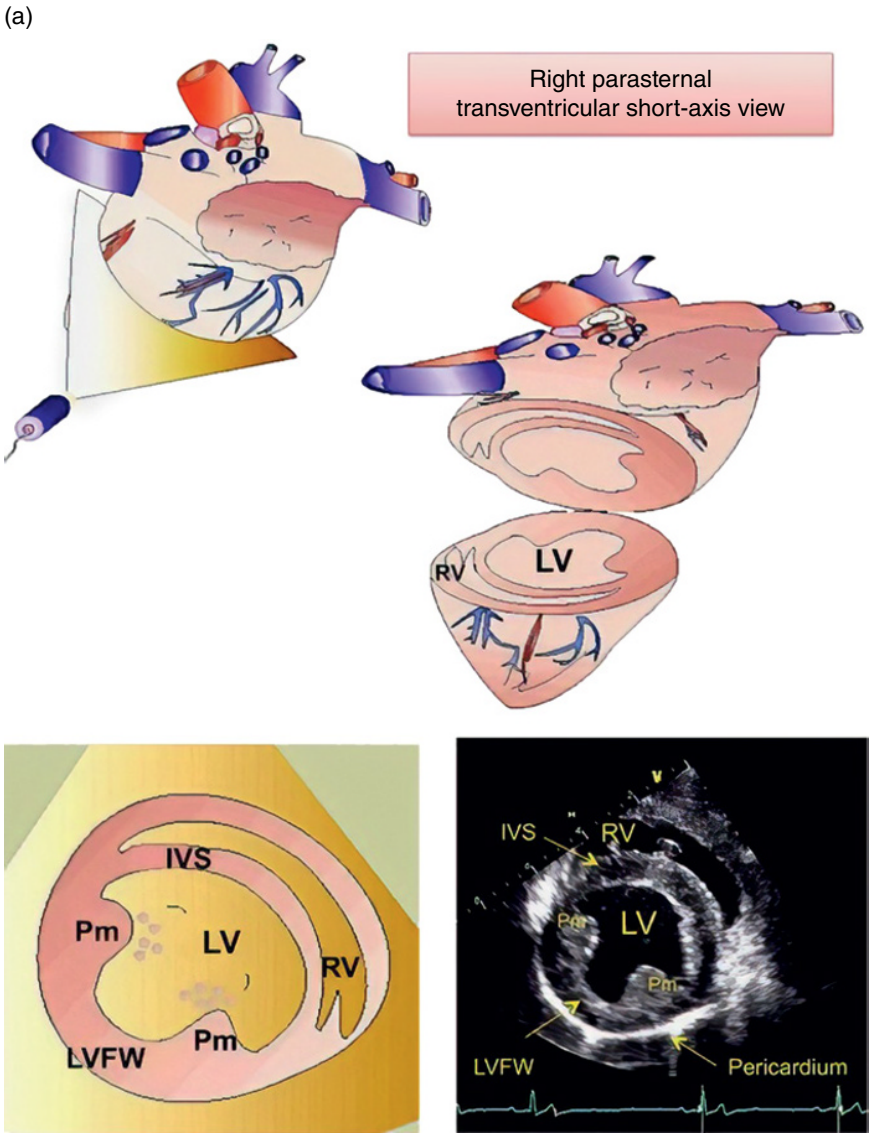


Figure 16.13 Two-dimensional right parasternal transventricular short-axis view in a normal dog (a) and in three dogs with heart diseases (b–d). (a) The top image shows spatial orientation of the ultrasound beam, with the transducer placed on the right side of the thorax. As shown on the middle image, the ultrasound plane goes first through the right ventricle (RV) and then the left ventricle (LV). Therefore, the real-time two-dimensional right parasternal transventricular short-axis view shows the crescent-shaped RV at the top of the sector image and the mushroom-shaped LV below, with the curved interventricular septum (IVS) between the two. Note the two symmetric papillary muscles (Pm) within the LV cavity and the left ventricular free wall (LVFW) at the bottom of the image. *Source:* Tessier-Vetzel D and Chetboul. In Chetboul *et al.* 2005. (b) In this dog with dilated cardiomyopathy, the right parasternal transventricular short-axis view taken in early systole shows an abnormal dilated and rounded (instead of mushroom-shaped) LV with thin myocardial walls and atrophied left Pm. (c) Unlike (b), in this dog with lipid storage myopathy and associated hypertrophic cardiomyopathy, note the reduced LV cavity, the hypertrophied myocardial walls and left Pm, associated with hyperechoic focal lesions (*arrows*) due to myocardial fibrotic remodeling. (d) In this dog with pulmonic stenosis, the IVS and the RV myocardial wall (RVW) are severely thickened. Note also the hypertrophied right Pm, the flattened IVS, and the reduced LV cavity.

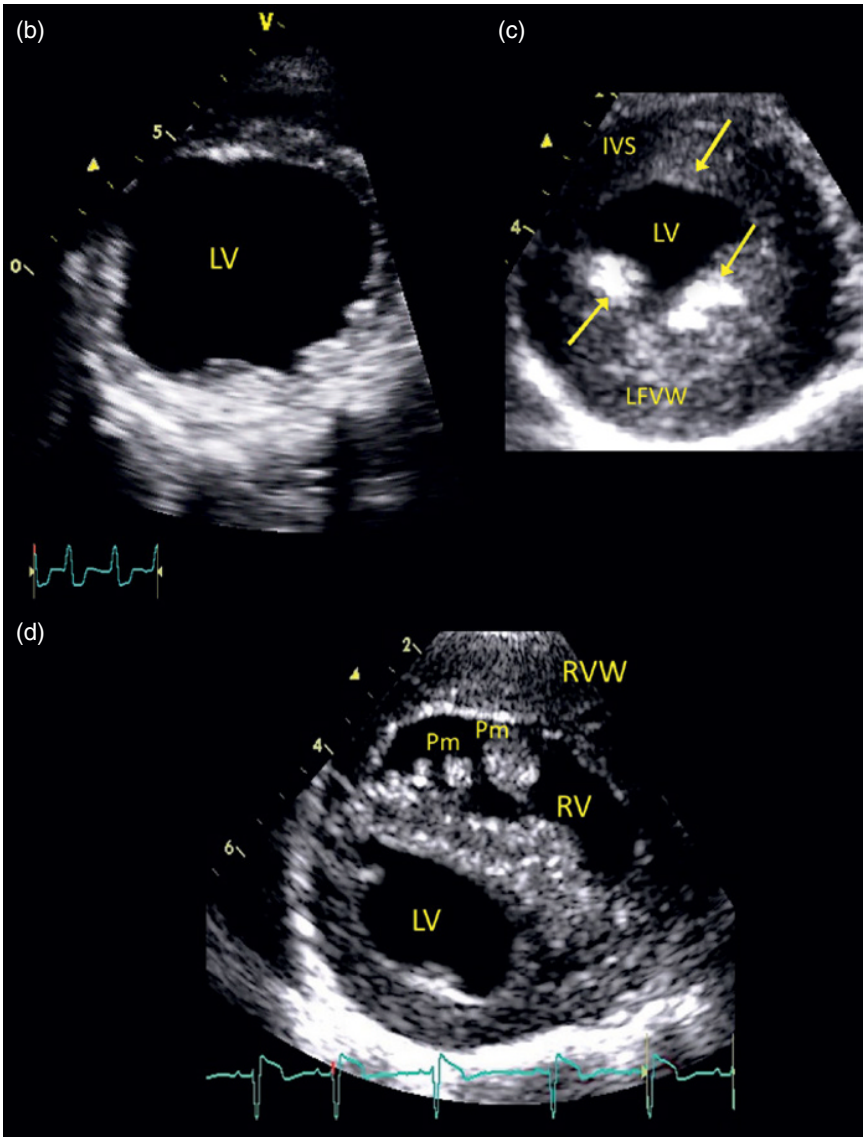


Figure 16.13 (Continued)

Normal Pulmonary and Aortic Systolic Flows

Pulmonary flow is assessed from the right or left parasternal transaortic short-axis views, whereas the left apical five-chamber view and the subcostal view are commonly used to analyze aortic flow. The subcostal view sometimes provides a better alignment than the left apical five-chamber view for imaging aortic outflow.

Both arterial flows are systolic (starting from the qRs complex and lasting until the end of the T-wave) and move away from the transducer. Pulmonary and aortic systolic flows are therefore encoded in blue with color flow Doppler mode, and the corresponding CW and PW systolic flow profiles are negative, with a symmetric or asymmetric appearance, respectively (Figures 16.21 and 16.22).

Peak arterial flow velocities are usually less than 2 m/s (Tables 16.4 and 16.5). Nevertheless, owing to left ventricular outflow tract morphology or high sympathetic tone, the laminar aortic flow profiles of some normal dogs may show higher peak values (between 2 and 2.5 m/s).

Normal Mitral and Tricuspid Diastolic Inflows

Mitral and tricuspid inflows are both assessed from left parasternal views (the left parasternal apical, or caudal, four-chamber view and the left parasternal cranial view optimized for right cavities, respectively).

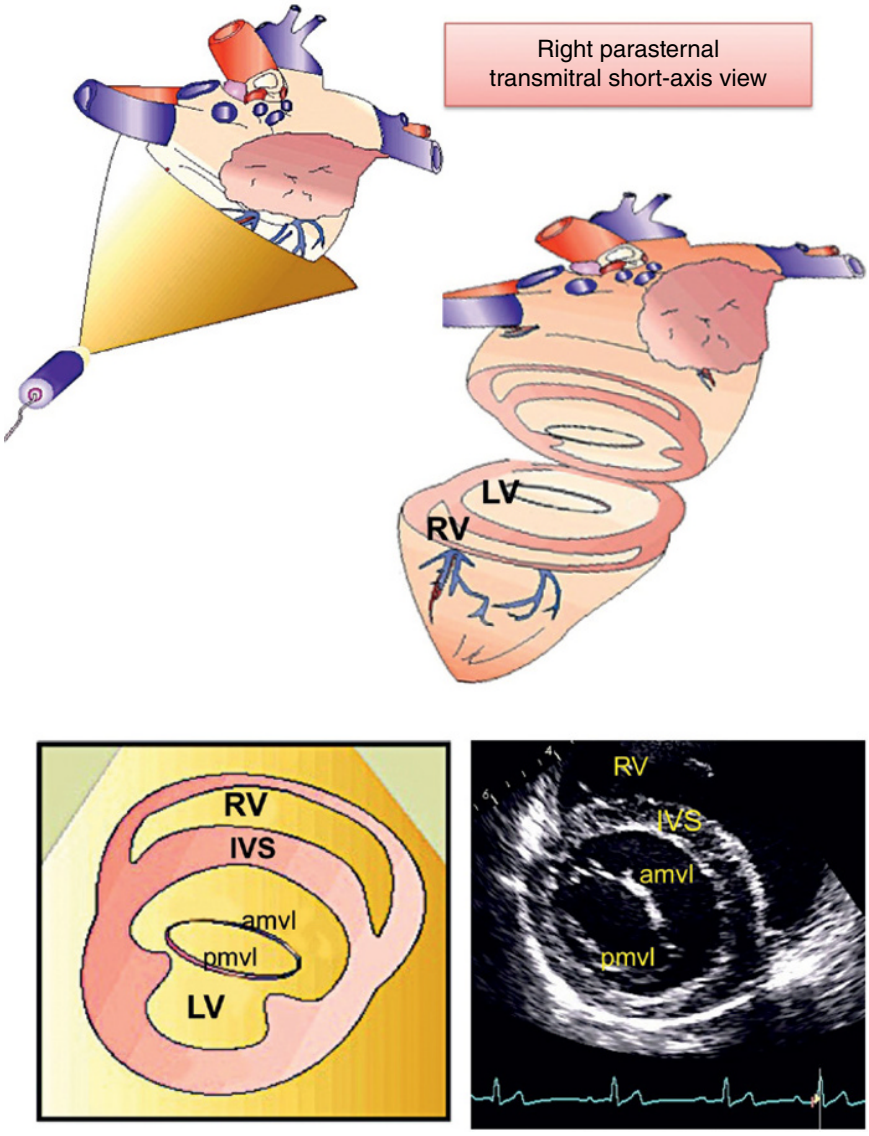


Figure 16.14 Two-dimensional right parasternal transmitral short-axis view. The top image shows spatial orientation of the ultrasound beam, with the transducer placed on the right side of the thorax. As shown on the middle image, the ultrasound plane goes first through the right ventricle (RV) and then the left ventricle (LV) at the mitral valve level. Therefore, the real-time two-dimensional right parasternal transmitral short-axis view shows the crescent-shaped RV at the top of the sector image and the rounded LV below, with the curved interventricular septum (IVS) between the two, and the two mitral valve leaflets within the LV cavity. amvl and pmvl: anterior and posterior mitral valve leaflets, respectively. *Source:* Tessier-Vetzel D and Chetboul. In Chetboul *et al*. 2005.

Unlike the above-described arterial flows, mitral and tricuspid flows are both diastolic (starting from the end of the T-wave and ending at the beginning of the qRs complex) and move toward the transducer. They are therefore encoded in red using the color flow Doppler mode, and the corresponding CW and PW diastolic flow profiles are positive, with a similar biphasic appearance (Figure 16.23) owing to an early rapid ventricular filling wave (E) and a late filling wave (A) resulting from atrial contraction. Peak early and late diastolic flow velocities are usually less than 1.5 m/s in dogs and cats (Tables 16.4 and 16.5), with an E/A ratio >1 except for healthy aged animals (as E/A ratio decreases with age). If the heart rate increases, E and A waves can fuse in a single summated signal, and this is commonly observed in the feline species.

(a)

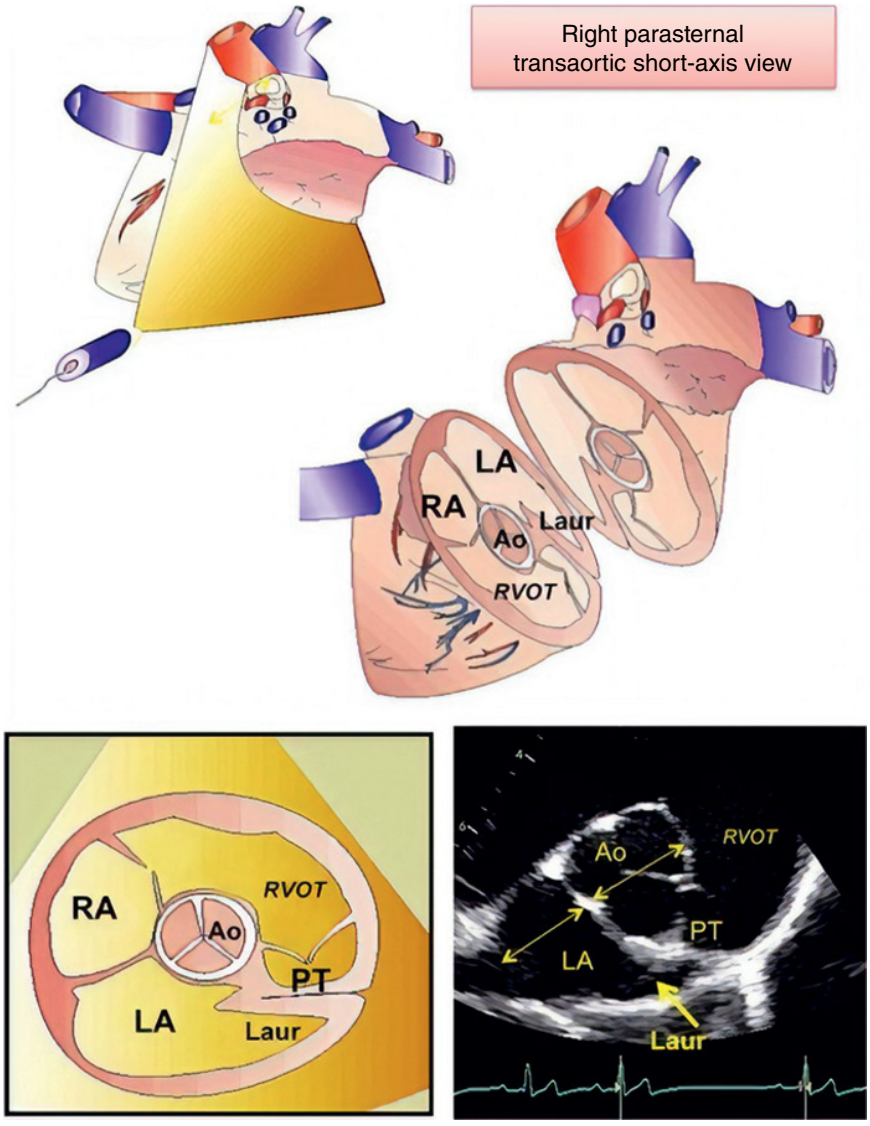


Figure 16.15 Two-dimensional right parasternal transaortic short-axis view in a normal dog (a) and in four dogs with heart diseases (b–e). (a) The right parasternal transaortic short-axis view is a transverse view of the heart base. The top image shows spatial orientation of the ultrasound beam, with the transducer placed on the right side of the thorax. As shown on the middle image, the ultrasound plane goes first through the right cavities including the right ventricular outflow tract (RVOT) and the right atrium (RA), then the aorta (Ao), and lastly the left atrium (LA). Therefore, the real-time two-dimensional right parasternal transaortic short-axis view shows the RVOT at the top of the sector image with the RA on the left, the circular-shaped Ao including the more or less visible aortic cusps at the center (appearing like the Mercedes car insignia), and the LA with the left auricle (Laur) at the bottom of the image. Note also the pulmonary trunk (PT) at the bottom right of the image. Measurements of the Ao and LA diameters can be obtained from this view, as follows: the internal short-axis Ao diameter is measured along the commissure between the noncoronary and left coronary aortic valve cusps, and the LA is measured in a line extending from and parallel to the commissure between the noncoronary and left coronary aortic valve cusps (*double arrows*). The LA/Ao ratio is then calculated (see Tables 16.4 and 16.5). *Source:* Tessier-Vetzel D and Chetboul. In Chetboul *et al*. 2005. (b) In this dog with end-stage degenerative mitral valve disease, the right parasternal transaortic short-axis view shows severe dilation of the LA and a markedly enlarged Laur (*arrow*). (c) In this dog with valvular pulmonic stenosis, the right parasternal transaortic short-axis view taken in systole shows thickened immobile pulmonic cusps (*arrow*) remaining in the center of the PT (instead of being "pushed" against the PT walls). (d) In this dog with severe heartworm infestation, the right parasternal transaortic short-axis view optimized for the pulmonary arteries shows several worms within the PT as well as the right and left pulmonary arteries (RPA and LPA, respectively). Heartworms appear as linear echoes (*arrow*) including two parallel lines separated by a thin hypoechoic line. (e) (same view as (d), taken in diastole) In this dog with severe pulmonary arterial hypertension associated with a right-to-left PDA, note the severe RPA, LPA and PT dilation (compared with the Ao) and the abnormal doming of the pulmonic cusps (*arrow*).

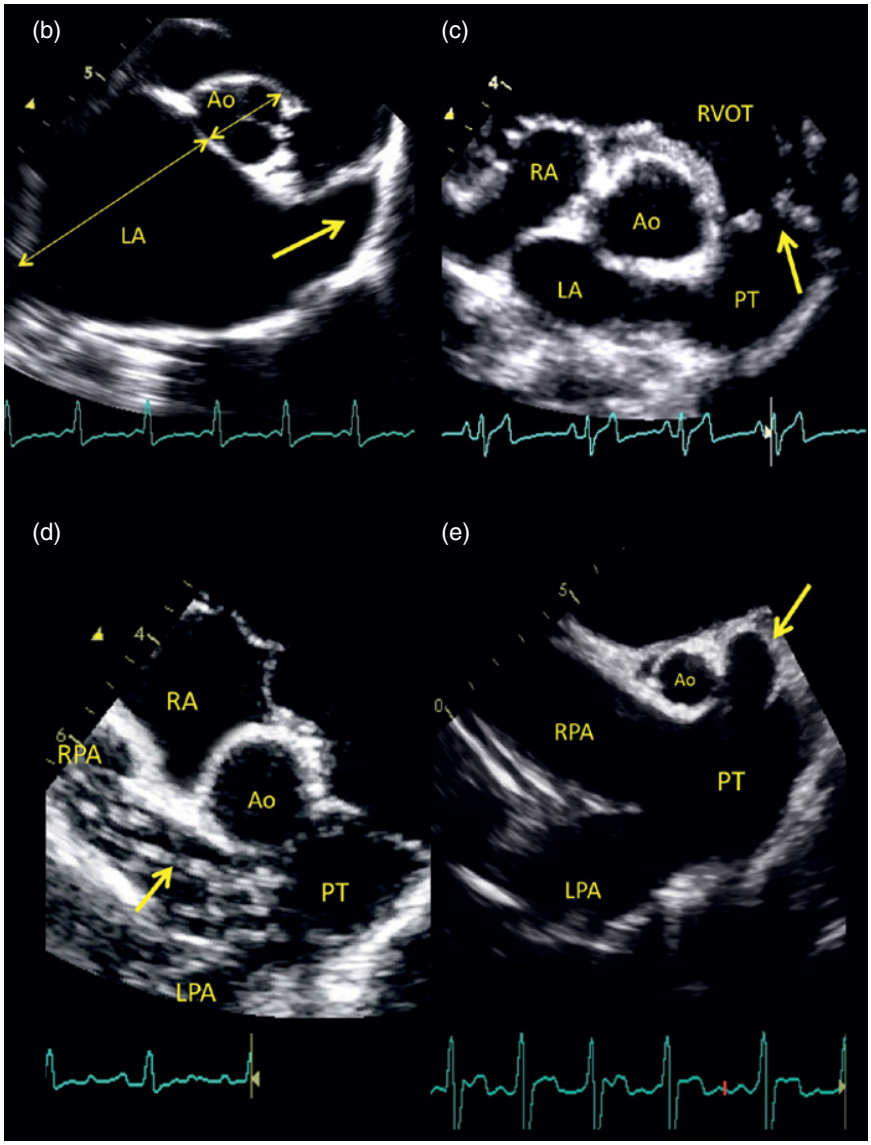


Figure 16.15 (Continued)

Physiologic Regurgitations

Many healthy dogs display trivial to mild physiologic regurgitations of the pulmonary and tricuspid valves. Physiologic systolic tricuspid regurgitation is also common in cats. Such physiologic regurgitations are commonly used to noninvasively assess pulmonary arterial pressure, and thus diagnose pulmonary arterial hypertension (see example in Figure 16.25). High regurgitant jet velocities of the tricuspid valve (>2.5 m/s in the absence of pulmonic stenosis) and the pulmonary valve (>2.0 m/s at end-diastole), detected by CW Doppler mode, are usually considered diagnostic for systolic and diastolic pulmonary arterial hypertension, respectively.

Standard Quantitative Doppler Echocardiographic Measurements

Conventional Doppler echocardiography using spectral Doppler modes provides accurate assessment of the direction and peak velocity (m/s) of blood flows. These velocity measurements can be used to estimate the maximum pressure gradients (ΔP in mmHg) across valves or between cardiac chambers with the modified Bernoulli equation:

$$\Delta P = 4 \times V^2$$

where V is the peak velocity (m/s) of blood flow distal to the orifice assessed by spectral Doppler modes.

Table 16.4 Standard echocardiographic and pulsed-wave Doppler data obtained from 100 healthy dogs of various breeds

Variable	Mean ± SD	Range
Heart rate (beats/min)	109 ± 20	70–171
Fractional shortening (%)	36.2 ± 3.5	30.1–49.0
Left atrium/aorta ratio at end-diastole (2D method)	0.90 ± 0.11	0.52–1.13
Systolic peak aortic flow velocity (m/s)	1.29 ± 0.22	0.92–1.88
Systolic peak pulmonary flow velocity (m/s)	1.05 ± 0.19	0.50–1.50
Mitral E wave velocity (m/s)	0.87 ± 0.13	0.58–1.17
Mitral A wave velocity (m/s)	0.61 ± 0.12	0.39–0.86
Mitral E/A ratio	1.46 ± 0.35	0.92–2.72
Tricuspid E wave velocity (m/s)	0.72 ± 0.11	0.50–0.98
Tricuspid A wave velocity (m/s)	0.43 ± 0.09	0.29–0.70
Tricuspid E/A ratio	1.75 ± 0.34	1.09–2.80

Source: Chetboul V, Carlos Sampedrano C, et al. Use of quantitative two-dimensional color tissue Doppler imaging for assessment of left ventricular radial and longitudinal myocardial velocities in dogs. *Am J Vet Res* 2005; **66**: 953–61.

Table 16.5 Standard echocardiographic and pulsed-wave Doppler echocardiographic data obtained from 100 healthy cats of various breeds

Variable	Mean ± SD	Range
Morphologic parameters		
Left atrium/aorta ratio at end-diastole (2D method)	0.9±0.1	0.5–1.2
Left ventricular end-diastolic diameter (mm)	15.9±2.3	9.7–21.2
Left ventricular end-systolic diameter (mm)	8.1±1.8	4.1–12.7
Left ventricular end-diastolic free wall (mm)	4.3±0.7	2.4–5.8
Left ventricular end-systolic free wall (mm)	7.5±1.1	4.2–10.3
Interventricular end-diastolic septum (mm)	4.6±0.6	2.9–5.9
Interventricular end-systolic septum (mm)	7.4±1.3	4.6–12.1
Interventricular subaortic septum in end-diastole (mm)	4.1±0.8	2.3–5.7
Systolic functional parameter		
Fractional shortening (%)	49±7	33–66
Systolic maximal ejection velocities		
Systolic peak aortic flow velocity (m/s)	1.1±0.2	0.8–1.9
Systolic peak pulmonary flow velocity (m/s)	0.9±0.2	0.5–1.6
Diastolic Doppler parameters in cats with distinct mitral E and A waves	(*n* = *89*)	
Mitral E wave (m/s)	0.7±0.1	0.5–1.1
Mitral A wave (m/s)	0.5±0.1	0.3–0.9
Mitral E/A ratio	1.5±0.3	1.1–2.9
Time parameters		
Isovolumic relaxation time (ms)	43±9	34–56
Heart rate (beats/min)	184±33	100–261

Source: Chetboul V, Carlos Sampedrano C, *et al.* Quantitative assessment of velocities of the annulus of the left atrioventricular valve and left ventricular free wall in healthy cats by use of two-dimensional color tissue Doppler imaging. *Am J Vet Res* 2006; **67**: 250–8.

Several indices of diastolic function can also be calculated. These include the mitral E/A ratio, E wave deceleration time, and the isovolumic relaxation time (time interval between end of aortic flow velocity and onset of transmitral flow), which is an index of active myocardial relaxation (Figure 16.23e).

Lastly, the volume of blood flowing through an orifice can be estimated by multiplying the area under the spectral Doppler curve (velocity time integral) by the cross-sectional orifice area assessed on 2D echocardiographic images.

Common Abnormal Flow Patterns

Abnormal Pulmonary Flow Patterns

Alterations in Systolic Pulmonary Flow

The most common causes of abnormal systolic pulmonary flow patterns are pulmonary arterial hypertension and congenital pulmonic stenosis.

Elevated pulmonary arterial pressures may induce an abnormal asymmetric PW Doppler pulmonary velocity profile with a short acceleration time and a delayed deceleration time, similar to the normal aortic flow profile. A midsystolic notch (Figure 16.26a) may also be seen, most commonly in the case of severe pulmonary arterial hypertension (prevalence of notched pulmonary velocity profiles of 38% for systolic pulmonary arterial pressures >40 mmHg). Peak systolic flow velocity may also be diminished.

Pulmonic stenosis is responsible for an increase in systolic pulmonary flow velocity (Figures 16.26b and 16.26c), which can be assessed without aliasing artifact using the CW Doppler mode (Figure 16.26c).

When the PW Doppler mode is used, the velocity spectrum is broadened, as the flow is turbulent (instead of laminar). Measurement of peak velocity using the CW Doppler mode and subsequent calculation of the maximum systolic pressure gradient across the stenotic lesion provides an accurate and noninvasive estimate of lesion severity (Figure 16.26c). Pulmonic stenosis is considered as severe when the pressure gradient across the stenotic orifice exceeds 80–100 mmHg. Color flow Doppler mode shows narrowing of the color-coded systolic pulmonary flow map, and is therefore useful to accurately localize the stenotic lesion (Figure 16.26b).

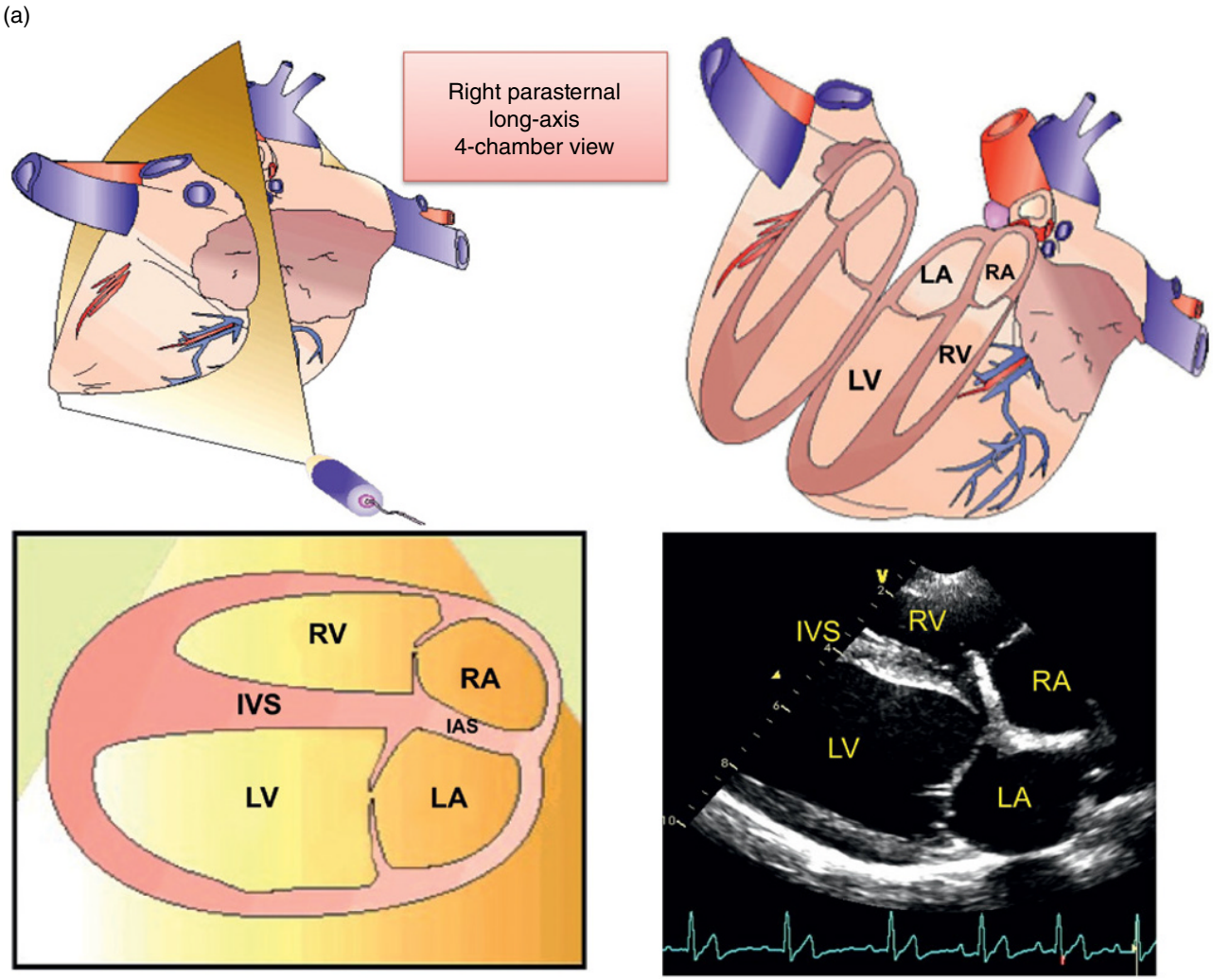


Figure 16.16 Two-dimensional right parasternal long-axis four-chamber view in a normal dog (a) and in two dogs with heart diseases (b,c). (a) The top image on the left shows spatial orientation of the ultrasound beam, with the transducer placed on the right side of the thorax. As shown on the top image on the right, the ultrasound plane goes first through the two right cavities, i.e., the right ventricle (RV) and the right atrium (RA), then the two left cavities, i.e., the left ventricle (LV) and the left atrium (LA). Therefore, the real-time two-dimensional right parasternal long-axis four-chamber view shows the RV and the RA separated by the tricuspid valve at the top of the sector image, and the LV and the LA separated by the mitral valve below. The interventricular septum (IVS) and interatrial septum (IAS) are also clearly seen. *Source:* Tessier-Vetzel D and Chetboul. In Chetboul *et al*. 2005. (b) In this dog presenting with exercise intolerance, a large defect (*arrow*) is located in the middle of the IAS (ostium secundum type atrial septal defect). (c) Two-dimensional right parasternal long-axis four-chamber view obtained in systole from a dog with degenerative mitral valve disease and chordae tendinae rupture. A portion of the ruptured chordae tendinae (*arrow*) still attached to the prolapsed anterior mitral valve leaflet is seen within the severely enlarged LA.

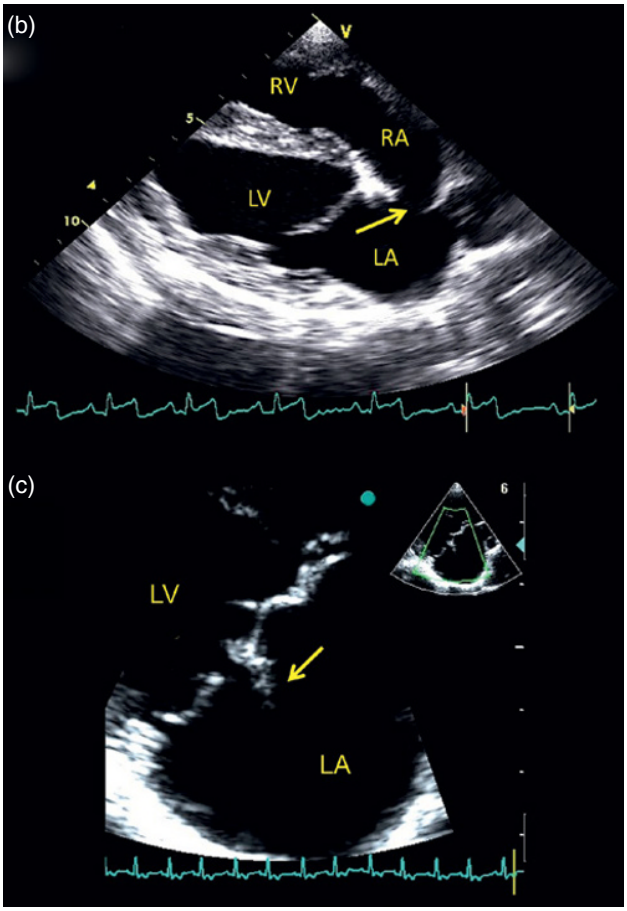


Figure 16.16 (Continued)

Nonphysiologic Pulmonary Regurgitations

Pulmonary regurgitation is often associated with congenital pulmonic stenosis, because of the abnormally thickened and irregular pulmonary leaflets (Figure 16.26c). Its severity may be mildly to moderately increased in patients with pulmonary stenosis that have undergone balloon valvuloplasty. In contrast, pulmonary regurgitation caused by infectious endocarditis is a very rare condition.

Physiologic diastolic pulmonary regurgitation becomes turbulent as well as of increased velocity, duration and extension in the case of diastolic pulmonary hypertension (see Figure 16.25 and above paragraph).

Abnormal Aortic Flow Patterns

Alterations in Systolic Aortic Flow

Aortic stenosis may result from infectious endocarditis. However, the two most common causes of systolic aortic flow obstruction in the dog and cat are congenital aortic stenosis and obstructive hypertrophic cardiomyopathy, respectively. Whatever the cause, aortic stenosis produces an accelerated turbulent systolic aortic flow, with similar spectral and color flow Doppler characteristics to those described for pulmonic stenosis (Figure 16.27).

Aortic Insufficiency

Common causes of aortic insufficiency include infectious endocarditis, congenital abnormal aortic valve (most often in association with subaortic stenosis), and degenerative valvular disease. Color flow Doppler mode criteria indicating severe aortic regurgitation are large insufficiency jet size, compared to the left ventricular outflow tract, and high extension of the diastolic jet within the left ventricle, that is, beyond the mitral leaflets tips. Severe aortic insufficiency also causes a rapid deceleration of the diastolic Doppler CW signal, owing to the marked decrease in the diastolic pressure gradient across the abnormal aortic valve over time. Examples of mild and severe aortic regurgitation jets are presented in Figures 16.27c and 16.28.

Abnormal Mitral Flow Patterns

Alteration in Diastolic Transmitral Inflow

Alteration in left ventricular diastolic function may induce transmitral inflow changes, including delayed relaxation and restrictive transmitral flow patterns (Figures 16.29a and 16.29b). Impaired relaxation may cause lower E wave velocity and higher A wave velocity (E/A <1), as well as prolonged isovolumic relaxation time, reduced flow acceleration time, and prolonged deceleration time (Figure 16.29a). However, in the case of delayed relaxation associated with increased left atrial pressure and left ventricular stiffness, the transmitral inflow may be normal (also called the "pseudonormal" transmitral flow pattern). The restrictive filling pattern is characterized by a shortened isovolumic relaxation time, a tall narrow mitral E wave, and a small A wave (Figure 16.29b).

Diastolic transmitral inflow is also altered in the case of congenital or acquired (endocarditis) mitral stenosis (Figures 16.29c and 16.29d).

In dogs with degenerative mitral valve disease, a high-velocity E wave (>1.5 m/s) suggests elevated left atrial pressure and therefore severe mitral regurgitation.

Mitral Regurgitation

One of the methods commonly used to assess mitral regurgitation severity in dogs with mitral valve dysplasia or degenerative mitral valve disease consists of

calculating the maximal ratio of the regurgitant jet area signal to left atrium area (ARJ/LAA ratio) using color flow Doppler mode (Figure 16.30). The major advantage of this color Doppler mapping method is the rapidity and ease of data acquisition. Nevertheless, this technique presents several limitations: the maximal value for the ARJ/LAA ratio is 100%, which precludes accurate discrimination between dogs with "significant" mitral regurgitation. Additionally, the ARJ/LAA ratio may be influenced by several factors including systemic arterial blood pressure, left atrial pressure, and spatial orientation of the regurgitant jet. Note that it may also be possible to quantify (rather than "semi-quantify") mitral valve regurgitation (in mL) using another Doppler technique, called the Proximal Isovelocity Surface Area (PISA) or flow convergence method.

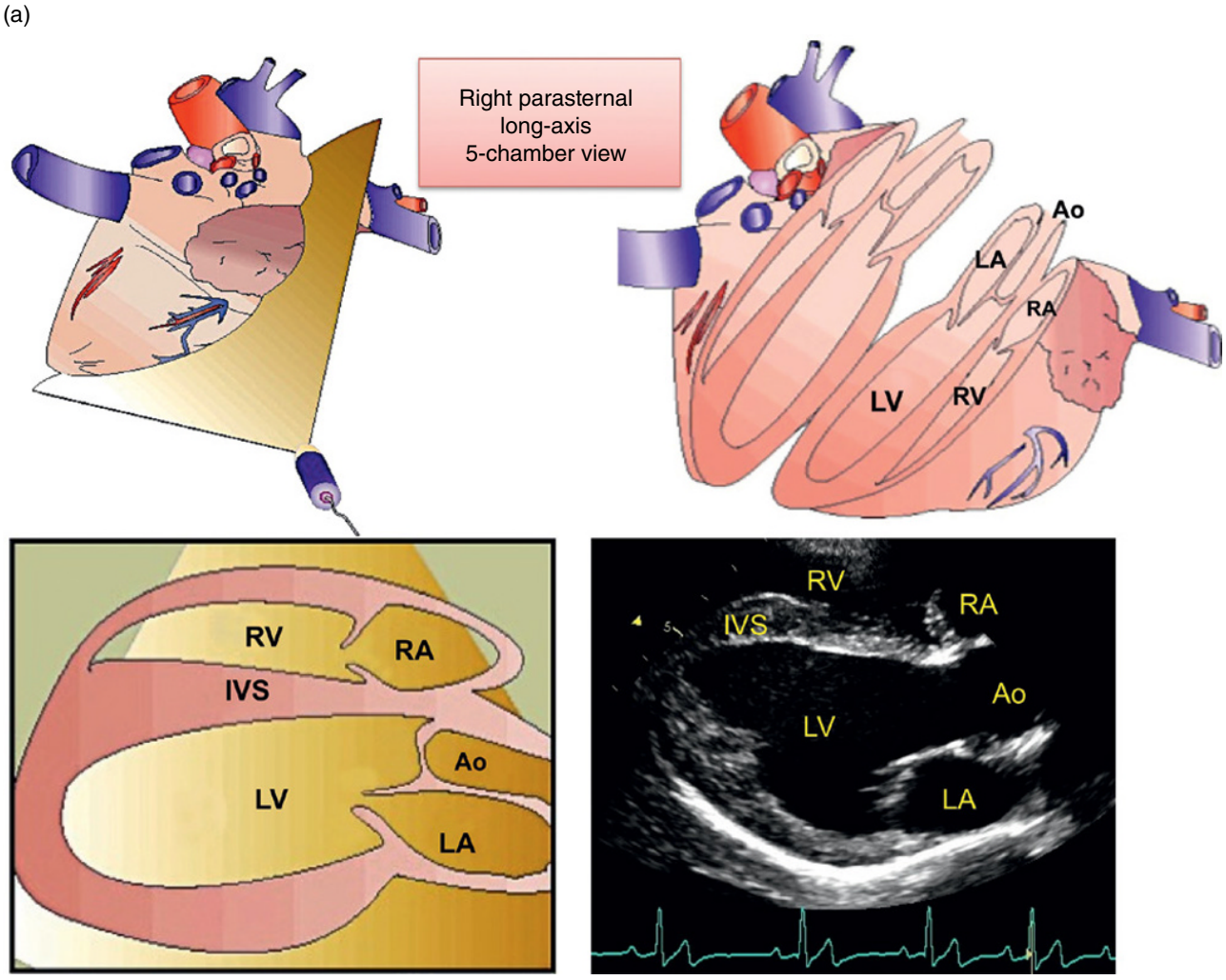


Figure 16.17 Two-dimensional right parasternal long-axis five-chamber view in a normal dog (a) and in three dogs with heart diseases (b–d). (a) The top image on the left shows spatial orientation of the ultrasound beam, with the transducer placed on the right side of the thorax. As shown on the top image on the right, the ultrasound plane goes first through the two right cavities, i.e., the right ventricle (RV) and the right atrium (RA), then the aorta (Ao), and the two left cavities, i.e., the left ventricle (LV) and the left atrium (LA). Therefore, the real-time two-dimensional right parasternal long-axis five-chamber view shows the RV and the RA separated by the tricuspid valve at the top of the sector image, the LV and the LA separated by the mitral valve below, and a long-axis image of the Ao too. The interventricular septum (IVS) is continuous with the anterior aortic wall. *Source:* Tessier-Vetzel D and Chetboul. In Chetboul *et al*. 2005. (b) A muscular bulge of the IVS into the LV outflow tract (*arrow*) creating outflow obstruction is clearly visible in this boxer dog with subvalvular aortic stenosis. (c) In this dog suffering from bacterial endocarditis, large vegetative lesions (*arrow*) are visible on the mitral valve leaflets. (d) In this dog presenting with exercise intolerance, a large ventricular septal defect (*arrow*) is seen just below the aortic valve. Note also the markedly enlarged right pulmonary artery (RPA).

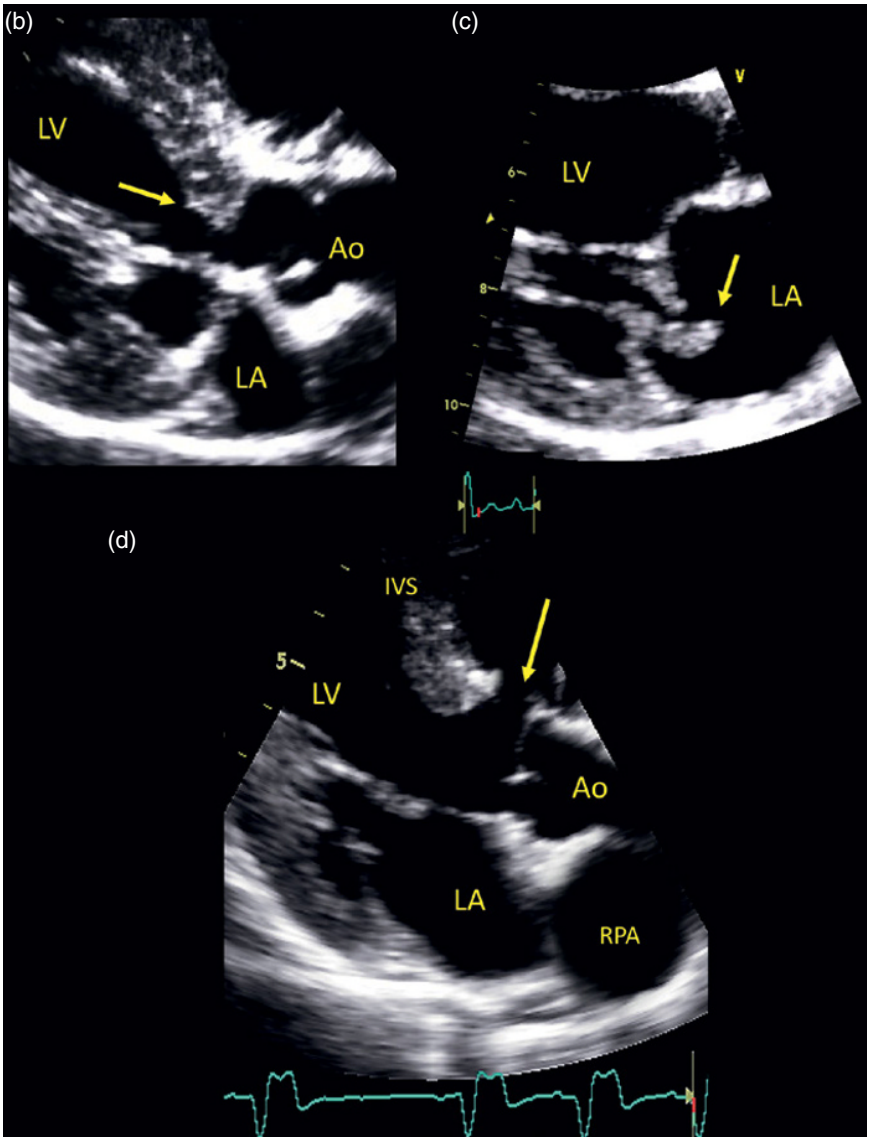


Figure 16.17 (Continued)

Abnormal Tricuspid Flow Patterns

Abnormal tricuspid flow patterns are similar to those described above for mitral inflow. In the case of systolic pulmonary hypertension, tricuspid regurgitation demonstrates increased velocity, duration, and extension. The CW Doppler recording of this high peak systolic tricuspid regurgitant velocity can be used to calculate the systolic right ventricle-to-right atrium pressure gradient across the tricuspid valve by applying the modified Bernoulli equation. The systolic pulmonary arterial pressure (equivalent to the systolic right ventricular pressure in the absence of pulmonic stenosis) is then calculated by adding the estimated right atrial pressure (5, 10 or 15 mmHg in patients with a normal sized right atrium, a dilated right atrium, or right-sided congestive heart failure, respectively) to the systolic right ventricle-to-right atrium pressure gradient.

Nonvalvular Abnormal Flows

Patent Ductus Arteriosus

Color flow Doppler shows the turbulent jet flowing from the ductus into the pulmonary trunk throughout the cardiac cycle (Figure 16.31a). Continuous-wave Doppler mode confirms continuous systolic and diastolic turbulent flows of high velocity into the pulmonary artery (>5 m/s in systole, around 4 m/s in diastole), and allows estimation of the aorta–pulmonary artery pressure gradient (Figure 16.31b). When the pulmonary

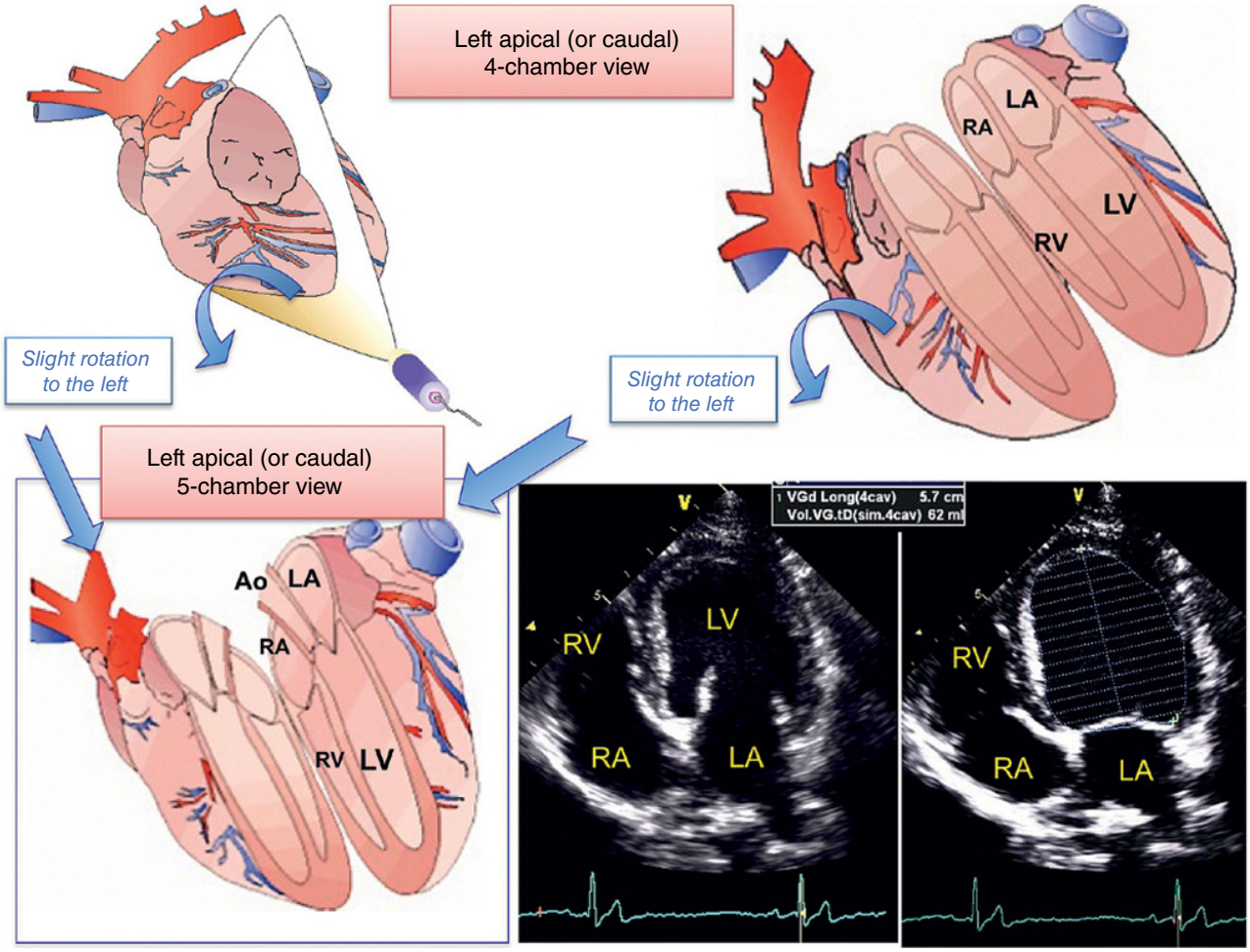


Figure 16.18 Two-dimensional left apical (or caudal) four- and five-chamber views. The top image on the left shows spatial orientation of the ultrasound beam, with the transducer placed on the left side of the thorax, to obtain the left apical four-chamber view. As shown in the top image on the right, the ultrasound plane goes first through the apex, then the right (RV) and left (LV) ventricles, and lastly the left and right atrial cavities (LA and RA, respectively). Therefore, the real-time two-dimensional left apical four-chamber view shows the apex and the two ventricles at the top of the sector image, and the two atrial cavities below, with the mitral valve opened during diastole and closed from end-diastole to end-systole (middle and right bottom images, respectively). The left apical four-chamber view can be used to measure maximum end-systolic and end-diastolic LV length as well as LV volumes. An example of calculation of end-diastolic LV volume using the Simpson's derived method of discs is provided on the bottom right image. The endocardial border has been traced and closed around the mitral annulus, thus delimiting the end-diastolic LV area. The end-diastolic LV volume, considered as the summation of parallel cylinders, whose diameters are derived from endocardial border tracing, is then automatically calculated using a specific software (62 mL). Another method, also called the length-area method, relies on the following simple formula: LV volume = $0.85A^2/L$, where A is the LV area, and L is the LV length measured on the same view. From the left apical four-chamber view, a slight rotation of the transducer to the left allows visualization of the left ventricular outflow tract and a long-axis image of the aorta (Ao), thus defining the left apical five-chamber view (bottom image on the left). See also Figures 16.22 and 16.27 as examples for use of the latter view. *Source:* Tessier-Vetzel D and Chetboul. In Chetboul *et al*. 2005.

Box 16.1 Measurement of ventricular volumes

Echocardiography can be used to measure ventricular volume using a variety of methods, including the Simpson's derived method of discs or length-area method (see explanation in the legend of Figure 16.18). The left ventricular ejection fraction (expressed as a percentage) can then be calculated according to the following formula: 100*(EDV-ESV)/EDV, with EDV and ESV corresponding to the end-diastolic and end-systolic left ventricular volumes. The end-systolic volume index, defined as the end-systolic left ventricular volume divided by the body surface area, may be used as an index of systolic myocardial function.

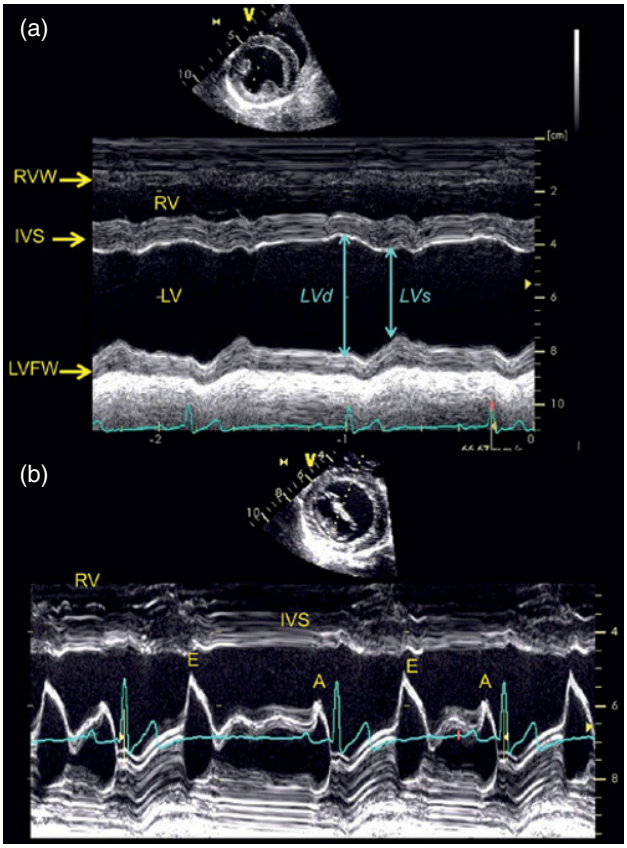


Figure 16.19 M-mode echocardiograms obtained from two normal dogs at the ventricular level (from the right parasternal transventricular short-axis view, (a)) and the mitral valve level (from the right parasternal transmitral short-axis view, (b)). (a) This ventricular M-mode echocardiogram displays the right ventricular myocardial wall (RVW) and the right ventricular cavity (RV) at the top of the image, the left ventricle (LV) and the LV free wall (LVFW) below, with the interventricular septum (IVS) between the two ventricular cavities. The M-mode cursor is placed perpendicular to the IVS and the LVFW between the two left papillary muscles. The LV end-diastolic (LVd) and end-systolic (LVs) diameters can be measured (*double arrows*), and the left ventricular fractional shortening (expressed in percentage and defined as the difference between the LVd and LVs divided by LVd) can then be calculated. (b) This M-mode echocardiogram at the mitral valve level shows the M-shaped motion of the anterior mitral valve leaflet during diastole. The E point and the smaller A point represent the maximum valve opening during the rapid ventricular filling phase and the atrial contraction, respectively. Closure of the mitral valve occurs after atrial contraction, at end-diastole.

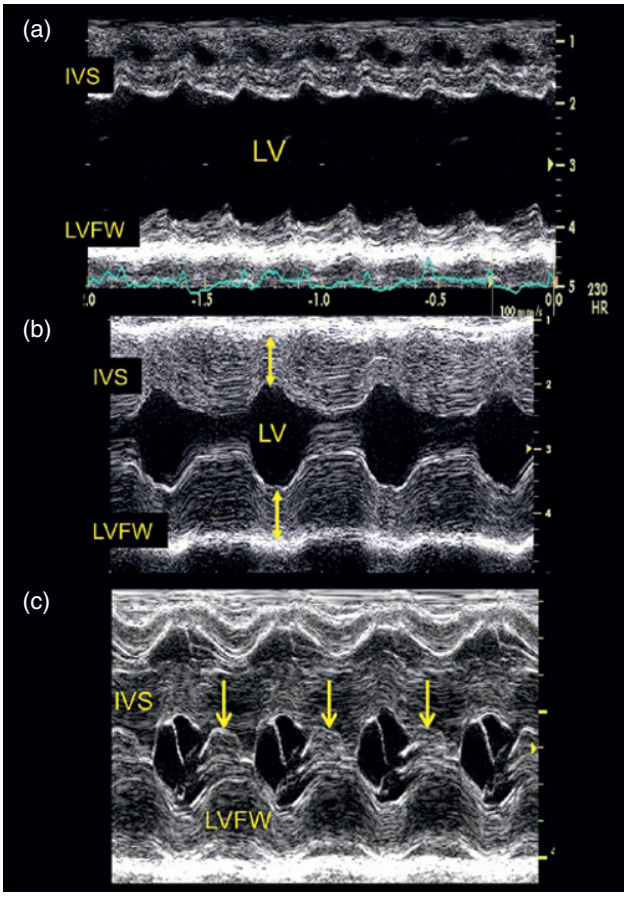


Figure 16.20 Abnormal M-mode echocardiograms obtained from three cats with heart diseases at the ventricular level (a,b) and the mitral valve level (c). (a) In this cat with taurine deficiency-induced dilated cardiomyopathy, the ventricular M-mode echocardiogram shows marked dilation of the left ventricular cavity (LV) with almost no difference between the end-diastolic and end-systolic LV diameters. (b) This ventricular M-mode echocardiogram in a Maine Coon cat with hypertrophic cardiomyopathy shows severe symmetric hypertrophy (end-diastolic interventricular septum and LV free wall >6 mm, double arrows). (c) This M-mode echocardiogram obtained at the mitral valve level in a cat with hypertrophic cardiomyopathy shows a significant systolic anterior motion of the mitral valve (*arrows*), which is characterized by an abnormal mitral valve septal contact during diastole, leading to LV outflow tract obstruction. IVS, interventricular septum; LVFW, left ventricular free wall.

vascular resistance increases, lower velocities are recorded across the ductus.

Septal Defects (Figures 16.31c and 16.31d)

Color flow Doppler echocardiography associated with spectral Doppler modes may identify small defects that cannot be visualized on 2D mode images. High-velocity flow across the ventricular septal defect (>5 m/s) associated with normal peak systolic pulmonary flow velocity is indicative of "restrictive" ventricular septal shunt, that is, hemodynamically not significant, with conservation of the left ventricle–right ventricle pressure gradient (at least 100 mmHg). Flow velocities across the atrial septal defect are typically low (<1 m/s), as the left atrium–right atrium pressure gradient is only several mmHg (Figure 16.31d).

Box 16.2 Advanced ultrasound techniques

Tissue Doppler imaging

Tissue Doppler imaging (TDI) is a relatively recently developed ultrasound technique which allows the quantification of regional myocardial function from measurements of myocardial velocities in real time (Figure 16.32). The 2D color TDI has been shown to be repeatable and reproducible in the awake cat and dog, and is more sensitive than 2D and M-mode echocardiography in detecting myocardial dysfunction of different etiologies in these species, even when overt myocardial changes are absent. This technique may therefore be used for the early detection of systolic and diastolic myocardial alterations associated with dilated or hypertrophic cardiomyopathies, and may be particularly useful in the case of equivocal 2D and M-mode results.

Strain and strain rate imaging

Strain and strain rate imaging are two quantitative TDI-derived imaging techniques, allowing measurement of myocardial segmental deformation (contraction or stretching) and rate of deformation, respectively (see Figure 16.32). Myocardial strain represents the deformation of a myocardial segment over time, and is expressed as the % change from its original dimension. Myocardial strain rate (expressed in s^{-1}) is the temporal derivative of strain, and therefore describes the rate of myocardial deformation. Strain and strain rate imaging therefore offer a direct evaluation of regional intrinsic active myocardial function.

Speckle tracking echocardiography

Two-dimensional speckle tracking echocardiography is the most recently developed ultrasound technique allowing quantitative assessment of regional myocardial function (Figure 16.33). This non-Doppler technique is based on identification and frame-by-frame tracking of speckle patterns created within the myocardium on routine 2D gray-scale echocardiographic images and subsequent assessment of myocardial motion (myocardial tissue velocity, strain and strain rate, and also LV rotation). One of its major advantages, compared to Doppler-based techniques (TDI or TDI-derived techniques), is its independence of both cardiac translation and the insonation angle.

Other ultrasound techniques

Three-dimensional (3D) echocardiography allows 3D visualization of the heart. Good-quality real-time or live 3D imaging of the beating heart can now be obtained thanks to advancements in computer technology and the development of fully sampled matrix-array transducers. One of the major advantages of 3D echocardiography over 2D imaging is its greater accuracy for the evaluation of cardiac chamber volumes (thus avoiding conventional echocardiographic geometric modeling). Another application of 3D imaging is to acquire realistic views of cardiac valves and assess complex or equivocal congenital abnormalities (e.g., shunts), which can be particularly useful when planning a surgical correction.

Transesophageal echocardiography uses a transducer mounted at the tip of a flexible endoscope and allows imaging of the heart from the esophagus (instead of through the chest wall, as for transthoracic echocardiography). The advantage of transesophageal echocardiography is the acquisition of high-quality images, as it avoids the anatomic structures (skin, subcutaneous tissue, ribs, lungs), which may affect the quality of conventional transthoracic echocardiography. Potential indications for transesophageal echocardiography in veterinary medicine include analysis of specific cardiovascular abnormalities (thrombosis, aneurysm, cardiac tumors), cardiac monitoring during anesthesia or catheterization, and evaluation of surgical procedures such as ductus arteriosus closure.

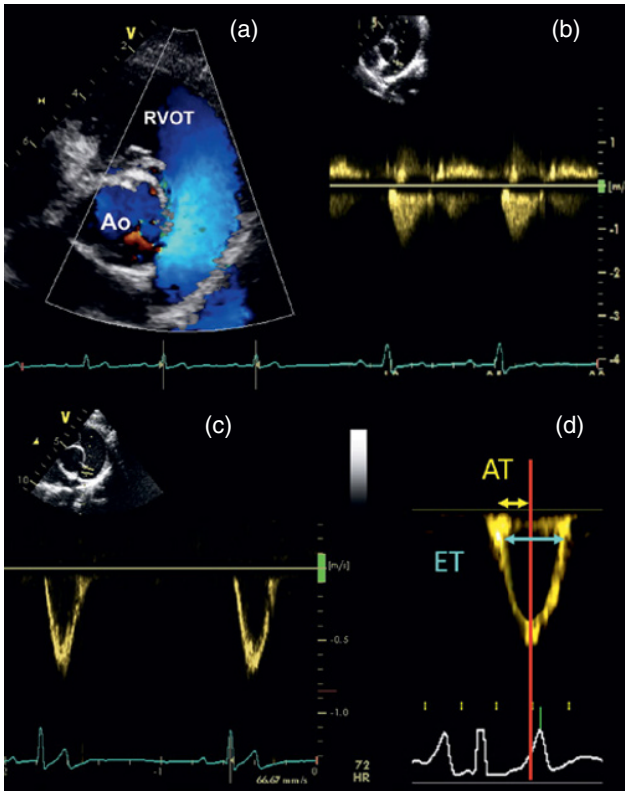


Figure 16.21 Doppler evaluation of systolic pulmonary flow in normal dogs using color flow (a), continuous-wave (b), and pulsed-wave (c,d) Doppler modes from the right parasternal transaortic short-axis view optimized for the right ventricular outflow tract (RVOT). The pulmonary flow is coded in blue (a), as it goes away from the transducer during systole. The spectral Doppler waveform (b–d) is typically negative and symmetric, with acceleration (AT) two times lower than the total ejection time (ET), as peak velocity is reached at midsystole. Using the pulsed-wave Doppler mode, the sample gate is placed in the main pulmonary artery just beyond the pulmonary valve, and the displayed flow profile is hollow as the flow is laminar. Using the continuous-wave Doppler mode, there is a filling in of the systolic pulmonary flow profile as numerous velocities are recorded all along the Doppler scan line. Some diastolic signals (corresponding to right ventricular inflows and physiologic pulmonary insufficiency) are also recorded. Ao, aorta.

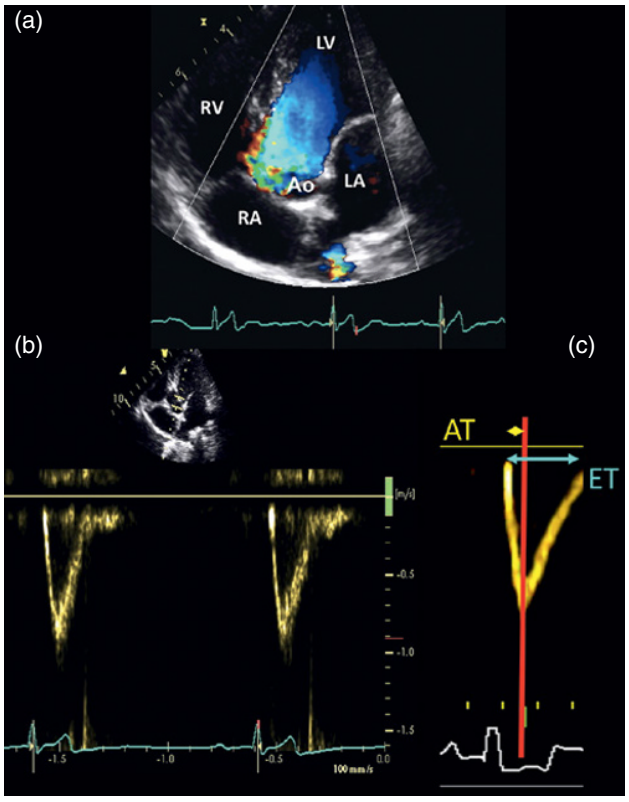


Figure 16.22 Doppler evaluation of systolic aortic flow in normal dogs using color flow (a) and pulsed-wave (b,c) Doppler modes from the left parasternal apical (or caudal) five-chamber view. The aortic flow is coded in blue (a), as it goes away from the transducer during systole. The spectral Doppler waveform (b,c) is typically negative and asymmetric, with acceleration (AT) much shorter than the half of the total ejection time (ET), as peak velocity is reached during the first third of systole. Using the pulsed-wave Doppler mode, the sample gate is placed just in the aorta beyond the aortic valve, and the flow profile is hollow as the flow is laminar. Ao, aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

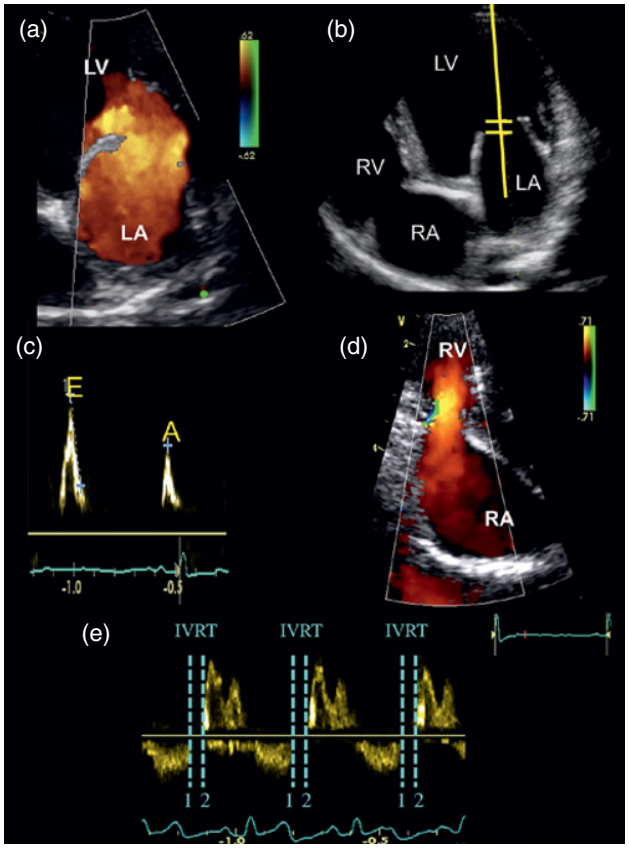


Figure 16.23 Doppler evaluation of diastolic mitral (a–c,e) and tricuspid (d) inflows in a normal dog, from the left parasternal apical and cranial four-chamber views, respectively, using color flow (a,d) and pulsed-wave (b,c,e) Doppler modes. Both flows are coded in red, as they go toward the transducer during diastole (a,d). For mitral inflow analysis using the pulsed-wave Doppler mode, the sample gate is placed at the tip of the mitral leaflets (b). The transmitral inflow pattern (c) is hollow (as the mitral inflow is laminar) and typically biphasic, including an early rapid positive filling wave (E) and a late positive filling wave (A) of lower velocity resulting from atrial contraction. The calculation of isovolumic relaxation time (IVRT) is shown in (e): IVRT represents the time between aortic valve closure (1) and mitral valve opening (2) and is an index of diastolic function. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

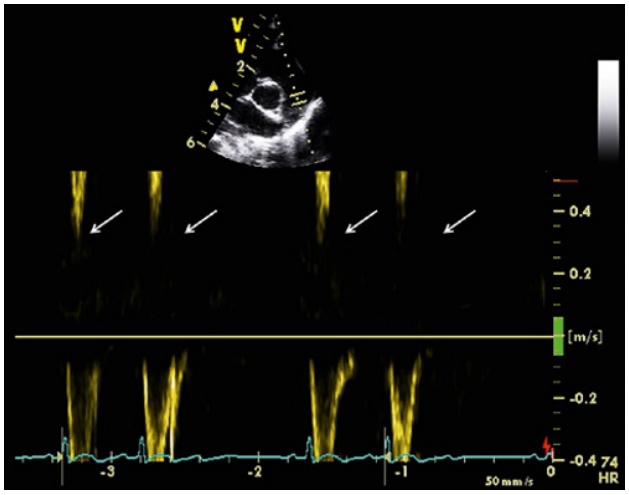


Figure 16.24 Aliasing artifact associated with the pulsed-wave Doppler mode. When blood flow velocities exceed the Nyquist limit (here 0.4 m/s for the pulmonary flow), the aliasing artifact occurs: the flow profile wraps around the image and becomes inverted (in this example positive instead of negative, arrows). The deeper the recorded blood flow, the lower the Nyquist limit.

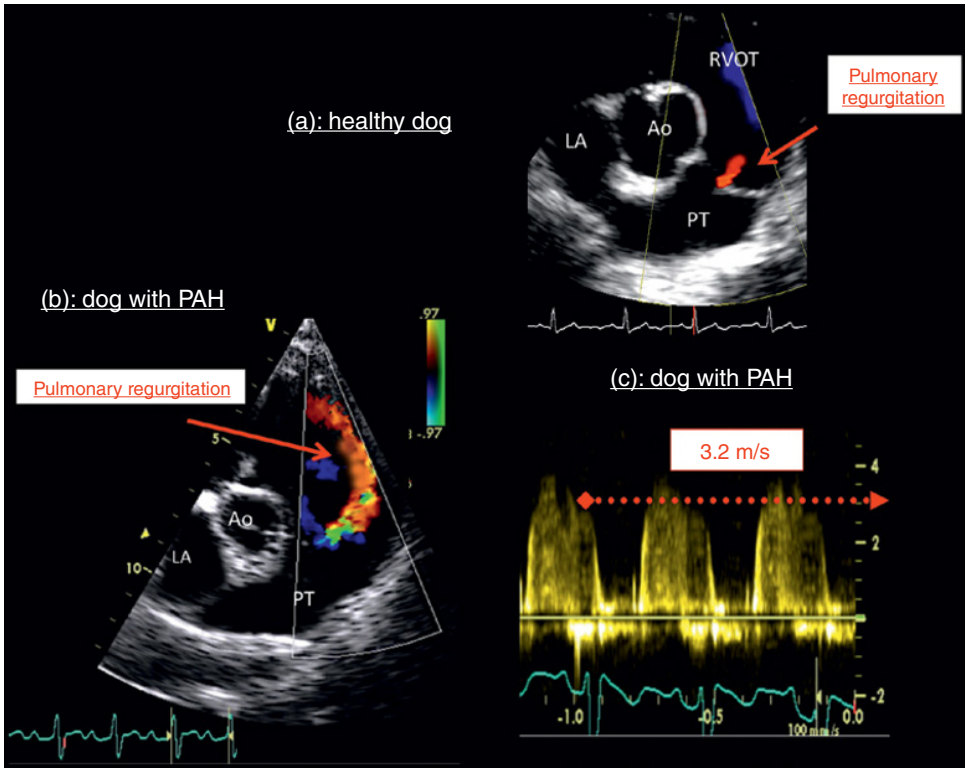


Figure 16.25 Use of pulmonary regurgitation for the diagnosis of diastolic pulmonary arterial hypertension (PAH). In the normal dog (a), color flow Doppler examination of the right ventricular outflow tract (obtained from the right parasternal transaortic short-axis view optimized for the pulmonary valve) allows the detection of a diastolic laminar mild pulmonary insufficiency. This physiologic regurgitation is encoded in red and does not extend above the most rightward level of the aortic valve. Conversely, in the dog with diastolic PAH (b,c), the color flow Doppler examination obtained from the same view shows a turbulent aliased diastolic pulmonary regurgitation going deeply into the body of the right ventricle. The maximum end-diastolic pulmonary regurgitant flow velocity measured by continuous-wave Doppler mode is high (3.2 m/s; c). According to the modified Bernoulli equation ($\Delta P = 4 \times \text{velocity}^2$), the end-diastolic pressure gradient (ΔP) across the pulmonary valve between the pulmonary trunk and the right ventricle is therefore 41 mmHg. This means that the diastolic pulmonary arterial pressure is at least 41 mmHg, which is indicative of diastolic Doppler-derived evidence of PAH (as the normal diastolic pulmonary arterial pressure is usually between 5 and 10 mmHg). Ao, aorta; LA, left atrium; PT, pulmonary trunk; RVOT, right ventricular outflow tract.

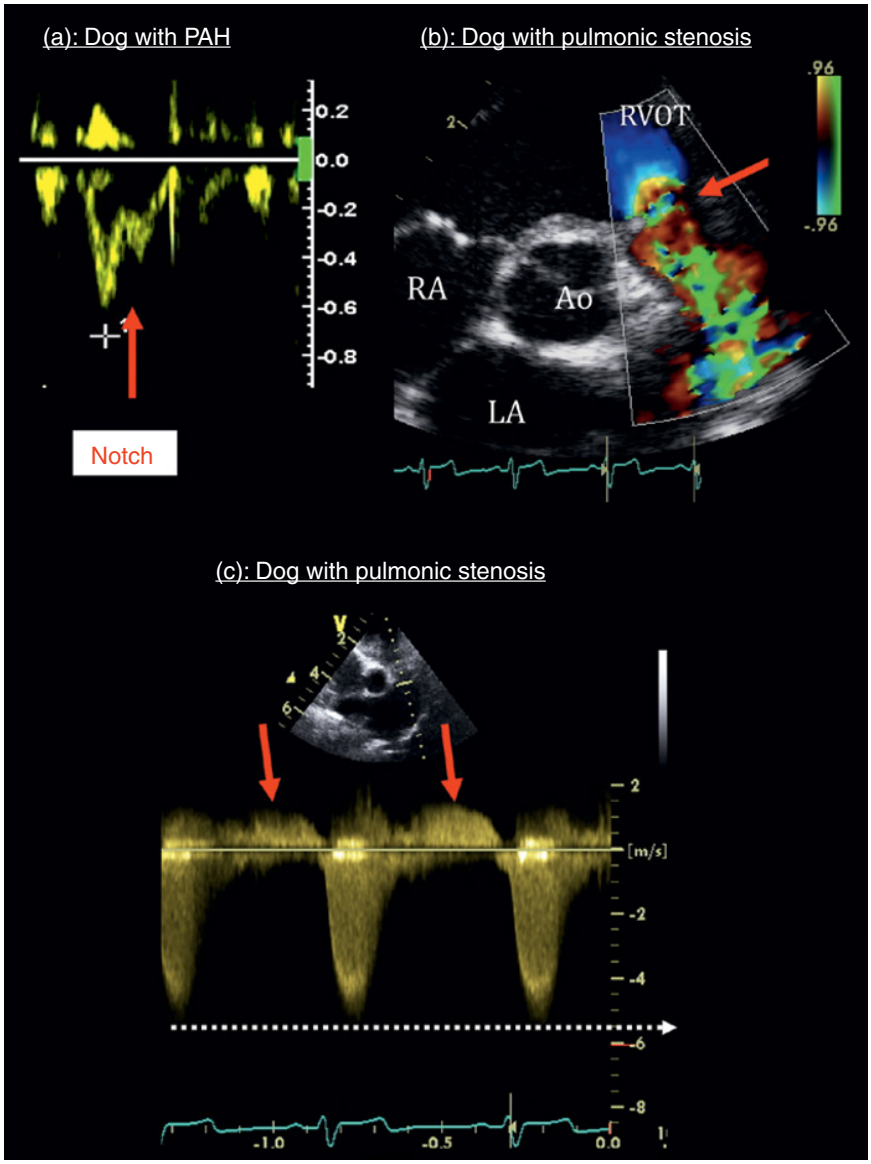


Figure 16.26 Examples of abnormal pulmonary flow patterns assessed by pulsed-wave, color flow and continuous-wave Doppler modes (a, b and c, respectively). (a) This pulsed-wave Doppler pulmonary flow velocity profile shows characteristic changes associated with pulmonary arterial hypertension, i.e., rapid acceleration time, delayed deceleration time with a midsystolic notch (*arrow*). (b,c) (dog with pulmonic stenosis) Color flow Doppler from the left cranial transaortic short axis view (b) shows blood flow acceleration proximal to the pulmonary valve and turbulences distally, with a marked narrowing of the systolic color flow map at the pulmonary valve orifice level (*arrow*), thus confirming valvular location of the pulmonic stenosis. Continuous-wave Doppler tracing of the pulmonary flow velocity confirms a severe pulmonic valve stenosis (peak diastolic flow velocity of 5.5 m/s; pressure gradient across the pulmonary valve of 121 mmHg according to the modified Bernoulli equation). Pulmonary regurgitant flow is also seen above the baseline in diastole (*arrows*). Ao, aorta; LA, left atrium; RA, right atrium; RVOT, right ventricular outflow tract.

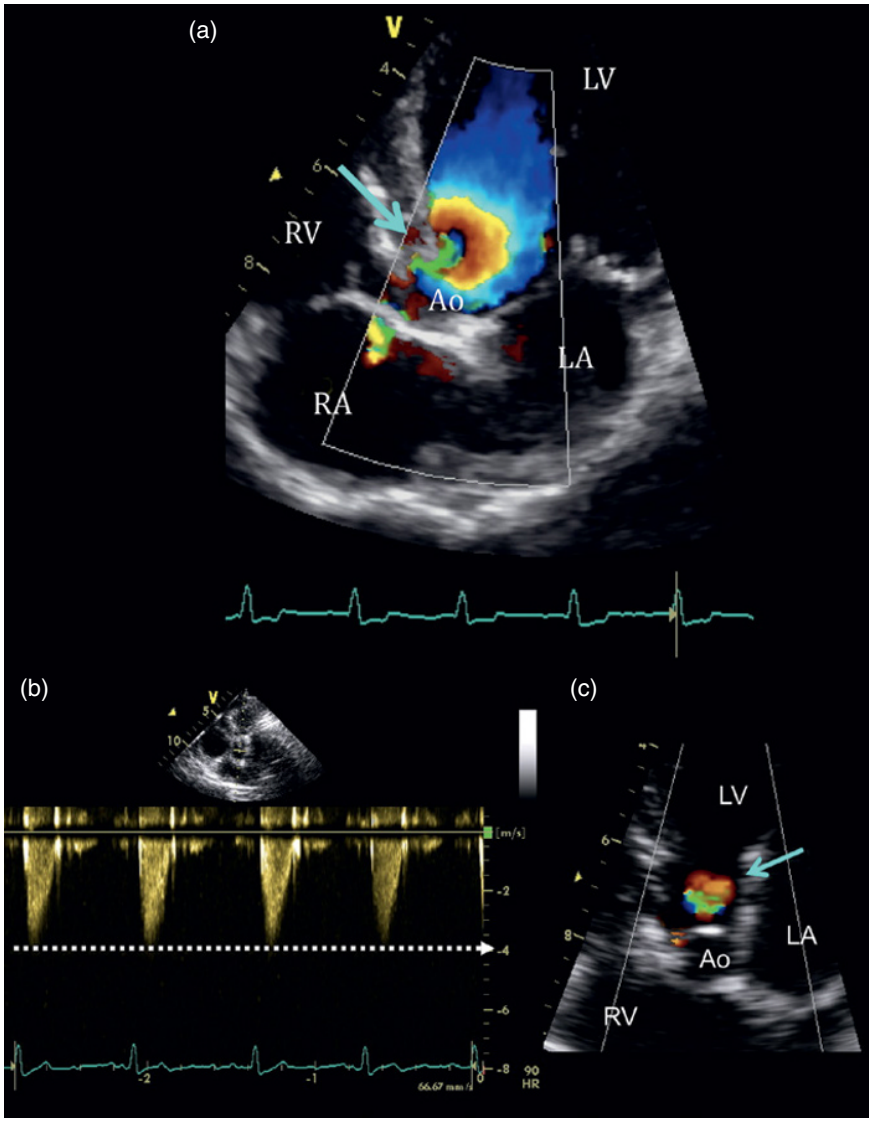


Figure 16.27 Examples of abnormal aortic flow patterns associated with subaortic stenosis assessed by color flow (a,c) and continuous-wave Doppler modes (b). (a) Color flow Doppler from the left apical five-chamber view shows blood flow acceleration proximal to the subaortic area, with a narrowing of the systolic color flow map (*arrow*), thus confirming subvalvular location of the aortic stenosis. (b) Continuous-wave Doppler peak systolic flow velocity (4 m/s) across the stenotic lesion from the same view is indicative of moderate aortic stenosis (pressure gradient across the pulmonary valve of 64 mmHg according to the modified Bernoulli equation). (c) Using the left apical five-chamber view (diastolic frame) a mild aortic insufficiency (*arrow*) is also detected just on the left ventricular side of the valvular coaptation point (beneath the aortic cusps). Ao, aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

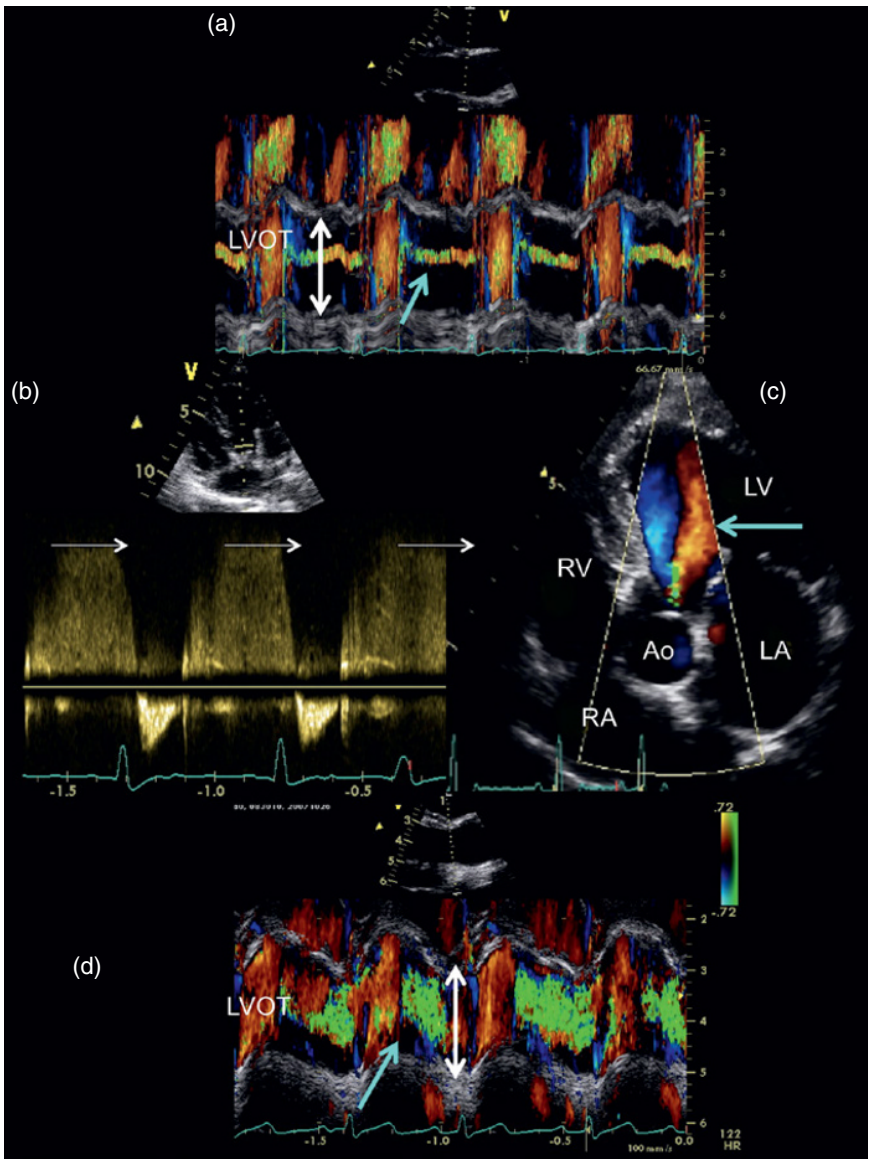


Figure 16.28 Evaluation of aortic insufficiency severity using color-coded M-mode (a,d), color flow (c) and continuous-wave Doppler modes (b). The color-coded M-mode from the right parasternal five-chamber view may be used to measure the height (or cross-sectional area) of the regurgitant aortic jet (*blue arrows*) relative to the height (cross-sectional area) of the left ventricular outflow tract (LVOT) (*double arrows*, a and d). (a) shows a mild aortic insufficiency as the jet height /LVOT height is only 8% (<25%). Conversely, the aortic insufficiency in (d) is considered as severe, as the jet height/LVOT height is high (i.e., 84%; >65%). In contrast to Figure 16.27c, a severe aortic insufficiency extending nearly to the apex (blue arrow) is also shown in (c). Continuous-wave Doppler mode confirms an aortic insufficiency signal above the baseline in (b). The aortic insufficiency velocity remains stable throughout the diastolic time (*white arrows*). This means that, despite the regurgitation, the pressure gradient across the aortic valve remains unchanged during diastole (no decrease in aortic diastolic pressure), which confirms that the regurgitation is mild. Ao, aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

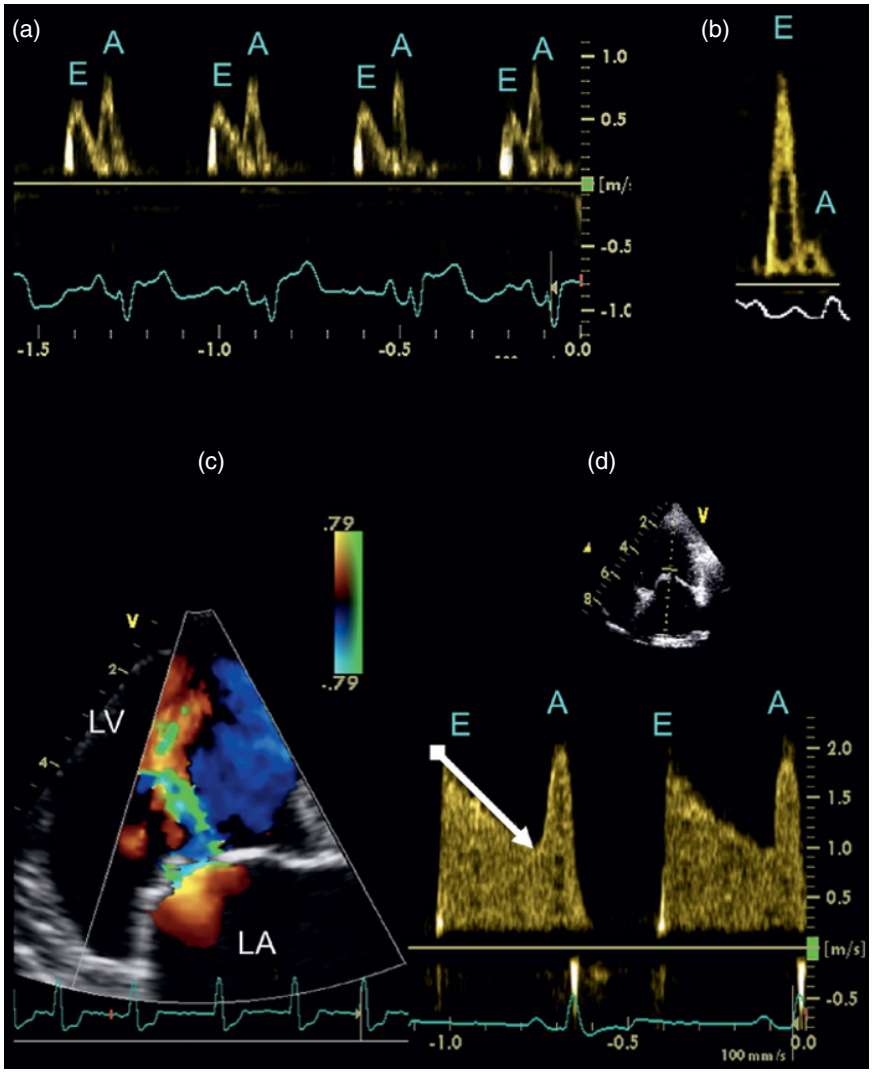


Figure 16.29 Examples of abnormal diastolic transmitral inflows obtained from left parasternal apical four-chamber views. (a) Delayed relaxation transmitral flow pattern in a cat, which is characterized by a delayed and prolonged early diastolic E wave (with an inverted E/A ratio). (b) Restrictive transmitral flow pattern, with a high early diastolic E wave (owing to high left atrial pressure) and a diminished A wave (owing to decreased left ventricular compliance) in a cat with restrictive cardiomyopathy. Doppler echocardiograms of two dogs with congenital mitral valve stenosis are presented in (c) and (d). (c) Color flow Doppler mode across the stenotic mitral valve shows a narrow aliased turbulent signal during diastole. (d) Spectral Doppler of the mitral inflow (continuous-wave Doppler mode) reveals a high peak diastolic E-wave velocity (1.9 m/s, reference range: 0.58–1.17 m/s; see Table 16.4) and a high peak diastolic A-wave velocity (2.1 m/s, reference range: 0.39–0.86 m/s; see Table 16.4). The pressure half time for the E wave, which is defined as the time needed for the peak transvalvular pressure gradient to fall to its half value, may be calculated automatically by tracing (*white arrow*) the deceleration slope of the E wave. In this case, the pressure half time is markedly prolonged (290 ms, reference range: <50 ms), thus confirming a severe mitral valve stenosis. LA, left atrium; LV, left ventricle.

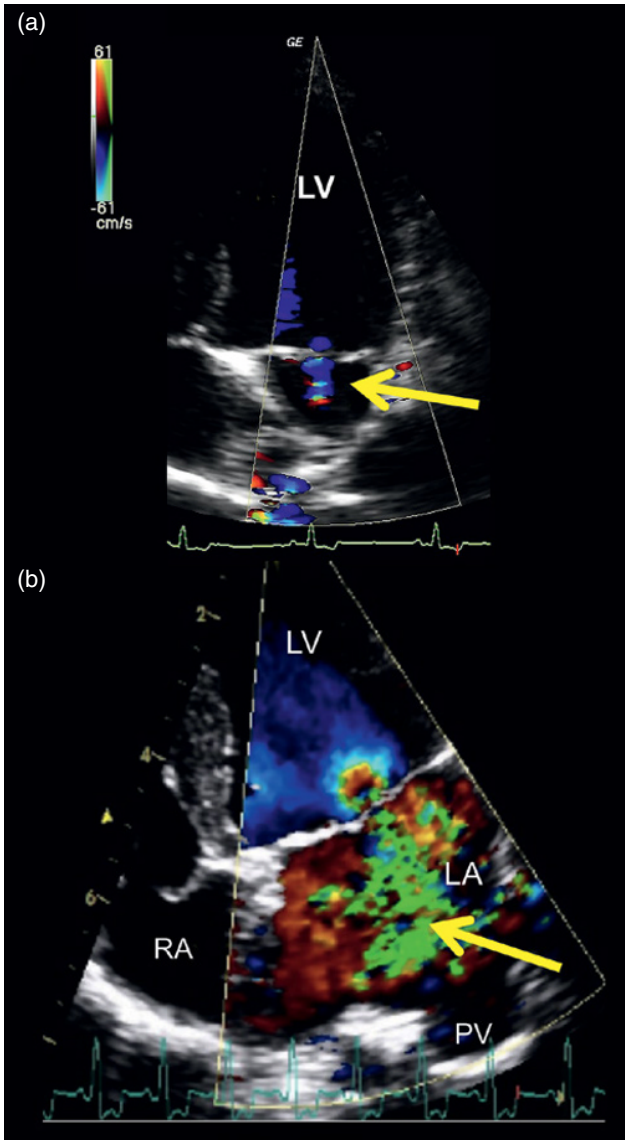


Figure 16.30 Semi-quantitative assessment of mitral insufficiency using the color flow Doppler mapping method in two dogs suffering from degenerative mitral valve disease of various grades (left parasternal apical four-chamber views). In (a), the color flow jet of mitral insufficiency (*arrow*) involves less than 20% of the left atrial chamber, which is consistent with mild valvular regurgitation. Conversely, in (b), the color flow aliased turbulent jet of mitral insufficiency (*arrow*) fills 100% of the left atrial chamber, which is consistent with severe valvular regurgitation. LA, left atrium; LV, left ventricle; RA, right atrium; PV, pulmonary vein.

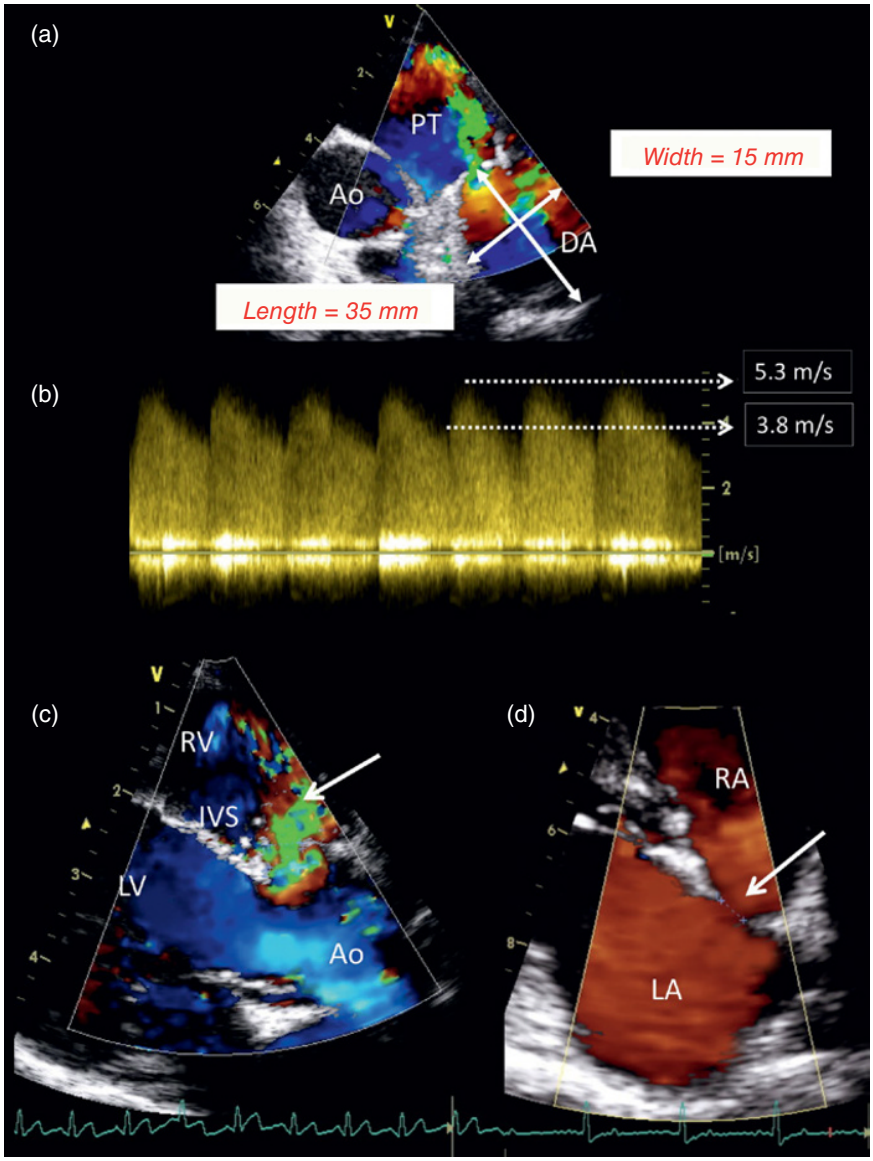


Figure 16.31 Assessment of left-to-right congenital shunts in dogs using Doppler echocardiography (a,b: patent ductus arteriosus; c: ventricular septal defect; d: atrial septal defect). (a) Image obtained from the left parasternal cranial transaortic short-axis view showing the aliased turbulent color flow jet coming from the large ductus arteriosus (DA) into the dilated pulmonary trunk (PT) during systole. Note that the DA diameter decreases abruptly at the point of insertion in the PT. (b) (same dog as in a) Continuous-wave Doppler mode confirms a continuous turbulent positive flow into the pulmonary artery of high velocity (5.3 m/s and 3.8 m/s during systole and diastole, respectively), which is consistent with a normal aortic-to-pulmonary artery pressure gradient (112 mmHg and 58 mmHg, respectively, according to the modified Bernoulli equation). (c) Color flow Doppler obtained from the right parasternal five-chamber view shows an abnormal aliased turbulent flow (*arrow*) from the left ventricle entering the right ventricle just below the septal tricuspid leaflet, through a moderate sized perimembranous ventricular septal defect. (d) Color flow Doppler obtained from the right parasternal four-chamber view shows a laminar flow (*arrow*) from the left atrium to the right atrium through a small ostium secundumtype atrial septal defect. Ao, aorta; IVS, interventricular septum; LA, left atrium; LV, left ventricle; RA, right atrium. RV, right ventricle.

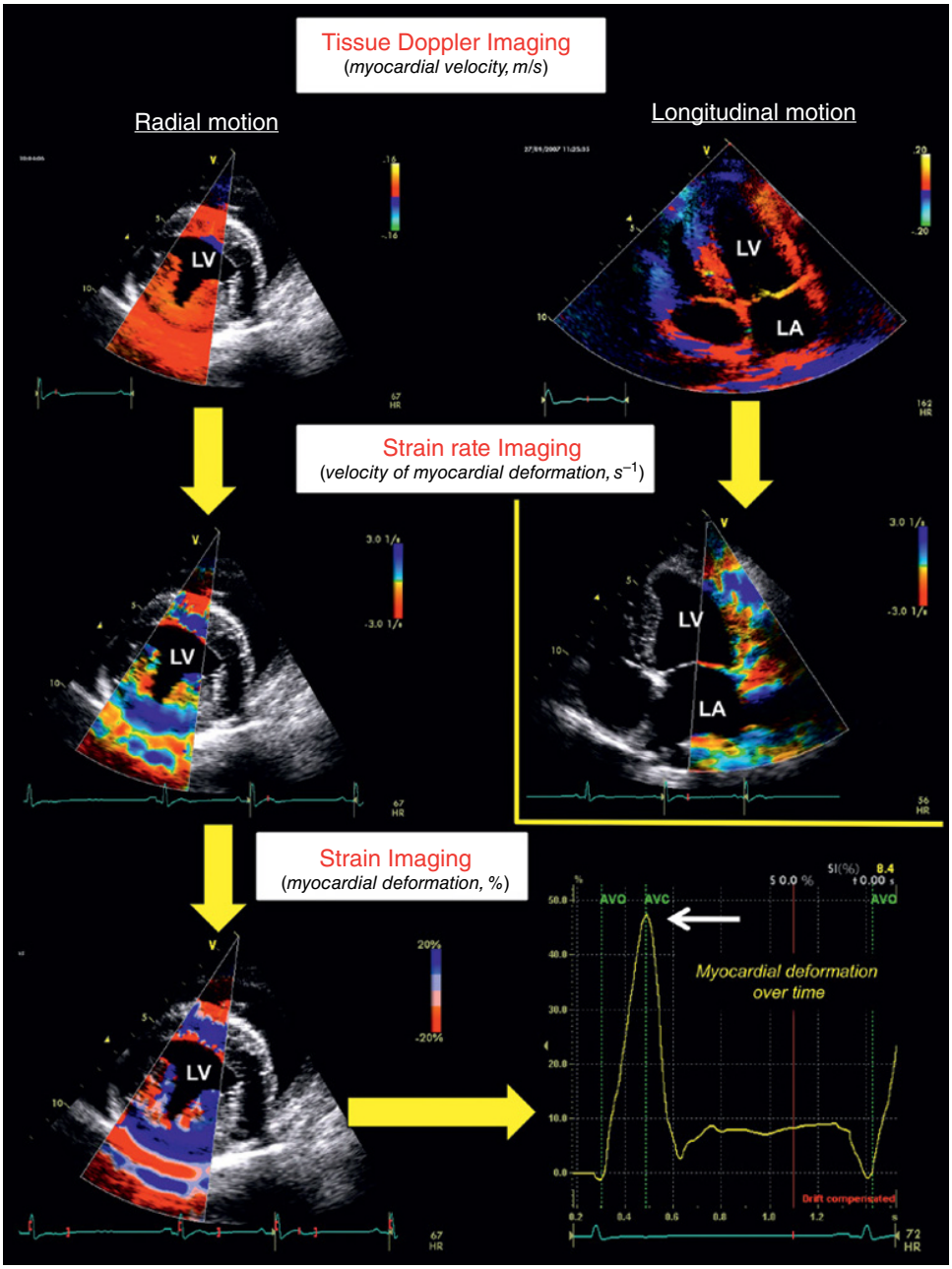


Figure 16.32 Tissue Doppler imaging (TDI) and TDI-derived techniques. Using the two-dimensional (2D) color TDI mode, myocardial velocities are superimposed in color on 2D mode images. Velocities toward the transducer are colored in red, whereas those away from the transducer are colored in blue on the right parasternal transventricular short-axis view (*left upper panel*) and the left apical four-chamber view (*right upper panel*) to analyze radial and longitudinal myocardial motions, respectively. A specific software is then used to quantify the myocardial velocities (m/s) in one or several segments. Strain rate imaging and strain imaging are two TDI-derived techniques that use the previously described velocity data to calculate deformation velocity (s^{-1}) and deformation (%) per myocardial segment length, respectively. As with 2D color TDI, the color display of strain rate and strain can be superimposed on 2D mode images using the same views (*left and right middle panels, left lower panel*). These variables can also be quantified over time by using a specific software. A normal radial strain profile of a left ventricular free wall segment in a dog is presented in the right lower panel: the radial strain (expressed in %) is positive and maximal in end-systole (*white arrow*), and then decreases during diastole, thus confirming regional systolic expansion (i.e., thickening) and diastolic compression (i.e., shortening), respectively.AVC, aortic valve closure; AVO, aortic valve opening; LA, left atrium; LV, left ventricle.

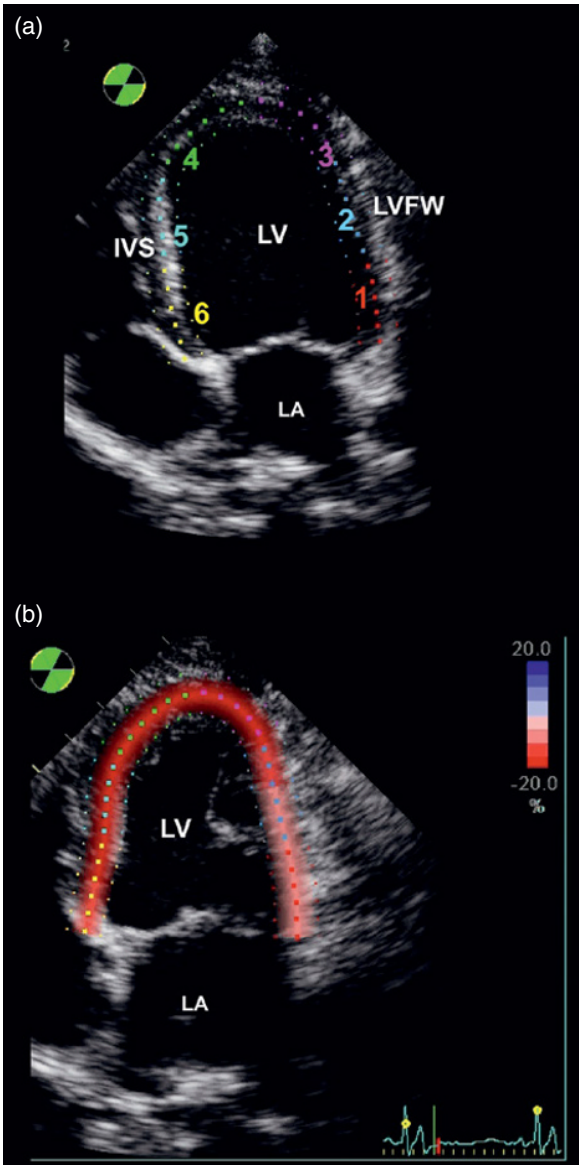


Figure 16.33 Longitudinal myocardial deformation (strain) assessed by speckle tracking echocardiography (STE). (a) The myocardial region of interest, including the interventricular septum (IVS) and the left ventricular free wall (LVFW), is automatically divided into six segments (segments #1 to #3 for the LVFW, and #4 to #6 for the IVS) using the left apical four-chamber view. (b) Example of normal two-dimensional (2D) color-coded strain obtained by STE in a healthy dog (same animal as in a). All six segments are colored in red, which means a negative strain for all six segments, thus confirming a homogeneous longitudinal shortening during systole. LA, left atrium; LV, left ventricle.

Further Reading

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17

Electrocardiography

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Cardiac arrhythmias are defined as variations of the cardiac rhythm from normal sinus rhythm. Some cardiac arrhythmias are benign and clinically insignificant and require no specific therapy whereas others can manifest with a variety of clinical signs, such as episodic weakness or collapse (syncope), exercise intolerance or inappropriate panting/restlessness or sudden death (i.e., ventricular fibrillation). In order to diagnose the nature of an arrhythmia and determine therapeutic strategies, it is imperative to acquire an electrocardiogram (ECG).

Indications for ECG Recordings

- Document arrhythmias detected by auscultation.
- Evaluate a patient presenting for syncope (fainting) or episodic weakness.
- Heart rate and rhythm monitoring during anesthesia.
- Heart rate and rhythm monitoring in critically ill patients.
- Monitoring changes in rate and rhythm following drug administration.
- Assessing changes in ECG morphology and heart rate due to electrolyte imbalances associated with extracardiac disease or drug toxicities.
- Detection of pericardial disease.
- Identifying conduction disturbances or axis shifts associated with myocardial hypertrophy or dilation.
- Ambulatory ECG recording (Holter) for long-term monitoring of intermittent arrhythmias.

ECG Lead Terminology and Acquisition Technique

Electrocardiography is used to record electric potentials generated by the heart muscle during each cardiac cycle. These potentials are detected on the surface of the body using electrodes attached to standardized locations on the limbs and chest wall. The electrical signals are amplified by the electrocardiograph machine and displayed on special graph paper in voltage and time. The limb leads are defined as RA = right arm, LA = left arm, and LL = left leg. The output from each electrode pair (differential recording) is referred to as a *lead* and numbered with the Roman numerals I, II, and III. The limb leads form the points of what is known as Einthoven's triangle (Figure 17.1). An imaginary line connecting the two electrodes is the lead axis. Each lead looks at the heart from a different angle within the animal's frontal plane.

The Six Limb Leads

There are six limb leads which depict the cardiac depolarization in the frontal plane. Leads I, II, and III are called *bipolar* limb leads because they record the electrical activity between two limb electrodes (Table 17.1).

Using the same electrodes as leads I, II, and III, the unipolar limb leads also measure the electrical activity between two terminals, but the recording electrode is always positive and the negative terminal (called Wilson's central terminal) is made up of the sum of the electrodes attached to the right arm, left arm, and left leg. These *unipolar* limb leads view the heart from different angles (or vectors) than the bipolar leads, because the negative electrode is zeroed out, allowing the positive electrode to become the "exploring" electrode. The unipolar limb leads generate a very low voltage signal, so need to be amplified by the ECG machine (augmented). These limb leads are named after their positive electrode, located on the **L**eft arm (aV**L**), the **R**ight arm (aV**R**), and the left **F**oot (aV**F**), where the "aV" stands for augmented voltage (Figure 17.2).

Together with leads I, II, and III, augmented limb leads aVR, aVL, and aVF form the basis of the hexaxial reference system (see Figure 17.7) which is used to calculate

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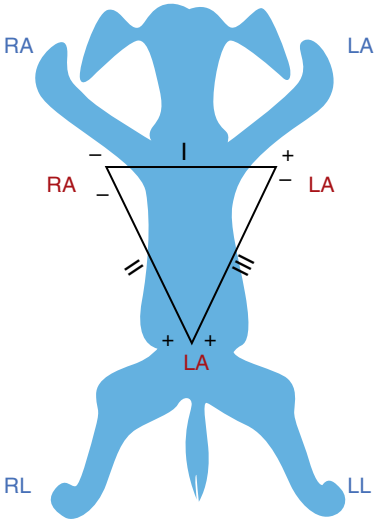


Figure 17.1 The standardized positions of the electrodes on the body are defined as RA = right arm, LA = left arm, and LL = left leg. The output from each electrode pair is referred to as a lead and numbered with the Roman numerals I, II, and III. The limb leads (I, II, III) form the Einthoven's triangle. The limb leads display the cardiac depolarization in the frontal plane.

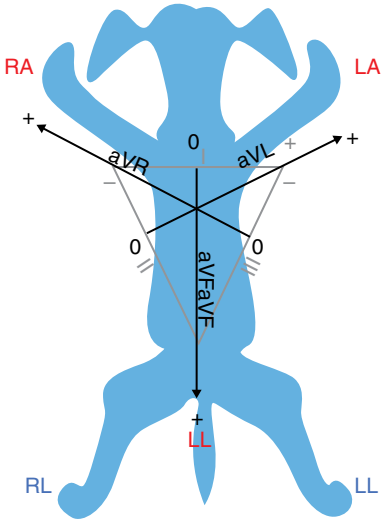


Figure 17.2 The augmented (unipolar) limb leads use the same electrodes as leads I, II, and III but the recording electrode is always positive and the negative terminal is made up of the sum of the electrodes attached to the right arm, left arm, and left leg. The augmented limb leads are named after their positive electrode, located on the **L**eft arm (aV**L**), the **R**ight arm (aVR), and the left **F**oot (aV**F**), where the "a" stands for augmented and "V" for vector.

Table 17.1 The positive and negative terminals of the six limb leads

Bipolar limb leads		Augmented unipolar limb leads	
I	R arm (–) to L arm (+)	aVR	R arm (+) to common terminal (–)
II	R arm (–) to L foot (+)	aVL	L arm (+) to common terminal (–)
III	L arm (–) to L foot (+)	aVF	L foot (+) to common terminal (–)

the heart's electrical axis (mean electrical axis) in the *frontal plane*. The positive and negative terminals of the six limb leads are listed in Table 17.1.

The Precordial or Chest Leads (V Leads)

The chest leads view the heart's electrical activity in the transverse plane. This complements the information regarding the electrical fields gained from the frontal plane (limb leads). The chest leads are termed V (*voltage*) leads. They are unipolar with the positive exploring electrode placed on the chest (precordium) coupled with Wilson's central terminal used for the negative electrode. The electrodes for the chest leads are placed directly on the chest. V1 is placed in the fifth right intercostal space just to the right of the sternum, V6 is placed in the left sixth intercostal space at the costochondral junction, while V2 to V5 are spaced equally between V1 and V6 in the sixth intercostal space on the left side. Because of their close proximity to the heart, they do not require augmentation. Left chest leads may be more sensitive than the limb leads for detection of right ventricular enlargement or allow better identification of P-waves.

Some ECG machines record one lead at a time but others can record all six or 12 simultaneous leads. The ECG signals are normally in the range of ±2 mV and require a recording bandwidth of 0.05–150 Hz. The ECG machine provides filters to reduce artifacts, such as 50 Hz cycle from inappropriate grounding (electrical interference). In cats, typically only the 150 Hz filter is used in order to include high-frequency components of the R- and S-wave. The ECG reference ground is provided through a separate electrode, either incorporated into one of the three limb leads or as a separate wire.

For ECG acquisition, the animal is positioned on its right side with the limbs perpendicular to the body and the alligator clips or patch electrodes are attached to the skin. Alcohol or a gel with a high ionic concentration is applied to the clips, acting as the transducer at the tissue–electrode interface. The size of the ECG waveform deflections depends on the distance between the heart and the electrode position. In dogs and cats, the limb leads are attached to the elbows and stifles, and color coded to identify their position. Table 17.2 lists the electrode positions.

Table 17.2 Electrode position for ECG recording in dogs and cats

ECG electrode	Position
Black	Left front leg at elbow
White	Right font leg at elbow
Red	Left back leg at stifle
Green	Right back leg at stifle

Genesis of the ECG Deflections

The ECG waveforms are generated by the spread of electrical activation through the specialized conduction system of the heart. Multiple activation wavefronts depolarize in various directions of the heart. The sum of all wavefront vectors at a point in time determines the overall magnitude and direction of the deflection in a particular surface ECG lead. The six- or 12-lead ECG provides information about the magnitude of the electrical activity of the heart and the direction of the moving depolarization wavefront in multiple orientations. A wavefront traveling towards the positive terminal of a lead results in a positive deflection of the ECG in that lead. When a wavefront travels away from the positive electrode, a negative deflection occurs.

Waveform Morphology and Intervals

The P-wave

The first electrical signal of each cardiac cycle is initiated in the sinus node. It is called the P-wave and represents the activation of the atria (Figure 17.3).

The P-wave is a small, upright wave in leads I, II, II,I and aVF, while it appears as a negative deflection in aVR and aVL. The P-wave amplitude is most prominent in lead II, because the average vector of the atrial depolarization is traveling towards the positive terminal of lead II (see Figure 17.3). Increased P-wave amplitude or duration is associated with either right or left atrial enlargement. Normal P-wave values for the dog and cat are shown in Table 17.3. Absence of P-waves is noted in instances of atrial fibrillation, atrial standstill, and sinus arrest. P-waves without corresponding QRS complexes (blocked Ps) are observed in cases of second- and third-degree atrioventricular (AV) node block. Negative P-waves may occur in conjunction with junctional or atrial premature and escape beats, indicating alternative conduction pathways or retrograde conduction across the atria.

The PR Interval

The PR interval measured from the beginning of the P-wave to the beginning of the QRS complex (see Figure 17.3) represents the time it takes for the electrical

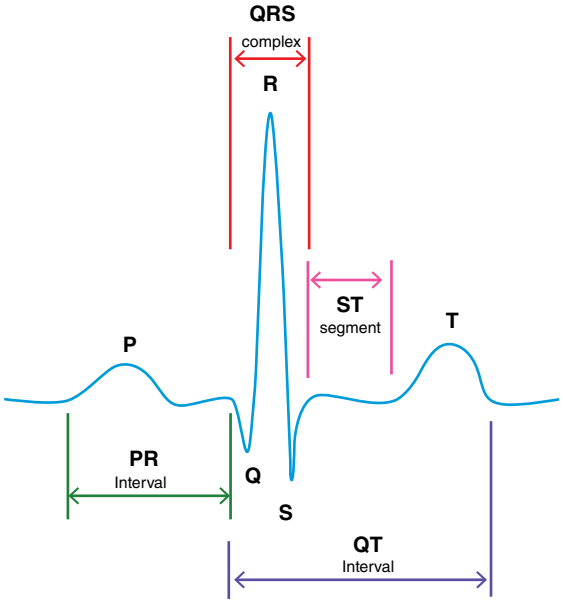


Figure 17.3 Major deflections and intervals of the ECG (lead II). See text for details.

Table 17.3 Normal ECG amplitudes and durations in the dog and cat

	Dog	Cat
Heart rate	Puppy: 70–220 bpm Adult: 70–180 bpm	120–240 bpm
Rhythm	Sinus rhythm Sinus arrhythmia	Sinus rhythm
P-wave		
Amplitude	≤0.4 mV	≤0.2 mV
Duration	≤0.04 s	≤0.04 s
PR interval	0.06–0.13 s	0.05–0.09 s
QRS		
Amplitude	≤2.5 mV, small breeds ≤3.0 mV, large breeds	≤0.9 mV
Duration	≤0.06 s	≤0.04 s
ST segment	No elevation or depression by >0.2 mV	No elevation or depression
T-wave	Positive, negative or biphasic, but ≤25% height of R-wave	Isoelectric or positive
QT interval	0.15–0.25 s (varies inversely with heart rate)	0.12–0.18 s (varies inversely with heart rate)
Mean electrical axis	+40° to +100°	0° to +160°

Source: Adapted from Tilley and Smith (2008).

impulse to conduct from the sinus node through the atria and the AV node and bundle of His. Conduction in the AV node is markedly slower, allowing time between the mechanical contraction of the atria and the ventricles. On the surface ECG, this conduction delay produces a short isoelectric segment following the P-wave, contributing to the PR interval. The normal PR interval in dogs and cats is shown in Table 17.3. Increased duration of the PR interval indicates abnormally slow conduction in the AV node, called first-degree AV block. Intrinsic AV node disease as well as certain drugs, if overdosed (beta-blockers or Ca channel blockers), may result in first degree AV block. Varying PR intervals are noted in cases of sinus arrhythmia or certain forms of second-degree AV block. Abnormally short PR intervals are rare and encountered in instances of accessory pathway-mediated arrhythmias.

The QRS Complex

When the electrical impulse emerges from the AV node, it enters the ventricles rapidly via the bundle of His, the right and left bundle branches and Purkinje network, producing the QRS complex on the surface ECG. The QRS complex thus represents ventricular depolarization. Standard nomenclature describes the first negative deflection as the Q-wave, the first positive deflection as the R-wave, and the first negative deflection following the first positive deflection as the S-wave (see Figure 17.3). Note that normal QRS complexes do not necessarily contain all three waveforms, and in dogs, a high degree of individual variability is seen. The normal sequence of ventricular depolarization results in a QRS complex of relatively short duration and with a net positive polarity in leads II, III, and aVF. The normal duration and amplitude of the QRS complex in the dog and cat are shown in Table 17.3.

A key component of ECG analysis is inspection of the QRS morphology in lead II, which can provide clues to the beat's origin, its conduction through the ventricle, and the potential presence of ventricular hypertrophy. QRS complexes generated by a beat of supraventricular origin (sinus node or supraventricular foci such as the atria or AV nodal junction) are typically narrow and positive in lead II, while those that originate from ventricular foci are wider (increased duration) and "bizarre" in their appearance compared to normal sinus beats. Conduction disturbances within the ventricles can also alter the morphology of the QRS complexes. For instance, the presence of a right or left bundle branch block slows conduction through the ventricular tissue in the respective side. This results in a QRS complex of longer duration (wide) despite the fact that the beat may have originated from a supraventricular focus or the sinus node (see Figures 17.10 and 17.12). Finally, ventricular hypertrophy can increase the amplitude and duration of the QRS complex (albeit to a lesser degree than a bundle branch block) or change the mean electrical axis (as in the case of right heart enlargement).

The T-wave

Following the QRS complex is another short, relatively isoelectric segment, the ST segment, followed by the T-wave, representing the ventricular repolarization. The ST segment connects the QRS complex and the T-wave (see Figure 17.3). However, since it is usually difficult to determine exactly where the ST segment ends and the T-wave begins, the relationship between the QT interval and T-wave should be examined together. In general, the ST segment should not be either elevated or depressed compared to baseline by more than 0.2 mV. In dogs and cats, ST segment abnormalities are occasionally detected in cases of myocardial disease (dilated cardiomyopathy), congenital heart disease (subaortic stenosis), electrolyte imbalances, acute hypoxia (anesthesia) or suspected myocardial infarction (rare).

The T-wave represents ventricular repolarization. The normal T-wave in both dogs and cats demonstrates a high degree of variability and can be positive, negative, biphasic, or of very low amplitude; however, the T-wave should be consistent from beat to beat during normal rhythm. The normal characteristics of the T-wave in dogs and cats are shown in Table 17.3. Compared to human patients, T-wave changes in the dog and cat are relatively nonspecific and poorly characterized. T-wave abnormalities can be seen in instances of electrolyte abnormalities, hypoxia, conduction abnormalities, or drug toxicity (i.e., digoxin).

The QT interval is a measure of the time between the start of the Q-wave (or R-wave if there is no Q) and the end of the T-wave and represents the entire depolarization and repolarization of the left and right ventricles. If abnormally prolonged or shortened, there is a risk of developing ventricular arrhythmias. Prolongation of the QT interval may be due to an adverse drug reaction (i.e., quinidine toxicity). Some antiarrhythmic drugs, like amiodarone or sotalol, work by creating a pharmacologic QT prolongation. A shortened QT can be associated with hypercalcemia (Box 17.1).

Evaluation of the ECG

Important features of the ECG that require analysis include heart rate, rhythm, mean electrical axis (MEA), waveform morphology, and criteria for heart enlarge-

Box 17.1 Summary of ECG waveforms

- The P-wave represents atrial depolarization
- The Q-wave is the first negative deflection representing ventricular septal depolarization
- The R-wave is the first positive deflection representing early ventricular depolarization
- The S-wave is the next negative deflection representing late ventricular depolarization
- The ST segment/T-wave represents ventricular repolarization

ment. In order to assess these characteristics, one must understand how paper speed and sensitivity settings affect ECG interpretation.

ECG Paper, Sensitivity, and Speed of Recording

ECG paper has a background pattern of small 1 mm squares and bold division lines every 5 mm in both horizontal and vertical directions, which form larger squares on the ECG paper (Figure 17.4). The ECG is typically recorded at one of two different paper speeds, either 25 mm/s or 50 mm/s. Paper speed denotes the speed at which the waveforms are being recorded. At 25 mm/s, each 1 mm square (little box, thin lined) represents 0.04 seconds and each 5 mm square (bold lined) represents 0.2 seconds, while at 50 mm/s, each 1 mm square represents 0.02 seconds and each 5 mm square represents 0.1 seconds.

ECG sensitivity refers to the amplitude of the waveforms based on electrical voltage. At standard sensitivity, an impulse of 1 millivolt (mV) will inscribe a waveform amplitude that is 10 mm tall. In cases where the ECG voltages are normally low (i.e., in cats), sensitivity can be increased (doubled) so that an impulse of 0.5 mV will create a waveform of 10 mm amplitude, thereby increasing the ability to visually inspect the individual ECG waveforms. Conversely, in animals with severe heart enlargement, sensitivity can be decreased (halved) so that waveforms do not extend past the borders of the recording paper.

Heart Rate

If the heart rhythm is regular, an "instantaneous" heart rate is easy to calculate: count the number of 1 mm squares (little boxes) between two heart beats (RR interval) and divide this number into 3000 if the paper speed is 50 mm/s (3000 is the equivalent of 1 min because 60 seconds × 50 = 3000) or into 1500 if the paper speed is 25 mm/s (Figure 17.5). This method is also useful if the animal has intermittent short runs of abnormal beats (i.e., ventricular tachycardia) and the rate of that rhythm has to be calculated.

If the heart rhythm is irregular, calculation of the average heart rate over a prescribed period of time is performed. It is useful to realize that 30 large squares (bold lined) or 150 mm represent 3 seconds at 50 mm/s or 6 seconds at 25 mm/s. Thus, heart rate is determined by

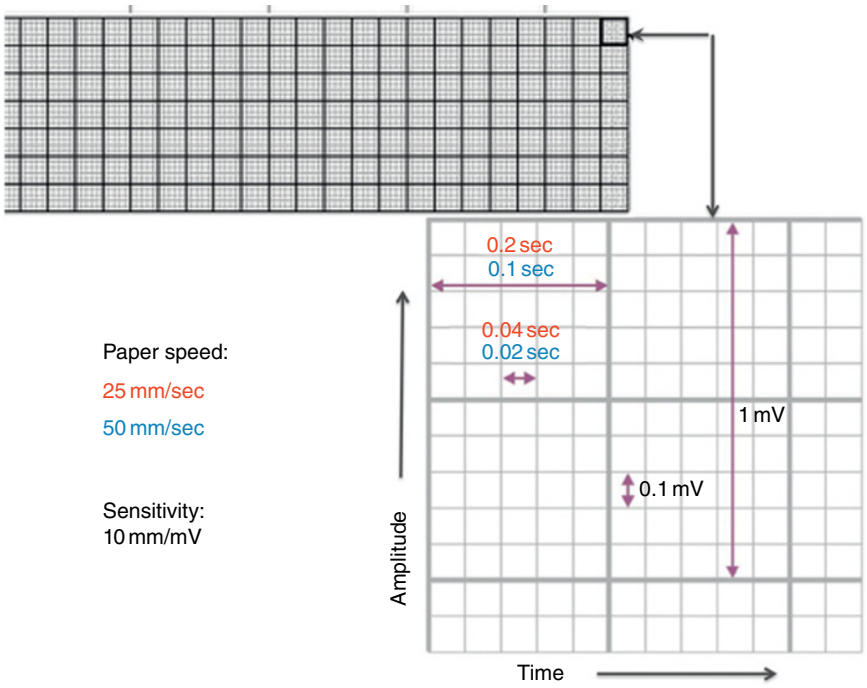


Figure 17.4 Calibration of ECG paper speed and sensitivity. See text for details.



Figure 17.5 Calculation of instantaneous heart rate between two beats is used when the rhythm is regular or if the heart rate of a short run of abnormal beats needs to be calculated. At a paper speed of 25 mm/s, the number of mm (little boxes) between two beats is divided into 1500 to calculate the heart rate per minute. At a paper speed of 50 mm/s, the number of mm between two beats is divided into 3000. See text for additional details.

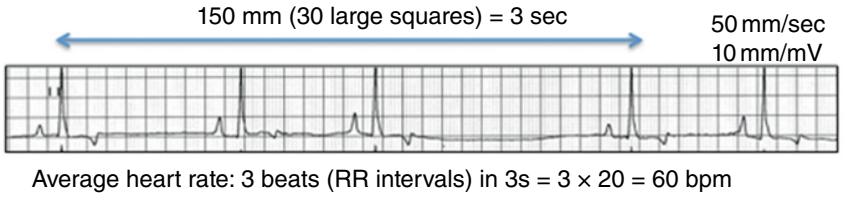


Figure 17.6 Calculation of average heart rate, used when rhythm is irregular. At a paper speed of 25 mm/s, the number of beats over a 150 mm segment of the ECG is multiplied by 10 to achieve number of heart beats per minute. At a paper speed of 50 mm/s, the number of beats over a 150 mm segment of the ECG is multiplied by 20 to achieve number of heart beats per minute.

counting the number of beats over 30 large squares and multiplying this number by 20 if the paper speed is 50 mm/s (Figure 17.6) or multiplying by 10 if the paper speed is 25 mm/s.

A commonly used shortcut takes advantage of the fact that most standard ballpoint pens are 150 mm in length. Thus, they can be placed on the ECG paper to denote a -3 or 6-second interval and the number of beats that are demarcated by the length of the pen can be quickly counted.

Rhythm

The heart rhythm describes the pattern of heart beats and sequence of the P-QRS-T-wave forms. When determining the heart rhythm, the following characteristics should be examined.

- The regularity of the heart beats: are the RR intervals regular or irregular?
- The relationship of the P-wave and QRS complexes: (a) is there a P-wave in front of every QRS complex and (b) is there a QRS complex following every P-wave?
- The origin of the heart beats: (a) sinus node or (b) ectopic (i.e., atrial, junctional, or ventricular).
- The heart rate.

In some instances, the heart rhythm changes or is composed of multiple different rhythms that each requires a separate description (Box 17.2).

Box 17.2 Rhythm analysis: important questions to ask

- Is the rate fast or slow (tachcardia vs bradycardia)?
- Is the rhythm regular or irregular? If irregular, is the rate slow, fast, or are there premature beats? A regular rhythm usually has less than 10% variation in the RR intervals.
- Are there P-waves? Are they normal (upright in lead II, i.e., is the rhythm sinus or not sinus)?
- Is there a P-wave for every QRS, is there a QRS for every P-wave? Normally there is a nearly fixed PR interval between the P-waves and the QRS complexes.
- Are the QRS complexes normal or abnormal (normal or abnormal conduction)?

Mean Electrical Axis

The mean electrical axis (MEA) describes the net direction of cardiac depolarization across the animal's frontal plane. The conventional six-lead ECG system divides the frontal plane into 12 segments, similar to the slices of a pie (Figure 17.7). By doing so, the six-lead ECG examination records the electrical activity of the heart from six different vantage points along the frontal plane in 30° increments.

The MEA normally points towards the caudal half of the animal. In the dog, the normal MEA is between +40° and +100° and in the cat, the normal MEA is

between 0° and +160°. Calculation of the MEA can be done in several ways. One way is to examine the polarity of the QRS complexes from each of the six limb leads and identify the ECG lead in which the QRS complex is isoelectric (Figure 17.8, step 1), that is, the lead in which the net polarity of the QRS complex is closest to zero. (i.e., the positive and negative deflections of the QRS waves cancel each other out). In some instances, this will be the lead in which the QRS waves are the smallest and in other instances the lead in which the amplitude of the positive R-wave is the same as the sum of the negative deflections (Q- and S-wave, i.e., net polarity of the QRS).

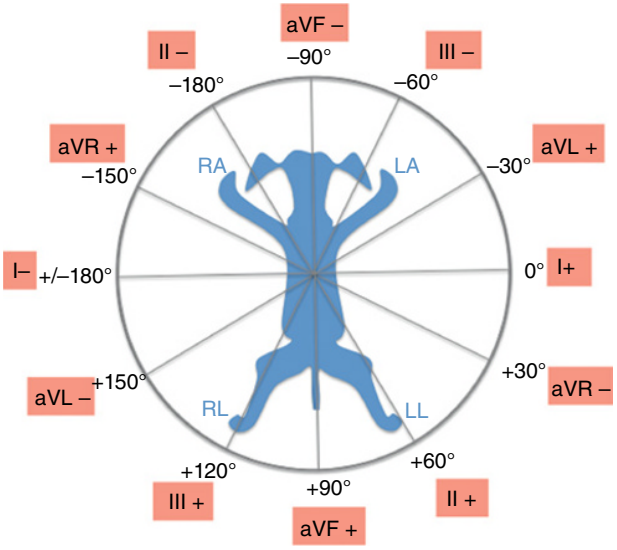


Figure 17.7 The hexaxial or six-lead ECG system divides the frontal plane into 12 segments, similar to the slices of a pie. By doing so, the six-lead ECG examination records the electrical activity of the heart from six different vantage points along the frontal plane in 30° increments.

Then identify the limb lead that is perpendicular to the isoelectric lead on the hexaxial lead system (Figure 17.8, step 2). The MEA will exist in a direction either towards the positive or negative pole of the perpendicular lead, depending on the polarity of the QRS complex in that lead (Figure 17.8, step 3). The net polarity of the QRS complex in lead II is positive in the ECG example in Figure 17.8, so the MEA points to +60° (Figure 17.8, step 4). This is considered a normal MEA for a canine.

To obtain a general direction of the MEA, a quick approach called the "pie method" may be useful (Figure 17.9). First, determine the net polarity of the QRS complex in lead I and aVF. These are the two leads which divide the heart into two perpendicular halves and create four equal pieces (quarters) of a pie.

With a normal MEA of depolarization, both lead I and aVF have a net positive polarity, and the overlapping

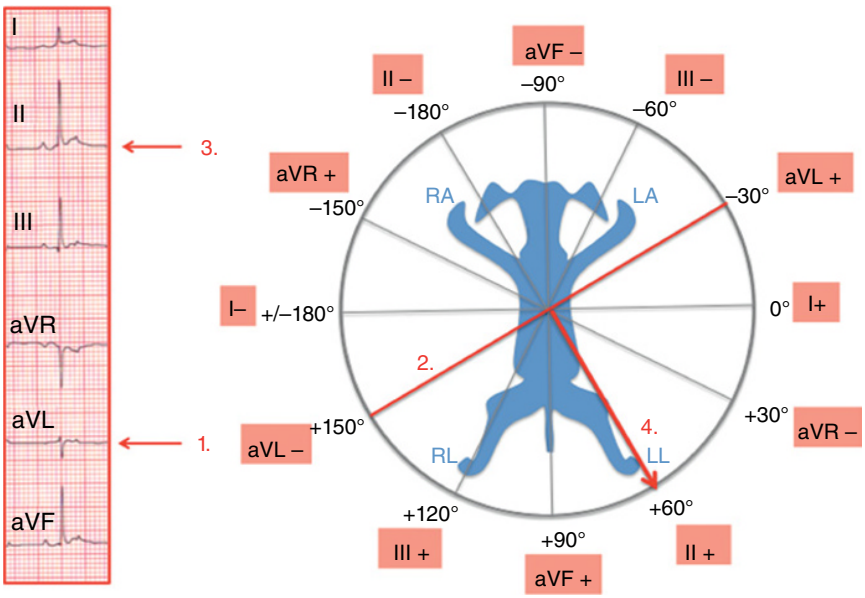


Figure 17.8 Calculation of the MEA is performed by first examining the polarity of the QRS complexes from each of the six limb leads and identifying the ECG lead in which the QRS complex is isoelectric, that is, the lead in which the net polarity of the QRS complex is closest to zero (i.e., the positive and negative deflections of the QRS waves almost cancel each other out) (step 1). Next, identify the limb lead that is perpendicular to the isoelectric lead on the hexaxial lead system (step 2). The MEA will point towards either the positive or negative pole of the perpendicular lead, depending on the polarity of the QRS complex in that lead (step 3). The net polarity of the QRS complex in lead II is positive, so the MEA points to +60° (step 4). This is considered a normal MEA for a dog.

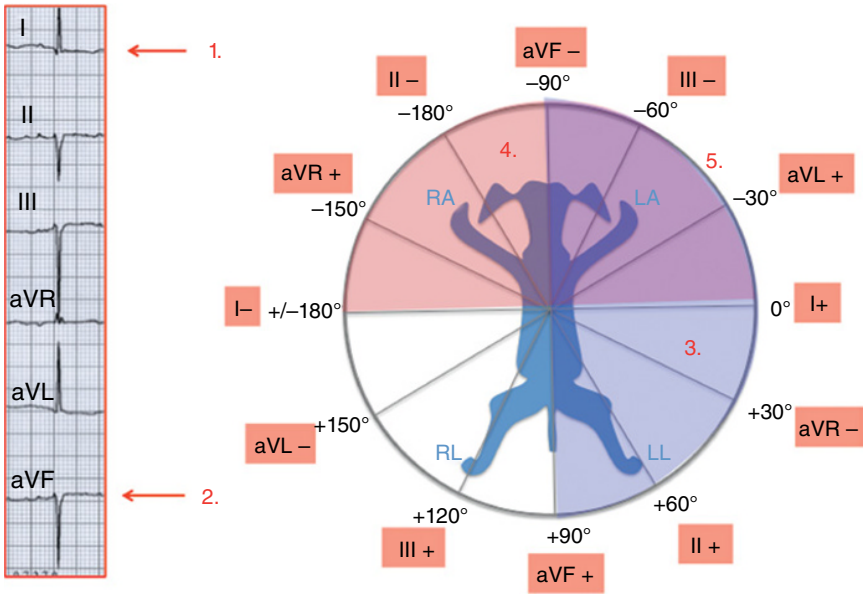


Figure 17.9 Calculation of the mean electrical axis using the "pie method." First, determine the net polarity of the QRS complex in lead I (step 1) and aVF (step 2). These two leads divide the heart into two perpendicular halves and create four equal pieces (quarters) of a pie. If the QRS in lead I is positive, the "half pie" pointing to the positive pole of lead I is shaded (step 3, blue half). If the QRS is negative in aVF, the "half pie" pointing to the negative pole of lead aVF is shaded (step 4, red half). The overlapping quarter (step 5, purple half) contains the MEA. Thus, if lead I is positive and aVF is negative, the overlapping section is 0° to –90°, indicating a left axis shift.

section thus is the pie piece (quarter) between 0° to 90°. If lead I is positive and aVF is negative, the overlapping section is 0° to –90° (see Figure 17.9) which indicates a left axis shift; if both lead I and aVF are negative, the overlapping section is 180° to –90° indicating a right axis shift.

The MEA can be within the normal range or to the right or left of the normal range. Common causes of right axis deviations include right ventricular hypertrophy (right axis shift with normal QRS duration) or right bundle branch block right axis shift with prolonged QRS duration) (Figure 17.10).

Common causes of left-axis deviations include partial left bundle branch block and left anterior fascicular block as seen in some cats with cardiomyopathies (see Figure 17.9). Note that left ventricular hypertrophy does not usually result in the left-axis shift as the normal MEA is already pointing in the direction of the left ventricular apex. Less commonly, mechanical displacement of the heart to either side of the thorax by space-occupying lesions or lung lobe atelectesis can change the MEA.

Criteria for Heart Enlargement

The criteria for heart enlargement in the dog and cat are shown in Table 17.4. In brief, atrial enlargement is manifest as P-wave of increased duration (P mitrale) or increased amplitude (P pulmonale) (Figure 17.11) or both.

Left ventricular enlargement can cause an increased R-wave amplitude and QRS duration whereas right ventricular enlargement can manifest as a right MEA shift and prominent S-waves.

Conduction Abnormalities or Bundle Branch Block

The bundle of His is specialized conduction tissue that forms the distal portion of the AV node, and divides into two main bundle branches that course left and right into the ventricular muscle. Right (RBBB) or left (LBBB) bundle branch block occurs when the impulse

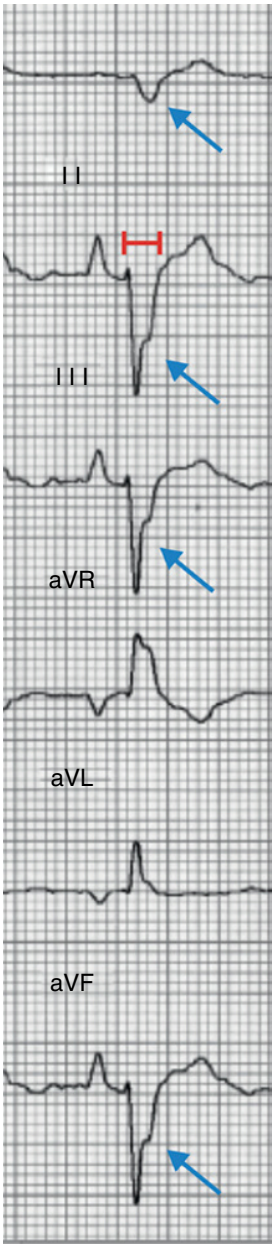


Figure 17.10 Six-lead ECG example of a right axis shift and right bundle branch block in a cat with right ventricular cardiomyopathy. The leads are I, II, III, aVL, aVR, aVF from top to bottom. The conduction disturbance is identified by the prolongation of the QRS complex (0.07 s, *red bar*) and a right axis deviation. The right axis shift is denoted by deep S-waves in leads I, II, III, and aVF (*blue arrows*) (50 mm/s; 10 mm/mV).

is blocked or slowed within either of the branches and block results in characteristic QRS waveform changes. In order to diagnose a bundle branch block, the MEA has to be determined, which requires a six-lead ECG recording. RBBB (see Figure 17.10) is characterized by a right shift of the MEA and markedly prolonged QRS duration (>0.08 s in the dog and >0.06 s in the cat), while LBBB (Figure 17.12) is characterized by a normal MEA and markedly prolonged QRS duration (>0.08 s in the dog and >0.06 s in the cat) (normal values listed in Table 17.3).

The QRS morphology with bundle branch block patterns may be confused with a ventricular rhythm. Impulse origin in most cases of bundle branch block is the sinus node, hence the rhythm is supraventricular, despite the marked change in QRS waveform morphology, and there is a P-wave associated with each QRS complex. RBBB may be a benign finding in both dogs and cats, or associated with right ventricular cardiomyopathy whereas LBBB is usually associated with significant underlying heart disease, such as dilated cardiomyopathy.

Table 17.4 ECG criteria for heart enlargement in the dog and cat

	Dog	Cat
Left atrial enlargement		
P-wave	>0.4 mV, >0.04 s	>0.04 s
	Notched	
Right atrial enlargement		
P-wave	>0.4 mV	>0.2 mV
Left ventricular enlargement		
R-wave	>2.5 mV in lead II, aVF	>0.9 mV in lead II
	>3.0 mV in large-breed dogs	
	>1.5 mV in lead I	
QRS duration*	>0.06 s	>0.04 s
Right ventricular enlargement		
S-wave	>0.35 mV in lead II	S-wave in leads I, II,
	>0.05 mV in lead I	III and aVF (>0.5 mV)
	S-wave in leads I, II III and aVF	
Electrical axis	Right shift (>+100°)	Right shift (>+160°)

Source: Adapted from Tilley and Smith 2008.
* QRS duration >0.08 s in the dog and >0.06 s in the cat can be associated with left or right bundle branch blocks. See text for more detail.



Figure 17.11 Atrial enlargement is manifest as a P-wave of increased amplitude in a poodle with degenerative AV valve disease and atrial enlargement. The blue arrow shows the tall P-wave (amplitude 0.6 mV) (50 mm/s; 10 mm/mV).



Figure 17.12 ECG example of a left bundle branch block in a rottweiler with dilated cardiomyopathy. The conduction disturbance is identified by the prolongation of the QRS complex (0.08 s; *blue bar*) but a normal MEA (50 mm/s; 10 mm/mV).

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18

Pathophysiology of Heart Failure

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Heart failure represents a potential sequela of nearly all congenital and acquired cardiac diseases in dogs and cats. Without an appropriate understanding of the pathophysiologic alterations that produce heart failure, and the knowledge of which therapies can successfully mitigate their consequences, veterinarians will be unable to treat this life-impairing and often life-threatening condition. Therefore, the goals of this chapter are to highlight the classification schemes for heart failure, discuss normal cardiovascular physiology along with the mechanisms that contribute to the maladaptive hemodynamic and neurohormonal alterations precipitating heart failure, and outline how understanding of these mechanisms leads to targeted medical therapy.

Components of the Circulatory System

The circulatory system is composed of the heart and its associated arteries, capillaries, and veins. Appropriate function of the circulatory system further requires all of the constituents of normal circulating blood. The heart, blood vessels, and blood carry essential substances to metabolizing tissues and effectively remove unneeded by-products of metabolism. Additional functions of the circulatory system include regulation of body temperature, humoral communication, and appropriate adjustments of blood delivery depending on the underlying physiologic condition.

Determinants of Normal Cardiac Function

Mechanical function of the heart requires coordinated filling of the cardiac chambers (diastolic function) followed by an effective contraction (systolic function) to propel blood from the right and left heart to the pulmonary and systemic circulations, respectively. Impaired mechanical function may occur with disorders of the myocardium, cardiac valves, or pericardium. Effective filling and emptying, along with an appropriate increase or decrease in the rate of contraction, further rely on coordinated activity driven by pacemaker cells within the sinoatrial (SA) node and the heart's conduction system. Therefore, perturbed systolic or diastolic function produced by alterations in myocardial function, valvular integrity, pericardial confinement, volume loading, increased resistance to ejection or electrical instability may all produce cardiac dysfunction with subsequent development of heart failure (Box 18.1).

Origin of Ventricular Contraction

The electrical impulse that produces ventricular systole begins within the SA node and propagates along the specialized conduction system and cell walls to produce atrial and ventricular myocyte depolarization. Calcium influx through the L-type calcium channels within the sarcolemma along the T-tubules contributes to a larger calcium release from the sarcoplasmic reticulum (so-called calcium-induced calcium release). The rise in cytosolic calcium enhances binding to troponin-C and enables configurational changes in the actin and myosin molecules so that cross-bridge cycling (and hence myocardial contraction during systole) can occur. Diastole (myocardial relaxation) occurs as calcium influx through the L-type calcium channel and release from the sarcoplasmic reticulum terminate, and calcium is resequestered by the sarco(endo)plasmic reticulum calcium ATPase (SERCA) into the sarcoplasmic reticulum. The fall in cytosolic calcium concentration during diastole results in inhibition of the interaction of

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Box 18.1 Disease conditions that may produce heart failure

Impaired cardiac filling

Pericardial disease

- Pericardial effusion with tamponade
- Constrictive pericarditis
- Uncommon forms of congenital pericardial disease (e.g., pericardial cysts)

Inflow obstructions

- Tricuspid/mitral valve stenosis
- Uncommon forms of congenital heart disease (e.g., cor triatriatum, supravalvular mitral stenosis)
- Neoplasia (e.g., obstructive heart base tumors)

Myocardial disease that has a primary component of diastolic dysfunction

- Hypertrophic cardiomyopathy
- Restrictive cardiomyopathy

Impaired cardiac ejection

Myocardial disease that has a primary component of systolic dysfunction

- Dilated cardiomyopathy (idiopathic)
- Ischemic, nutritional (e.g., taurine deficiency), toxic (e.g., adriamycin), or infectious (e.g., Chagas disease) myocardial disorders
- Arrhythmogenic right ventricular cardiomyopathy

Increased resistance to ejection

- Pulmonic/aortic valve stenosis
- Pulmonary/aortic thromboembolism or obstruction (e.g., tumors)
- Pulmonary hypertension

Volume overload

Altered blood flow resulting in volume overload

- Valvular insufficiencies (congenital dysplasia, degenerative or infective)
- Left to right shunting (e.g., patent ductus arteriosis, ventricular septal defect, atrial septal defect, arteriovenous fistulas)

Disease conditions associated with chronically elevated cardiac output

- Anemia
- Hyperthryoidism

Disorders of impulse formation or conduction

Sustained tachyarrhythmias (e.g., supraventricular tachycardia, atrial fibrillation)

Sustained bradyarrhythmias (e.g., high-grade AV block, sinus bradycardia)

Wolff–Parkinson–White syndrome

actin molecules and myosin heads that is required for contraction to occur.

Determinants of Ventricular Systolic Function

The primary determinants of ventricular systolic function are preload, afterload, and contractility. Heart rate and ventricular synchrony are additional factors that influence systolic function.

It has long been recognized that increased cardiac filling enhances systolic performance. In the normal heart, increased preload, which represents the end-diastolic distending force of the ventricular wall, produces this enhanced performance as defined by Starling's law of the heart. Surrogates for preload include the end-diastolic volume, diameter, or end-diastolic pressure. Therefore, preload is dependent on venous return, total blood volume, and distribution of the blood volume within the vascular system. The recognition that the ascending limb of the Starling curve in skeletal muscle is dictated by the extent and "optimization" of actin-myosin filament overlap does not appear to be solely responsible for enhanced systolic performance in cardiac muscle. An alternative mechanism, termed *length-dependent activation*, seems to account for augmented ventricular systolic function with diastolic stretch. The exact mechanisms behind length-dependent activation remain controversial but the basic premise is that up to a maximum length, the myofilaments become sensitized to calcium as sarcomere length increases.

The force, tension or stress experienced by the ventricular myocytes during contraction is termed the *afterload*. Afterload is the degree of interference to ventricular ejection and is determined primarily by the systemic (or pulmonary) vascular resistance with a contribution from aortic (or pulmonary arterial) impedance. Impedance is dependent on the physical properties of the vascular wall and the blood (e.g., blood density and viscosity, arterial wall diameter, and viscoelasticity) and represents the ratio of aortic pressure to flow. The Anrep effect dictates that an acute increase in afterload enhances ventricular function via stimulation of sarcolemmal stretch receptors and increased cytosolic calcium levels.

Contractility is the inherent ability of the cardiac myocytes to shorten and generate force independent of preload, afterload, or heart rate. Increased contractility represents either increased calcium movement or sensitization of the contractile proteins at a given level of cytosolic calcium. Although criticisms of this concept include the lack of noninvasive measures of isolated contractility and the impossibility of separating the molecular mechanisms of enhanced function from preload and afterload from contractility, this concept is still useful as we discuss the pathophysiology of heart failure.

The Bowditch staircase effect (also known as the Treppe effect or the positive force-frequency relationship) defines that increased heart rate not only increases cardiac output via more frequent contractions, it also enhances the force of ventricular contraction. It is hypothesized that an increased rate of depolarization and the subsequent increased sodium and calcium current across the sarcolemma produce overload of the sodium–potassium pump. The activity of the sodium–calcium exchanger is therefore augmented in the "reverse" mode, extruding sodium from the cell in exchange for increased calcium into the cell. Cross-bridge cycling is supported by the higher cytosolic calcium level.

A final determinant of ventricular systolic function is the coordinated activation (and hence contraction) of the ventricular walls, termed *ventricular synchrony*. An altered activation sequence and the lack of coordinated mechanical contraction, as witnessed with ventricular arrhythmias, right ventricular apical pacing, or in humans with markedly prolonged QRS durations, can contribute to functional and clinical deterioration. Cardiac (pacemaker) resynchronization therapy has been shown to offset some of these negative consequences in people.

The Failing Heart

Definition of Heart Failure

The 2013 American College of Cardiology Foundation and American Heart Association (ACCF/AHA) guideline for the management of heart failure defines heart failure broadly as "a complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection of blood." The biochemical mechanisms behind this complex syndrome continue to be elucidated but the macroscopic view and description of heart failure has not varied significantly from the conclusion of a panel of the National Heart, Lung and Blood Institute in 1994. They stated:

> Heart failure occurs when an abnormality of cardiac function causes the heart to fail to pump blood at a rate required by the metabolizing tissues or when the heart can do so only with an elevated filling pressure. The heart's inability to pump a sufficient amount of blood to meet the needs of the body tissues may be due to insufficient or defective cardiac filling and/or impaired contraction and emptying. Compensatory mechanisms increase blood volume and raise cardiac filling pressures, heart rate, and cardiac muscle mass to maintain the heart's pumping function and cause redistribution of blood flow. Eventually, however, despite these compensatory mechanisms, the ability of the heart to contract and relax declines progressively, and the heart failure worsens.

Although common long-standing cardiac conditions typically contribute to volume overload and development of pulmonary (left-sided) or systemic (right-sided) congestion, there are conditions (e.g., cardiac tamponade, acute pulmonary thromboembolism, acute severe valvular insufficiency) that may severely impair the ability to provide vital organs with their necessary cardiac output without fluid accumulation. Therefore, the term *heart failure* is often preferred over congestive heart failure.

Classification of Heart Failure

The American College of Veterinary Internal Medicine (ACVIM), for animals, and the ACCF/AHA, for humans, recognize a functional classification scheme, and a separate, complementary classification system that emphasizes the risk, development, and progression of heart disease. The modified New York Heart Association (NYHA) functional classification is defined as follows.

- Class I describes patients with asymptomatic heart disease (e.g., heart disease is present but there are no clinical signs even with exercise).
- Class II describes patients with heart disease that causes clinical signs only during strenuous exercise.
- Class III describes patients with heart disease that causes clinical signs with routine daily activities or mild exercise.
- Class IV describes patients with heart disease that causes severe clinical signs even at rest.

A newer veterinary system outlined in the ACVIM Consensus Statement detailing canine valvular heart disease highlights four basic stages of heart disease and failure. Because this system was devised for valvular heart disease, it is not always easily incorporated into discussion of other forms of congenital and acquired heart disease in dogs and cats, but nonetheless it is still useful for discussion of heart failure. The stages of this classification scheme are defined as follows.

- Stage A identifies patients at high risk for developing heart disease but that currently have no identifiable structural disorder of the heart (e.g., every Cavalier King Charles spaniel without a heart murmur, boxers without evidence of arrhythmia or myocardial dysfunction).
- Stage B identifies patients with structural heart disease but that have never developed clinical signs caused by heart failure. This stage is further subdivided.
  - Stage B1 refers to asymptomatic patients that have no radiographic or echocardiographic evidence of cardiac remodeling.
  - Stage B2 refers to asymptomatic patients that have hemodynamically significant cardiac disease as evidenced by radiographic or echocardiographic findings of heart enlargement.
- Stage C denotes patients with past or current clinical signs of heart failure associated with structural heart disease.
- Stage D refers to patients with end-stage disease with clinical signs that are refractory to "standard therapy."

The ABCD system is useful because it enables veterinarians to educate owners that their animal is at risk for developing heart disease even in the absence of an audible murmur, gallop or arrhythmia. This system is also useful because treatment and subsequent resolution of signs attributable to heart failure alters patient classification with the modified NYHA model whereas animals that have previously displayed heart failure always remain a Stage C or D with the newer system.

Phases of Heart Failure

Discussion of heart failure can center around three distinct phases. Phase 1 constitutes the initial cardiac injury and in most veterinary patients, this phase passes silently, without detectable clinical signs, because the disease is mild and slowly progressive (e.g., valvular disease, feline cardiomyopathies). However, some conditions (e.g., development of cardiac tamponade subsequent to bleeding of right atrial hemangiosarcoma or pulmonary thromboembolism) can produce severe life-threatening signs commensurate with the initial cardiac injury. Phase 2 is the stage wherein short-term and ultimately long-term compensatory mechanisms are activated for stabilization of cardiac output and normalization of afterload. Unfortunately, cardiac disease is often progressive and the heart's ability to hypertrophy may ultimately be overwhelmed. A heart murmur, gallop rhythm, cardiac arrhythmia, or cardiomegaly is more likely to be identified in this second phase despite the absence of significant or activity-limiting clinical signs. The hallmarks of phase 3 of heart failure are the emergence of clinical signs (e.g., exercise intolerance, lethargy, coughing, tachypnea) at rest or with minimal activity.

Phase 1 – Initial Insult

Cardiovascular disease is encountered commonly in daily veterinary practice. Patent ductus arteriosus, subaortic stenosis, and pulmonic valve stenosis are common congenital conditions in dogs while ventricular septal defect and atrioventricular valve dysplasia are more common in cats. Chronic degenerative valvular disease (CDVD) and dilated cardiomyopathy (DCM) are the most common acquired cardiac diseases in dogs while hypertrophic cardiomyopathy (HCM) is the most common acquired cardiac disease in cats. Although identification of disease at its exact onset is next to impossible, it is useful to highlight some of the available data on disease prevalence.

Congenital cardiac malformations are uncommon, with data from several veterinary schools suggesting a prevalence of 0.46–0.85%. Feline congenital heart disease is even less common with a reported prevalence of 0.2%. Although these data are several decades old, they still highlight that even at large referral centers, the prevalence of congenital heart disease is low.

However, identification of acquired cardiovascular disease is much more common and represents the majority of dogs and cats that ultimately develop heart failure. Dilated cardiomyopathy is encountered most often in large- and giant-breed dogs with a reported prevalence of 0.16–1.1%, depending on the study cited and the population investigated. In some breeds and age groups, the prevalence of DCM is much higher. For example, a study of Doberman pinschers in Europe found that only 3.3% of Dobermans 1 to <2 years of age were affected while 43.6% aged 6 to <8 years of age were affected. The prevalence of CDVD is also dependent on the breed and age of the dog, but it also varies based on the method of disease detection (e.g., auscultation, echocardiography, necropsy). While these variables cloud clear documentation of disease prevalence, there is little debate that CDVD is the most common acquired cardiac condition in dogs and represents the most common etiology for development of heart failure. Hypertrophic cardiomyopathy is the most common myocardial disease in cats although various other forms of cardiomyopathy (CM), including restrictive CM, arrhythmogenic right ventricular CM, dilated CM, and unclassified CM, may also contribute to heart failure.

Primary cardiomyopathies are a diagnosis of exclusion and true disease confirmation would require necropsy. Because of this limitation, echocardiography is most often considered the gold standard for diagnosis of CM in cats. A study in an apparently healthy, nonreferred population of 103 cats found echocardiographic alterations

consistent with CM in 16 cats (15.5%). Eleven of the 16 cats with cardiomyopathy did not have an auscultable murmur. None of the 16 cats exhibited left atrial enlargement, and hence their risk of cardiac-related complications was presumably low. But this study highlights that many asymptomatic animals have underlying heart disease and may have active maladaptive compensatory mechanisms and cardiac remodeling even in the absence of clinical signs.

Phase 2 – Compensatory Phase

With a reduction in cardiac output, the body depends on a number of short- and long-term compensatory mechanisms to maintain perfusion pressure to vital organs. The principal short-term compensatory mechanisms, activated within seconds to minutes, include activation of several neurohormonal systems and subsequent utilization of the Frank–Starling mechanism. These short-term mechanisms promote the long-term adaptive response which is myocardial remodeling/hypertrophy. Each of these mechanisms has inherent limitations and as the disease progresses, their once beneficial properties become detrimental.

Short-Term Adaptive Responses

Sympathetic Nervous System Baroreceptors in the carotid sinus and aortic arch, along with cardiopulmonary baroreceptors, cardiovascular low-threshold polymodal receptors, and peripheral chemoreceptors, are responsible for the sympathetic nervous system (SNS) outflow to the heart and peripheral circulation. Hypotension, whether related to dehydration, blood loss or cardiovascular disease, will enhance release of norepinephrine from terminal neurons to the sinoatrial and atrioventricular nodes and cardiomyocytes, and increase release of epinephrine and norepinephrine into the circulation from the adrenal gland. The catecholamines bind to cardiac beta-receptors and increase cytosolic cAMP levels via G-protein coupling to increase contractility, heart rate, the rate of ventricular relaxation, and the speed of impulse conduction through the heart. Beta-receptor stimulation also produces hyperpolarization of the pacemaker cells (possibly via increased activity of the sodium–potassium pump), reducing the membrane potential into the range of funny current (I_f) activation. Increased conductance of sodium through the funny channels further enhances the heart rate response to sympathetic activation.

The release of norepinephrine from the terminal neurons of the systemic vasculature results in vasoconstriction via activation of postsynaptic alpha-1 receptors. Occupancy of the receptor promotes breakdown of phosphatidylinositol, via phospholipase C, to inositol triphosphate (IP3) and diacylglycerol (DAG). IP3 transiently increases smooth muscle cytosolic calcium, thereby initiating the contractile cycle while DAG activates protein kinase C and is thought to induce sustained vascular contraction. The subsequent increased vascular tone promotes arterial vasoconstriction to maintain systemic blood pressure and enhanced venoconstriction to promote increased venous return. Augmented preload contributes to enhanced length-dependent activation and cardiac output via the previously described Starling's law of the heart.

Renin-Angiotensin-Aldosterone System Decreased renal perfusion pressure also stimulates the renin-angiotensin-aldosterone system (RAAS). The RAAS is complementary to the SNS wherein it provides a hemostatic mechanism for blood pressure through maintenance of sodium balance and intravascular volume. Additional stimuli for the RAAS include reduced sodium delivery to the macula densa and increased adrenergic activity.

Renin, released from the juxtaglomerular apparatus, cleaves angiotensinogen to the decapeptide angiotensin I. Angiotensin converting enzyme (ACE) cleaves the C-terminal dipeptide from angiotensin I, forming the potent vasoconstrictor angiotensin II (AT II). Similar to alpha-1 receptors, AT II promotes vascular smooth muscle contraction and maintenance of blood pressure via IP3 and DAG. ACE is also capable of cleaving the C-terminal dipeptide from the vasodilatory substance bradykinin, hence making it inactive. Therefore, ACE appears to be a regulator between vasoconstrictive/sodium retaining and vasodilatory/natriuretic mechanisms. Although all their roles have not been elucidated, four receptors for AT II have been identified and classified as AT_1, AT_2, AT_3, and AT_4 receptor subtypes. Critical activities of AT II beyond potent vasoconstriction include stimulation of aldosterone release, potentiation of presynaptic norepinephrine release, stimulation of antidiuretic hormone release, promotion of renal tubular sodium resorption, and cardiomyocyte necrosis, apoptosis, and ventricular fibrosis.

Understanding of the RAAS continues to evolve with identification of a new homolog of ACE, called ACE 2, and additional biologically active metabolites of AT II, including the angiotensin-(1-7) peptide. Additional enzymatic pathways, including chymase, cathepsin G, elastase, tonin, and tissue plasminogen activator, have been identified although their role in maintenance of blood pressure and the pathophysiologic alterations that contribute to heart failure is uncertain. In addition to the conventional circulating RAAS, all its constituents are also found in a variety of tissues, including the brain, myocardium, vasculature, kidney, and adipose tissue. The importance of tissue RAAS is likely organ, species, and disease dependent although there is growing

evidence that locally produced AT II plays a role in cardiac remodeling under certain conditions.

While AT II directly increases systemic vascular resistance to maintain blood pressure, it is also the primary stimulus for aldosterone synthesis and release from the adrenal glands. Aldosterone binds to mineralocorticoid receptors in the cytoplasm, followed by migration of the complex into the nucleus. Within the nucleus, the aldosterone–mineralocorticoid receptor complex promotes gene activation, transcription, and protein synthesis of Na+/K+ exchangers along the luminal surface of the distal tubule and collecting ducts to promote sodium and water retention in exchange for potassium excretion. Similar to the venoconstrictive effects of the sympathetic nervous system, aldosterone-mediated water retention increases preload and enhances cardiac output via the Starling mechanism. Additional rapidly acting, nongenomically mediated actions of aldosterone continue to be investigated, including cellular ion regulation, altered cellular volume, negative inotropy, and cardiac hypertrophy, fibrosis and remodeling. Increased potassium levels, corticotropin, catecholamines, endothelin-1, arginine vasopressin, and reduced hepatic clearance are additional mechanisms that contribute to increased aldosterone activity.

Additional Compensatory Mechanisms The mechanisms that maintain blood pressure and enhance preload extend beyond the SNS and RAAS. Arginine vasopressin (AVP), also called antidiuretic hormone, is released from the pituitary in response to increased plasma osmolality or hypovolemia. The SNS and RAAS also promote release of AVP. Vasoconstriction and weak inotropic actions of AVP are mediated via adherence to V_{1A} receptors. Solute free water resorption is accomplished via binding of AVP and V_{2A} receptors. Receptor activation triggers insertion of aquaporin-2 channels into the luminal surface of the epithelial cells lining the distal tubule and collecting ducts, thereby providing enhanced water retention. Endothelin-1 is another modulator of systemic arteriolar tone that acts via either ET_A receptors, to promote vasoconstriction and positive inotropic effects, or ET_B receptors, to produce endothelial-dependent vasodilation.

Long-Term Adaptive Responses

While augmentation of preload and afterload via the previously described mechanisms is able to maintain cardiac output and perfusion pressure in the short term, myocardial hypertrophy serves as the body's long-term compensatory mechanism for cardiac dysfunction. The concept of the afterload experienced by working myocytes is more readily understood in terms of wall stress as described by Laplace's law:

$$\text{Wall stress} = \frac{\text{pressure} \times \text{radius}}{2 \times \text{wall thickness}}$$

Normalization of wall stress serves as an adaptive response to reduce myocardial oxygen consumption while maintaining cardiac performance. Hence, if cardiac hypertrophy is capable of normalizing cardiac output, the previously activated short-term compensatory responses may be able to return to basal levels.

Changes in myocardial workload produce rapid and dramatic responses from the molecular mechanisms that regulate protein synthesis. The isolated heart shows increased RNA and protein synthesis within two hours of a loading stimulus while the intact heart displays similar increases within 24 hours. This tight regulation between hemodynamic function and cardiac growth has at least three signaling mechanisms: stretch-activated signals, agonists, such as AT II, catecholamines and endothelin-1, that link to protein kinase C, and growth factors, including insulin-like growth factor-1, transforming growth factor-beta, and platelet-derived growth factor, that are linked to receptor tyrosine kinases. The mechanisms behind translation of these signals to cardiac hypertrophy are complex and continue to be elucidated, but seem linked to the family of mitogen-activated protein kinases.

Increased systolic wall stress, such as systemic hypertension or severe subaortic stenosis, necessitates increased pressure generation by the left ventricle to overcome the forces opposing ejection. Laplace's law dictates that normalization of wall stress is achieved via increased left ventricular wall thickness, termed *concentric hypertrophy*, with sarcomeres replicating in parallel. The ventricular radius remains normal or may actually decline secondary to encroachment of the thickened left ventricular walls. Increased diastolic wall stress, as observed with volume overload secondary to mitral valve insufficiency, instead promotes eccentric hypertrophy. This pattern of hypertrophy is characterized by sarcomeres replicating in series, producing a larger diameter and more spherical left ventricular chamber. The wall thickness increases only modestly to try and maintain normal wall stress.

Phases of the hypertrophic response have been detailed for decades and include:

- the initial stage of developing hypertrophy where workload exceeds the output that is normal for the initial mass of the heart
- compensatory hypertrophy where work-induced growth of the myocardium normalizes wall stress
- an exhaustion phase characterized by cardiomyocyte death, myocardial fibrosis, and ventricular dilation with decreasing work output per unit of cardiac mass leading to heart failure.

Progression between these phases seems most dependent on the magnitude and type of overload wherein acute pressure overload triggers the earliest onset and fastest rate of hypertrophy. It has been postulated that while hypertrophy prevents acute cardiac insufficiency, the unbalanced "growth" at the level of the organ, tissue, cell, and intracellular organelles ultimately becomes the cause of chronic cardiac insufficiency of the hypertrophied heart.

Phase 3 – Transition to Heart Failure (Figure 18.1)

Hypertrophy may be unable to maintain cardiac output in the face of chronic and progressive cardiovascular disease and the previously beneficial short- and long-term compensatory mechanisms ultimately prove detrimental. The transition from compensated hypertrophy to the exhaustion phase is mediated by molecular mechanisms that produce:

- myocyte growth
- reexpression of fetal myocyte phenotype with a reduction in the expression of the adult phenotype
- alteration in the expression and/or function of the proteins involved in excitation-contraction coupling
- necrosis and apoptosis of cardiomyocytes
- changes within the extracellular matrix

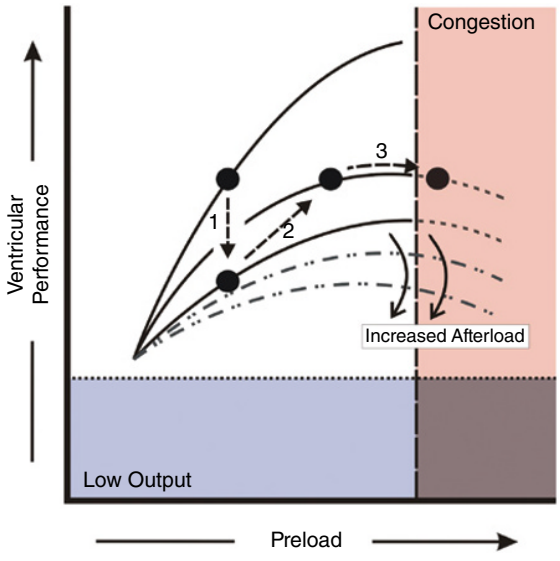


Figure 18.1 A family of Frank–Starling curves highlighting the progression to heart failure. (1) Ventricular performance declines following a cardiac insult. (2) The short-term and long-term compensatory mechanisms are activated and ultimately return ventricular performance to normal, albeit at a higher filling pressure. (3) The underlying disease progresses, myocardial remodeling becomes maladaptive and the previously beneficial compensatory mechanisms become detrimental. Further preload expansion no longer enhances ventricular performance on the flat portion of the Frank–Starling curve and instead congestion develops. Increases in afterload depress ventricular performance even further down the Frank–Starling curves.

- alterations in myocardial energetics. These alterations reduce the number of viable myocytes and/or decrease the intrinsic contractility of individual myocytes, thereby impairing cardiac performance.

The previously beneficial augmentation of preload and afterload now only serves to promote development of congestion or amplify contractility-afterload mismatch.

This cycle of disease progression continues as venous pressures continue to rise, cardiac output declines, congestion develops, and clinical signs of heart failure begin to emerge.

Myocyte Loss

A reduction in the number of viable myocytes or dysfunction of the viable myocytes may account for a component of reduced myocardial contractile function. Cardiomyocyte death appears to occur via necrosis, apoptosis, and autophagy although it is uncertain if all three are distinctive events or a continuum of overlapping processes. Exposure of norepinephrine to cultured mammalian cardiomyocytes produces a concentration-dependent decrease in viability and pathophysiologic levels of AT II also promote myocytolysis. Therefore, it seems that myocyte loss can occur via mechanisms beyond ischemia and many of these mechanisms, including catecholamines, AT II, reactive oxygen species, nitric oxide, inflammatory cytokines and mechanical strain, are increased in the failing myocardium.

Reexpression of Fetal and Neonatal Genes and Altered Contractile Proteins

Heart failure seems to alter both quantitative and qualitative protein expression, which may impair cardiac contractility. Isoforms of contractile proteins that are present during fetal and neonatal life, when protein synthesis is rapid, have been identified in some animal models of hypertrophy and myocardial failure. Pressure overload hypertrophy in rats produces a shift from the rapid myosin heavy chain (MHC) isoform (V_1) to the slow MHC isoform (V_3), enabling normal tension generation but at a lower energy cost by reaching the tension more slowly. However, in species with a predominant V_3 ventricular MHC isoform, including dogs, cats, and humans, this change seems less critical to development of heart failure. Fetal phenotypic expression of other contractile proteins, including myosin light chain, troponin-I and troponin-C, has been identified in the myocardium of humans with heart failure and may contribute to a decrease in cardiac contractile function.

Altered Excitation-Contraction Coupling

Calcium is a critical ion in regulating myocardial contraction and relaxation. Alterations in calcium conductance across the sarcolemma, release from the sarcoplasmic

reticulum, or its resequestration into the sarcoplasmic reticulum may exert profoundly negative consequences on cardiac performance. Myocytes from humans with heart failure exhibit a prolonged action potential with a blunted rise in intracellular Ca^{2+} during depolarization and a slowed rate of decline during repolarization. Slower Ca^{2+} delivery to the contractile proteins during systole and excessive cytosolic Ca^{2+} during diastole may contribute to both systolic and diastolic dysfunction. The failing myocardium also displays a negative force–frequency relationship. Rather than progressive increases in ventricular contractility with increasing heart rate, humans with heart failure have little or no increase in contractility with increased frequency of stimulation. This alteration is presumably related to impaired Ca^{2+} cycling between the sarcoplasmic reticulum and the cytosol.

Calcium conductance, release, and resequestration are critical components of normal cardiac function and numerous pumps and channels are responsible for coordinating events. Studies in failing human myocardium have found that mRNA and protein levels of SERCA, voltage-dependent Ca^{2+} channels, and the calcium release channel on the sarcoplasmic reticulum are reduced. Alterations in proteins responsible for Ca^{2+} cycling in dogs have also been identified. Therefore, altered expression or function of these proteins may negatively impact systolic and diastolic function.

Changes within the Extracellular Matrix

Ventricular remodeling is a key feature of heart failure regardless of the underlying cardiac disease or underlying phenotype (e.g., volume overload, pressure overload, primary cardiomyopathy). Changes within the ventricular geometry and function must be viewed as a summation of events occurring at the level of the cardiomyocyte, the vascular compartment, and within the extracellular matrix (ECM). Although once only viewed as scaffolding, there is now growing recognition that the ECM mediates mechanical and biological signals that contribute to the progression of heart failure.

Regulation and turnover of the ECM is a complex process dictated by mechanical stress, neurohormonal activation, inflammation, and oxidative stress. Accelerated growth of both the myocyte and ECM produced by pressure overload yield left ventricular concentric hypertrophy. Left ventricular thickening negatively impacts both of the fundamental processes that dictate diastolic function – active relaxation and passive stiffness. Shifting isoforms and phosphorylation sites of cytoskeletal proteins (e.g., titin) can impair myocyte relaxation and hamper active relaxation/early cardiac filling. Accumulation of collagen within the ECM increases ventricular stiffness, thus reducing myocardial compliance and impairing passive ventricular filling. Volume overload triggers left ventricular eccentric hypertrophy/remodeling with increased ECM turnover via an increase in the matrix metalloproteinases (MMPs)/tissue inhibitors of matrix metalloproteinases (TIMPs) ratio. The MMPs degrade collagen and other matrix components while the TIMPs either inhibit or prevent MMP activation. Isoform shifts from type I to type III collagen further contribute to a net degradation of collagen with resultant chamber dilation and progressive wall thinning.

During the compensated phase, the remodeling contributes to increased ventricular compliance with preserved systolic function. Ultimately, the progression to decompensated failure is complex and includes a combination of ECM degradation and profibrotic synthesis mediated concomitantly at different subcellular locations and within different regions of the ventricle.

Alterations in Cardiac Metabolism

The heart requires a high rate of adenosine triphosphate (ATP) hydrolysis because of its continuous mechanical work and therefore requires a constant supply of oxygen and fuel. Oxidation of fatty acids (FA) accounts for approximately 70–90% of ATP production in the fasted state while glucose utilization increases in the fed state. Because of the fundamental roles metabolism and ATP generation have in maintenance of cardiac structure and function, it is reasonable to hypothesize that alterations in cardiac metabolism have a role in the pathophysiology of heart failure. Studies in animal models and humans with advanced heart failure and systolic dysfunction have reported a decrease in the phosphocreatine/ATP ratio, ATP content, and ATP movement through creatine kinase. It is uncertain whether these alterations serve as a primary contributor to the progressive nature of heart failure or are simply an adaptation to decreased ventricular function, but significant mitochondrial changes are present in various models of cardiac hypertrophy and failure.

Decreased cardiac energy production may be secondary to impaired substrate use or altered mitochondrial function. Studies of heart failure with systolic dysfunction have identified reduced mRNA and protein expression of FA transporters with reduced cardiac FA utilization and ATP production. Studies of glucose oxidation are variable with reports of decreased, unchanged or increased glucose uptake. Varying results likely depend on the stage and type of disease, but these results may also be influenced via the channeling of pyruvate into anaplerotic pathways. Flux of pyruvate through anaplerotic pathways appears to be a hallmark of metabolic remodeling and reduces its availability for oxidation and energy production by pyruvate dehydrogenase. Nicotinamide adenine dinucleotide phosphate (NADPH) is also consumed by induction of anaplerotic pathways

which may lead to dysregulation of cellular oxidative stress, thereby contributing to the progressive nature of heart failure. Mitochondrial reactive oxygen species may produce mitochondrial damage, activation of mitogen-activated protein kinases, cardiac hypertrophy and fibrosis, again suggesting that alterations in organelles of metabolism may contribute to ventricular remodeling. The reactive oxygen species and mitochondrial damage are also strong mediators of autophagy in certain settings and may serve as an additional mechanism for remodeling and progression to heart failure.

Hemodynamics of Heart Failure and Development of Pulmonary Edema

Progressive disturbances of systolic and diastolic function may ultimately lead to development of systemic or pulmonary venous congestion as a consequence of elevated venous pressure. Increased plasma volume (via sodium and water retention) and reduced venous capacitance (via venoconstriction) no longer augment systolic function in the failing heart and instead merely precipitate clinical signs associated with congestion.

Pulmonary capillary wedge pressures exceeding 25 mmHg are likely to precipitate signs of left-sided heart failure, including cough and increased respiratory rate and effort. Pulmonary edema develops when the movement of fluid from the blood to the interstitial space, and in some instances to the alveoli, exceeds the return of fluid from the interstitial space to the blood and its drainage through the lymphatics. There is normally a continuous exchange of fluid, colloid, and solutes from the vasculature into the interstitial space so a pathologic state exists only when there is an increase in the net flux of fluid, colloid, and solutes from the vasculature into the interstitial space. The total microvascular filtration rate can change as a result of changes in filtration surface area, membrane permeability to water, hydrostatic and colloidal osmotic pressures, and membrane permeability to protein. Lymphatic flow will similarly be dictated by the hydrostatic pressure of the interstitium, the pumping pressure within the lymphatics, the systemic venous pressure, and the resistance to flow.

During stage 1 of pulmonary edema development, the interstitial volume remains normal due to the compensatory increase in lymphatic flow. In most tissues, the increase in the hydrostatic interstitial pressure with the development of interstitial edema would serve to inhibit microvascular filtration and enhance lymph flow. However, the interstitial pressure rarely reaches high enough values to use this protective mechanism because (a) the increase in the interstitial compliance allows large volume increases with small pressure increases and (b) alveolar flooding occurs at relatively low interstitial pressures (2–3 mmHg). The more protective mechanism in the lung is the decreased resistance to lymphatic flow as microvascular filtration increases. The proposed mechanism is believed to be subsequent to "tethering" of the initial lymphatics to surrounding structures which pull the lymph vessels open as the interstitial volume increases, thus increasing the radius and filtration of the lymphatics.

Stage 2 occurs when the lymphatics' capacity to remove the interstitial fluid is overwhelmed. During this stage, fluid and colloid accumulate in the interstitial areas around bronchioles, arterioles, and venules. Fluid accumulation occurs within the peribronchial and perivascular interstitial space (versus adjacent to the alveolar capillary membrane) because of its more negative pressure and more compliant properties. The enlarged lymphatics and free fluid form cuffs around the bronchioles and pulmonary blood vessels and may subsequently compress the small airways and blood vessels. Gas exchange may be relatively unaffected in the early stages of edema if there is no increase in the alveolar-capillary membrane thickness along the thin side of the interstitial space. But as capillary filtrate continues to accumulate, the less compliant interstitium around the alveolar-capillary septa also fills, the interstitial pressure rises, and alveolar flooding begins (stage 3). Arterial oxygenation decreases and in severe cases death may ensue.

Therapeutic Implications

Understanding of the pathophysiologic mechanisms of heart failure enables development of therapeutic strategies to provide symptomatic benefit and slow the natural history of disease progression. With the long-standing recognition that fluid retention and poor pump function contribute to pulmonary and systemic venous congestion and low cardiac output, the initial therapeutic strategies were to reduce preload and afterload while augmenting contractility. We continue to use these strategies today via the administration of diuretics and inodilators to combat many forms of heart failure. With further advances in the understanding of cardiac remodeling, agents capable of blocking critical neurohormonal pathways, including ACE inhibitors, beta-blockers, and aldosterone antagonists, were developed to prolong survival without imposing significant alterations in cardiac loading conditions. And with further advances in the understanding of myocyte loss, altered gene expression, dysregulation of excitation-contraction coupling, degradation of the extracellular matrix and deranged cardiac metabolism, new therapeutic agents will continue to be identified in an effort to one day halt the inevitable cycle that leads to heart failure.

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19

Management of Heart Failure

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Successful management of both acute and chronic heart failure typically involves alleviation of congestion, improvement in cardiac output and organ perfusion, and maintenance of normal blood pressure and cardiac rhythm. Patients with heart failure can be categorized into those with subtle symptoms such as mild exercise intolerance or respiratory signs versus patients with debilitating and life-threatening clinical signs such as severe respiratory distress, collapse, syncope, or cardiogenic shock. Congestive heart failure (CHF) specifically refers to patients with evidence of congestion in the form of pleural or abdominal effusion, pulmonary edema or, much less commonly, peripheral edema.

A variety of cardiac medications are used to restore and maintain adequate cardiac function, along with diet changes, nutritional supplements, and body cavity centesis. During therapy of both acute and chronic heart failure, patient hydration status, electrolytes, renal function, blood pressure, urine output, respiratory rate and effort, and body weight are monitored. During this time, patient quality of life can remain very high in the absence of significant amounts of congestion or adverse medication side-effects. As heart disease progresses, doses and number of cardiac drugs are increased along with increasing risk of adverse effects. In this chapter, the therapy of chronic, acute, and refractory heart failure will be presented.

Management of Chronic Heart Failure

The major goals of treatment of CHF are to alleviate and prevent mild clinical signs, reduce likelihood of recurrent episodes of acute life-threatening heart failure, and increase longevity.

Management begins with a thorough medical history and physical examination. Subtle changes in the resting respiratory rate and/or exercise capacity can be useful gauges that help clinicians formulate or modify treatment plans. In this capacity, owner education and home monitoring are essential components of successful therapy. Rarely do canine or feline patient with early CHF cough nor do they exhibit dramatic changes in activity or exercise. Thus, daily monitoring of their resting home respiratory rate is often the most effective monitoring tool to detect CHF symptoms in their early stages.

Common oral medications for treatment of chronic heart failure can be divided into the following five main groups: diuretics, vasodilators, modulators of neurohormonal systems, antiarrhythmic agents, and positive inotropes. Some medications will have effects in more than one group. In addition to these conventional therapies, nutritional supplements and dietary modification are often beneficial. In order to limit adverse reactions to medications, close monitoring of electrolytes, biochemical parameters, hydration status, and blood pressure along with serial cardiac-specific tests (i.e., chest radiographs, electrocardiograms, echocardiograms) aid the practitioner in achieving effective treatment. Each patient responds to medications differently and therapy is individualized to each cardiac patient.

Treatment of chronic heart failure depends almost entirely on medical therapy. Exceptions would include CHF due to bradycardia that is treated with artificial pacing, or CHF due to congenital heart defects such as patent ductus arteriosus that are treated using surgery or minimally invasive catheter-based techniques. Advancements in the surgical management of degenerative valve disease have been made over the past few years but due to cost and limited surgical centers that perform the surgery, surgical valve repair or replacement is not a widely available option for most pet owners. Due to the lack of controlled clinical trial data, some of the therapy for both chronic and acute heart failure is based on expert opinion.

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Drugs for Treatment of Chronic Heart Failure (Table 19.1)

Diuretics

Diuretics increase production of urine through affecting the kidney's physiologic handling of water and electrolytes. Diuretics result in an increased loss of sodium (natriuresis) that is followed by water and other electrolytes. Diuretics are the first-line therapy in patients with chronic CHF, but despite their efficacy in resolving and preventing congestion, they are not typically used as monotherapy due to their activation of the renin-angiotensin-aldosterone system (RAAS). One instance when diuretics are contraindicated for the treatment of CHF is in patients with pericardial effusion and cardiac tamponade. In this group, cardiac output is markedly dependent on preload, and aggressive diuresis will worsen cardiac output, potentially leading to cardiogenic shock.

Furosemide

Furosemide is first-line therapy in the management of chronic CHF. The goal of therapy is to prescribe the lowest diuretic dose required to control the clinical symptoms of congestion and edema. Compared to treatment of pulmonary edema, relatively higher diuretic dosages are often required to help resolve body cavity effusions, such as pleural or abdominal effusion. In these instances, routine thoracocentesis or abdominocentesis can aid in minimizing the dose of furosemide needed.

There is a wide range of doses reported in the veterinary literature. In the authors' experience, furosemide doses of 1–4 mg/kg orally every 8–24 hours are utilized in treating chronic CHF in the dog. The typical starting dose of oral furosemide for a dog with first-time CHF is 2–3 mg/kg/day. Cats are particularly sensitive to the dehydrating effects of furosemide and dosages of 1–2 mg/kg every 12–48 hours are preferred, with most cats receiving a total of 1–2 mg/kg/day for first-time CHF. Lower doses spread over shorter dosage intervals may result in less diuretic resistance as high doses can lead to rebound effects and resistance due to greater stimulation of the RAAS. Pet owners who become adept at monitoring respiratory rates and effort can often make small adjustments in furosemide dosing at home to prevent recurrent CHF symptoms.

Adverse effects of diuretics include electrolyte imbalances such as hypokalemia (often mitigated with the concurrent use of angiotensin converting enzyme inhibitors (ACEI) or spironolactone), hyponatremia, azotemia, dehydration, and urinary incontinence. Renal function and serum electrolytes should be routinely monitored. The frequency of monitoring is based on furosemide dosage, concurrent medications, previous bloodwork results, and presence of concomitant conditions such as renal insufficiency. The authors recommend checking serum blood profiles within the first 10 days after starting or changing an existing dose of furosemide, after which routine rechecks every 3–6 months are performed. Doses of furosemide might also be adjusted after adding concomitant agents that can affect renal perfusion (i.e., vasodilators, positive inotropes, other diuretics, nonsteroidal antiinflammatory agents, etc.).

Spironolactone

Spironolactone is a diuretic as well as a neurohormonal blocking agent due to its inhibition of aldosterone. In chronic CHF, benefits of spironolactone involve modest diuresis and antiremodeling effects on the myocardium, kidneys, and vasculature through its blockade of aldosterone receptors. In humans and experimental animal models, spironolactone reduces pathologic tissue hypertrophy and fibrosis. In both human and veterinary patients, spironolactone improves survival times in patients with chronic CHF. Based on anecdotal experience, one author (SR) recommends considering spironolactone therapy in patients with progressive heart enlargement that have not yet experienced CHF, as well as those patients with chronic heart failure. In dogs with abdominal or pleural effusion, spironolactone is often co-administered with furosemide to help slow the recurrence of the effusion. Typical spironolactone dose in dogs is 2 mg/kg/day. Monitoring of renal function and electrolytes is recommended in a fashion similar to furosemide. The benefit of spironolactone in cats with CHF is unknown. Previous study in cats suggests that 1.7–3.3 mg/kg/day was well tolerated.

In dogs, adverse reactions include anorexia and hypersalivation that may be mitigated by administration with food or in a gelatin capsule, azotemia, and electrolyte imbalances. Reformulated and flavored preparations of spironolactone are difficult to administer due to their still unpleasant taste. Due to its potassium-sparing effects, spironolactone can also predispose to hyperkalemia. This is most common when spironolactone is used in combination with an ACEI.

Vasodilators

In the late 1980s and early 1990s, the use of vasodilators became part of the standard CHF treatment in both human and veterinary medicine. The benefits for the hemodynamic and, in the case of ACEI, neurohormonal aspects of heart failure contributed to widespread use across many different species and many types of heart disease. ACEI, nitrates, amlodipine, hydralazine, and sildenafil are the most common agents utilized in veterinary patients. The majority of clinical data in veterinary medicine involves ACEI for the treatment of chronic

Table 19.1 Commonly used drugs for the treatment of chronic heart failure

Drug	Indications	Dose	Comments/Adverse Effects
Diuretics			
Furosemide	Relief of congestion	Dog: 1–4 mg/kg q8–24h	Azotemia, dehydration
		Typical first-time CHF: 2–3 mg/kg/day	Electrolyte disturbances
		Cat: 1–2 mg/kg q12–24h Typical first-time CHF: 1–2 mg/kg/day	Monitor renal function
Spironolactone	Antialdosterone Hypokalemia Relief of congestion	Dog: 2 mg/kg/day Cat: 1-2 mg/kg/day	Weak diuretic Potassium sparing
Hydrochlorothiazide	Relief of congestion Refractory heart failure	Dog/Cat: 2 mg/kg q12h If used in addition to furosemide: starting at 0.5 mg/kg SID or 1 mg/kg q48h	Moderate diuretic Azotemia, dehydration Often used in refractory CHF combined with furosemide
Torsemide (Torasemide)	Relief of congestion	Dog/Cat: 0.1–0.6 mg/kg SID Typical CHF: 0.1–0.3 mg/kg SID Dose adjustments in 0.1 mg/kg/day increments	Potent diuretic, azotemia Electrolyte disturbances Monitor renal function
Vasodilators			
ACE-inhibitor	Anti-RAAS Hypertension	Enalapril Dog/Cat: 0.5 mg/kg q12–24h Benazepril Dog/Cat: 0.25–0.5 mg/kg q12–24h Lisinopril Dog: 0.25–0.5 mg/kg q24h Ramipril Dog: 0.25 mg/kg q24h Imidipril Dog: 0.25–0.5mg/kg q24h	Azotemia, hypotension Monitor renal function
Amlodipine	Hypertension Afterload reduction	Dog/Cat: 0.1–0.4 mg/kg q24h	Hypotension
Hydralazine	Hypertension Afterload reduction	Dog: 0.2–2.0 mg/kg q12h	Hypotension Gastrointestinal signs Tachycardia
Isosorbide dinitrate/ mononitrate sustained release	Preload reduction	Dog/Cat: 0.5–2.0 mg/kg q12h	Tolerance develops quickly
Sildenafil	Pulmonary hypertension	Dog: 1–3 mg/kg q8h	Variably effective Can be expensive
Positive inotropes			
Pimobendan	Increase contractility Arterial vasodilation	Dog/Cat: 0.25 mg/kg q12h	Contraindicated if outflow obstruction present
Digoxin	Increase contractility Supraventricular tach	Dog: 0.005–0.0075 mg/kg q12h Cat: 0.03125 mg/cat q24–48h	Long-half life Monitor serum levels Gastrointestinal signs
Beta-adrenergic blockers			
Atenolol	HCM Atrial fibrillation	Cat: 6.25–12.5 mg/cat q12–24h Dog: Atenolol 0.25–1.0 mg/kg q12h; Carvedilol 0.1 mg/kg q12h then titrated to 0.5–1.0 mg/kg q12h; Metoprolol 0.2–0.4 mg/kg q12h or 0.4–1.0 mg/kg q24h for sustained release	Bradycardia, hypotension Titrate doses in dogs with heart failure

(Continued)

Table 19.1 (Continued)

Drug	Indications	Dose	Comments/Adverse Effects
Calcium channel blockers			
Diltiazem	HCM Atrial fibrillation	Cat: 7.5 mg/cat q8h Cat: Cardizem CD 10 mg/kg q24h Cat: Dilacor 30 mg/cat q12h	Bradycardia, hypotension Gastrointestinal signs
	Atrial fibrillation	Dog: 0.5–1.5 mg/kg q8h Cardizem CD or Dilacor XR (sustained release) 3 mg/kg BID	
Verapamil	HCM	Cat: 1–5 mg/kg q12h	Potent negative inotrope Titrate over 2–3 weeks
Calcium Channel Blocker			
Aspirin	Antiplatelet	Dog: 1–5 mg/kg q24h Cat: 20–81 mg/cat q72h	Gastrointestinal signs
Clopidogrel	Antiplatelet	Cat: 18.75 mg/cat q24h Dog: 3–5 mg/kg q24h	Well tolerated
Nutritional supplements			
Taurine	Taurine deficiency	Dog: 35 mg/kg q12h	Long-term supplementation needed
L-carnitine	L-carnitine deficiency	Dog: 50 mg/kg q8h	Unknown efficacy

ACE, angiotensin converting enzyme; BID, twice a day (*bis in die*); CHF, congestive heart failure; HCM, hypertrophic cardiomyopathy; RAAS, renin-angiotensin-aldosterone system; SID, once a day (*semel in die*).

CHF and ACEI are considered the first-line choice for vasodilator therapy in dogs and cats with CHF. In humans, angiotensin receptor blockers can be used if ACEI are not tolerated (intractable cough is a common side-effect), but relatively little is known about the use of angiotensin receptor blockers in veterinary patients with chronic CHF.

ACE Inhibitors

ACE inhibitors are commonly used, including benazepril (0.25–0.5 mg/kg PO q12–24h in dogs and cats), enalapril (0.5 mg/kg PO S-BID in dogs and cats), lisinopril (0.25–0.5 mg/kg PO SID in dogs), ramipril (0.25 mg/kg PO SID in dogs), and imidipril (0.25–0.5 mg/kg PO SID in dogs). There is no obvious clinical benefit of one ACEI over the other and their differences lie in their absorption, metabolism, and excretion. Benazepril is activated in the liver to benazeprilat and, in dogs, is equally excreted by the biliary and renal routes while in cats, benazepril is primarily excreted by the biliary route. Enalapril is activated in the liver to its active metabolite, enalaprilat, and excreted by the kidneys. Lisinopril is absorbed in its active form and excreted by the kidney while ramipril may have more effect on tissue-specific RAAS and is partially excreted in the urine and feces.

The authors typically use enalapril as the first choice due to long-standing clinical experience with this agent as well as the convenient sizes of commercially available tablets in the US (2.5, 5, 10, and 20 mg). In instances of known renal dysfunction, benazepril is often the ACEI of choice due to its nonrenal excretion, especially in feline patients. Lisinopril is absorbed in its active form and does not require hepatic metabolism to be active. Lisinopril is excreted in the urine, and this drug could be chosen for patients with concurrent cardiac and hepatic disease.

In general, ACEI are well tolerated. The most common adverse events are azotemia and hypotension. In the authors' experience, initiating full dosing of an ACEI during concomitant aggressive diuretic treatment of acute CHF can occasionally lead to hypotension and severe azotemia. ACEI do not appear essential for the successful resolution of acute CHF, and the authors usually initiate ACEI therapy only once patients are stable with only mild or no remaining CHF (see Treatment of Acute Heart Failure later) and when hydration status and blood pressure are adequate. ACEI are not particularly potent arterial vasodilators and their benefits are most likely due to the long-term suppression of the RAAS. The authors recommend checking a baseline renal and electrolyte profile and within the first 10 days after starting the medication. Owners should be instructed to monitor for poor appetite, lethargy, vomiting, or changes in water consumption or urine output.

In instances where underlying renal insufficiency or volume depletion is present, the authors occasionally start enalapril at either 0.5 mg/kg q24h or 0.25 mg/kg BID for the first 3–5 days of treatment and titrating to a

higher dose over the first 7–10 days of treatment. Blood pressure, renal function, and electrolyte monitoring is performed every 3–6 months thereafter. In humans, idiosyncratic nocturnal cough is an important adverse effect, but this has not been reported in dogs, and any coughing is usually due to concurrent chronic airway disease.

Other Vasodilators

Other vasodilators used for treatment of chronic CHF include hydralazine, amlodipine, and nitrates. These agents are discussed in the section regarding treatment of refractory heart failure.

Positive Inotropes

Use of positive inotropes for the treatment of heart failure has been a subject of controversy due to a potential increase in the risk of sudden death due to arrhythmias. Conventional positive inotropes such as digoxin, dobutamine, and dopamine act by increasing cytosolic calcium that improves cardiac contractility but might also precipitate cardiac arrhythmias. The objective of positive inotropic therapy is to increase myocardial contractility and improve cardiac output and organ perfusion. Digoxin and pimobendan are the two most commonly used agents for the treatment of chronic CHF in the veterinary patient.

Digoxin

Digoxin is one of the oldest cardiac medications known and has positive inotropic and negative chronotropic (slowing conduction through the atrioventricular [AV] node) effects, as well as beneficial effects on the baroreceptors and neurohormonal axis such as the RAAS. Even though it has been used for over 200 years, its benefits for survival have not been proven. In dogs, pimobendan has largely supplanted digoxin as the positive inotrope of choice. Digoxin is associated with a high incidence of adverse reactions including gastrointestinal upset and cardiac arrhythmias. The recommended canine dose is 0.005–0.0075 mg/kg q12h. In cats, digoxin is not commonly used, in part due to the drug's long half-life. The feline dose is ¼ of a 0.125 mg tablet (0.03125 mg) every other day for smaller cats and once a day for larger cats. The dosage in patients with renal disease is reduced since digoxin is excreted by the kidneys. Dosage should be based on lean body mass and reduced in obese pets or those with significant ascites. Oral absorption of digoxin can be altered by the formulation, concurrent medications, or food. The elixir (0.05 mg/mL) is better absorbed than the tablet formulation although is not palatable to most cats. As such, slightly lower doses are often prescribed when using the elixir over tablets. Antacid agents like sucralfate will reduce the absorption of digoxin, as will diets high in fiber. Certain antibiotics like tetracyclines will alter the bacterial flora and may increase serum digoxin levels.

The primary indication for digoxin in dogs (and to a much lesser extent in cats) with heart disease is to slow AV nodal conduction and ventricular response rate in patients with atrial fibrillation. Digoxin is indicated for the treatment of atrial fibrillation, persistent atrial and sinus tachycardias, and progressive myocardial dysfunction. It may also help reduce syncope in patients with severe mitral regurgitation due to its pharmacologic effects, including its effects on baroreceptors. Contraindications for use include complex ventricular arrhythmias, renal disease, atrioventricular block, certain types of ventricular preexcitation, and sinus node dysfunction.

Due to the risk of toxicity, serum digoxin levels are typically monitored 10–14 days after initiation or any dose changes. Blood should be drawn 6–8 hours post pill to assess "trough" concentrations. Traditionally, serum digoxin levels between 0.8 and 2.0 ng/dL have been considered to be therapeutic. Based on recent data in humans, the authors commonly target a lower serum level of 0.6–1.2 ng/dL as lower levels remain beneficial but with a lower incidence of adverse reactions. In the authors' experience, gastrointestinal upset and anorexia can occur at levels as low as 1.5 ng/dL. Anecdotally, miniature schnauzers and Doberman pinschers are more sensitive to digoxin and lower starting doses are recommended for these breeds (no greater than 0.125 mg q12h as a starting dose in Dobermans regardless of their body weight). Pet owners are recommended to administer the digoxin along a consistent interval and regimen. Since certain foods and medications can alter absorption, the owner should continue the same feeding and dosing regimen once therapeutic serum levels are achieved. Changes in renal function will affect digoxin excretion, and digoxin and electrolyte levels are routinely evaluated every six months or when changes are made in concurrent medications.

Pimobendan

Pimobendan is widely used for the treatment of canine heart failure secondary to dilated cardiomyopathy (DCM) and myxomatous mitral valve disease (MMVD). Recently, studies have shown the benefits of this agent in the preclinical stage of MMVD once a moderate degree of radiographic and echocardiographic cardiac enlargement has developed.

Pimobendan is a calcium sensitizer and phosphodiesterase inhibitor and its benefits are a result of the combination of positive inotropic properties along with effects as a vasodilator. Its dual action is often indicated by the term "inodilator." Pimobendan is used as the first-line

positive inotrope and forms part of standard "quadruple therapy" for CHF in dogs along with ACEI, furosemide, and spironolactone. The recommended dose in dogs is 0.5 mg/kg/day divided into two doses given 12 hours apart. Pimobendan has also been shown to prolong time to CHF and death in asymptomatic Doberman pinschers with echocardiographic evidence of reduced systolic function and ventricular enlargement consistent with preclinical DCM. In humans, positive inotropes exacerbate cardiac arrhythmias that can lead to increased risk of sudden death, and use of pimobendan in Doberman pinschers with preclinical DCM and severe ventricular arrhythmias has not been specifically evaluated.

In general, pimobendan is well tolerated. The most common adverse reaction is anorexia and diarrhea that often resolves at lessened dosage. Pimobendan should be used with caution in disorders with a ventricular outflow tract obstruction such as congenital subvalvular aortic stenosis or hypertrophic obstructive cardiomyopathy.

Pimobendan does not have an approved use in cats with CHF, but has been occasionally used in cats with heart failure. Pimobendan is not recommended in the preclinical stages of feline cardiomyopathy or in cats with left ventricular outflow tract obstruction. Pimobendan is most often used in cats with systolic myocardial dysfunction that is associated with dilated cardiomyopathy as well as end-stage hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), and arrhythmogenic right ventricular cardiomyopathy cases. Most reports of pimobendan use in cats utilize the same dosing protocol that is used in dogs (0.25 mg/kg BID). The overall safety and efficacy of pimobendan in cats requires further study.

Beta-Adrenergic Blockers

Beta-adrenergic blockers (BB) are part of standard care in humans with systolic dysfunction. Chronic administration of BB such as carvedilol or metoprolol results in improved contractility, myocardial protection from circulating catecholamines, and improved survival. Whether or not BB benefit veterinary patients with heart disease or failure is unknown as there are relatively limited data compared to ACEI and pimobendan. The three most common clinical situations for which BB are typically considered are rate control of atrial fibrillation wherein BB are co-administered with digoxin, in the preclinical or stable heart failure phase of DCM in dogs, and in cats with HCM or RCM, with special consideration for cats with dynamic left ventricular outflow tract obstruction.

Beta-adrenergic blockers are often used in conjunction with digoxin to treat persistent supraventricular arrhythmias such as atrial fibrillation (see Chapter 21). The BB dose can be gradually up titrated to achieve target heart rate. Overly aggressive combinations of digoxin, BB, and calcium channel blockers can produce bradycardia. Some cardiologists recommend BB during the preclinical phase of DCM in dogs. Successful institution and titration of BB is regarded as easier in the preclinical phase as opposed to starting BB after development of CHF. Sudden withdrawal of BB can result in reflex tachycardia so that dosing should continue even if CHF eventually occurs. However, the dosage may require adjustment based on clinical symptoms, blood pressure, and heart rate. Limited studies in dogs indicate that titration of BB is relatively well tolerated by patients, but the long-term effect on cardiac function and survival is unknown.

In general, BB should only be introduced in patients free of active CHF as their negative inotropic properties can acutely reduce cardiac function and exacerbate clinical signs. When used in dogs with DCM, BB are typically titrated upward over 4–8 weeks. The initial prescribed dosage of BB is as little as 1/10th of the target dose and titrated upward based on heart rate and blood pressure. The authors will often temporarily increase the dose of concurrent furosemide while introducing BB in patients with advanced disease. Gradual reduction in the dosage over several weeks is recommended if a decision is made to cease treatment with chronic BB. Systemic hypotension can be seen when BB are used concomitantly with vasodilatory drugs such as ACEI or pimobendan. BB use in the preclinical phase of MMVD is not recommended. BB are commonly used to slow heart rate in cats with HCM or RCM, especially if left ventricular outflow tract obstruction due to systolic anterior motion of the mitral valve is present (see Chapter 27). BB are usually not prescribed to cats with active CHF; rather, they are used in the preclinical or stable heart failure phases. Typically, BB are titrated to achieve in-hospital heart rate less than 160 bpm in cats. Monitoring of heart rate, systolic blood pressure, and severity of left ventricular outflow tract obstruction is recommended in cats with HCM.

The various BB are classified according to their selectivity for different beta-receptors. Additionally, there are differences involving lipophilicity, metabolism, antiarrhythmic effects, and vasodilatory properties amongst the various BB. The most common BB used in veterinary cardiology include atenolol, carvedilol, metoprolol, and sotalol.

Atenolol is a beta-1-specific antagonist dosed at 0.25–1 mg/kg BID in dogs and 6.25–12.5 mg/cat q12–24h in feline patients. Atenolol is commonly used in the treatment of HCM in cats and congenital subvalvular aortic stenosis in dogs. Carvedilol is a nonspecific BB, acting on both beta-1 and beta-2 receptors, and has adjunctive alpha-1-adrenergic blocking effects leading to vasodilation. Carvedilol is metabolized in the liver and

there are rare reports of hepatotoxicity. Initial dosage of carvedilol is 0.05–0.1 mg/kg BID and is slowly titrated upward over 4–8 weeks to a final target dose of 0.5–1.0 mg/kg BID. Metoprolol is a beta-1-specific antagonist that is metabolized by the liver. Target dose is 0.2–0.4 mg/kg BID and 0.4–1 mg/kg q24h for the sustained-release preparation. In humans, studies suggest a benefit of sustained-release formulations due to more stable blood levels. Sotalol is a nonselective BB with potassium channel-blocking antiarrhythmic properties. It is primarily used as an antiarrhythmic agent in dogs with DCM or arrhythmogenic right ventricular cardiomyopathy and is dosed at 1–3 mg/kg BID in dogs and 2 mg/kg BID in cats (see Chapter 20).

Calcium Channel Blockers

Diltiazem, amlodipine, and rarely verapamil are calcium channel blockers (CCB) used in the management of chronic heart failure. Differences in the three agents center around their propensity for cardiac effects on heart rate and myocardial contractility versus peripheral effects of smooth muscle relaxation and peripheral vasodilation. Among the most commonly used CCB, amlodipine has the greatest vasodilatory properties, followed by diltiazem and then verapamil. Conversely, verapamil is a potent negative cardiac chronotrope and negative inotrope, followed by diltiazem and then amlodipine, the latter of which has very little effect on cardiac myocardial tissue.

In dogs, the most common indication for diltiazem is for ventricular rate control in atrial fibrillation and is dosed at 0.5–1.5 mg/kg q8h (See Chapter 21) Sustained-release preparations (Cardizem® CD and Dilacor®) are dosed at 3 mg/kg BID in dogs. Diltiazem is often prescribed in cats with HCM with or without atrial fibrillation and including cats with left ventricular outflow tract obstruction. The authors use either diltiazem or atenolol in cats with severe HCM and echocardiographic evidence of diastolic dysfunction. Diltiazem is typically added to the treatment regimen once the cat is receiving furosemide, ACEI, and antithrombotic agents. In cases of active CHF, the authors often delay initiation of CCB or BB until after the patient is stable on the aforementioned cardiac drugs to try to reduce the incidence of adverse reactions, such as bradycardia or hypotension. In cats, diltiazem is dosed at 7.5 mg/cat q8h. Sustained-release diltiazem preparations are available (Cardizem CD, 10 mg/kg q24h; Dilacor XR 30 mg/cat q12 h).

Canine patients generally tolerate diltiazem while cats have a higher incidence of gastrointestinal upset, loss of appetite, and hypersalivation. The authors recommend administering diltiazem with food or encapsulating the tablet in a gelatin capsule to hide the adverse taste from the cat. Diltiazem has some negative inotropic effects that can exacerbate signs of CHF, although this is less common than with BB. Diltiazem also has mild vasodilatory properties and monitoring blood pressure and heart rate is recommended.

Verapamil is rarely used in veterinary patients although it is commonly used in humans with HCM. One author (SR) has seen benefit in feline HCM patients with severe left ventricular hypertrophy and dynamic left ventricular outflow tract obstruction. Verapamil provides heart rate control in addition to supposed effects on diastolic function. Gastrointestinal side effects are common when using verapamil and can be minimized by administering with food. In cats, verapamil has a starting dose of 1 mg/kg BID with upward titration based on clinical signs, heart rate, and blood pressure over 2–3 weeks to a maximal dose of 5 mg/kg BID, with a target heart rate between 120 and 160 bpm. Amlodipine will be discussed under the refractory treatment of congestive heart failure.

Antithrombotic Therapy

Thromboembolism is a common risk factor in human patients with chronic heart failure, especially in the presence of atrial fibrillation. In dogs, clinical systemic arterial thrombosis is uncommon while in cats, arterial thromboembolism is a devastating clinical complication of cardiomyopathy. The exact mechanism behind arterial thrombosis is complex and the most effective strategy to prevent and treat is unknown.

Chronic oral agents commonly administered to reduce the risk of thrombosis are aspirin and clopidrogrel. Less commonly, warfarin or injectable unfractionated or low molecular weight heparin are used. More recently, the use of factor Xa inhibitors like rivaroxaban and apixaban has been recommended for patients with recurrent emboli or poor tolerance to other antithrombotic agents. In one study, clopidogrel was more effective than aspirin in preventing reoccurrence of thromboembolism in cats with a previous history of thrombus. Antithrombotic agents are also empirically administered in cases with a perceived increased risk thromboembolism. These risk factors include the presence of an intracardiac thrombus, spontaneous echocardiographic contrast ("smoke"), severe left atrial dilation, protein-losing nephropathies, hypoproteinemia, pulmonary hypertension, immune-mediated hemolytic anemia or heartworm disease. For aspirin therapy, the authors utilize 20–81 mg/cat q72h in cats and 1–5 mg/kg q24h in dogs. Clopidrogrel is dosed at ¼ of a 75 mg tablet (18.75 mg) q24h in cats and 3–5 mg/kg q24h in dogs. Cats, in particular, often do not like the taste of clopidrogel, which can lead to vomiting, hypersalivation, anorexia, and difficulties in pill administration.

Antithrombotics agents can lead to adverse reactions when used with corticosteroids or nonsteroidal antiinflammatory agents and might reduce the efficacy of

some cardiac therapies such as diuretics or spironolactone. During administration, renal function is monitored and pet owners are instructed about possible gastrointestinal side-effects. Chronic monitoring of coagulation profiles is not required with aspirin and clopidrogel and thus they are more commonly used in veterinary patients than anticoagulant agents such as warfarin or heparin.

Dietary Modifications

Maintenance of caloric intake is essential in the management of chronic heart failure. Traditionally, restriction of sodium was regarded as beneficial for the management of heart disease despite concern that very low sodium diets may further activate the RAAS. Diets that are mildly (80–100 mg Na/100 kcal) or moderately (50–80 mg Na/100 kcal) restricted in sodium should be considered for patients with chronic CHF. Severely sodium-restricted diets (<50 mg Na/100 kcal) are reserved for patients with advanced heart failure, severe hypertension, or cardiogenic body cavity effusions. Monitoring of blood electrolytes, in particular sodium and potassium, is important if severely sodium-restricted diets are fed.

Chronic heart failure is a catabolic state and results in a progressive loss of body condition and muscle tone. This "cardiac cachexia" requires adequate caloric and protein intake. In patients with concurrent renal disease, protein intake needs to be balanced between these competing conditions. The catabolic state is partly a result of inflammatory mediators and some evidence suggests the benefit of fish-based omega 3 fatty acids to help slow weight loss. Supplementation with the omega 3 fatty acids is typically considered in patients with weight loss and muscle wasting as well as in patients with ventricular arrhythmias (see Chapter 26). Care should be taken to avoid the fish oils that are combined with other sources such as flax seed oil or cod liver oil due to the potential for vitamin D toxicosis. Fish oil is dosed based on the amount of beneficial omega 3 fatty acids provided. In dogs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are dosed at 40 mg/kg and 25 mg/kg per day, respectively.

Taurine deficiency is a known cause of dilated cardiomyopathy in cats, but due to universal supplementation in commercial cat food, this form of cardiomyopathy is rarely detected. In rare cases of feline taurine deficiency, patients are supplemented with taurine at 250 mg PO BID. Taurine deficiency has also been reported in various breeds of dogs, including Newfoundlands, American cocker spaniels, and golden retrievers. In these dogs, taurine-deficient DCM is treated with 35 mg/kg taurine BID. A complete diet history and whole blood or plasma taurine assay are recommended by the authors in any dog with apparent DCM diagnosed in a breed other than the "typical" breeds (i.e., Doberman pinscher, Great Dane, boxer, mastiff, or Irish wolfhound) known for this disease. L-carnitine (50 mg/kg PO TID) and coenzyme Q10 (30–90 mg PO BID) are two additional supplements. L-carnitine is most commonly considered in American cocker spaniels that are taurine deficient. Unlike taurine deficiency, diagnosis of L-carnitine deficiency requires myocardial biopsy, which is rarely performed. In a small unpublished evaluation of Dalmatians with dilated cardiomyopathy, one of the authors (SR) found improved survival times when taurine, carnitine, and coenzyme Q10 were administered along with conventional cardiac therapy.

Therapy for Refractory Chronic Heart Failure

As previously described, conventional treatment of chronic CHF in dogs consists of "quadruple" therapy with furosemide, ACEI, pimobendan, and spironolactone. In patients with refractory CHF despite conventional therapy, additional treatments are provided in order to combat recurrent symptoms of heart failure.

Additional Diuretics

Recurrent CHF necessitates gradual increases in the doses of diuretics such as furosemide and spironolactone. A common clinical observance is the apparent reduction of diuretic efficacy as furosemide doses approach 6–12 mg/kg/day in dogs and 3–4 mg/kg/day in cats. The reasons for diuretic resistance are varied and complex. One cause is the reduction of oral bioavailability and resultant decrease in plasma concentration. This, coupled with poor organ perfusion due to low cardiac output, reduces the delivery of furosemide to the nephron. In cases of advanced CHF, and particularly in cases of recurrent abdominal or pleural effusion, the authors often consider replacing one or more oral administrations of furosemide with a daily subcutaneous injection of furosemide. Anecdotal experience indicates that restoration of diuresis can often be achieved using this strategy. As with insulin injections, owners can quickly learn to how administer SC injections at home. Injectable furosemide is light sensitive and owners are instructed to keep the drug out of direct light. Injectable furosemide is relatively alkaline and may cause reactions at the injection site that include local scabbing or plaque formation. In the authors' experience, these appear less common when using the Salix® brand of furosemide.

A common strategy in patients with refractory CHF is to layer additional diuretics onto the existing furosemide therapy. This strategy of "sequential nephron blockade" involves adding diuretics that act at sites other than the loop of Henle. Addition of hydrochlorthiazide (0.5 mg/kg SID or 1 mg/kg q48 h) or, if not already being administered, spironolactone (2 mg/kg/day) can be considered. Adverse reactions to high-dose or multiple diuretics include severe azotemia, anorexia, dehydration, and electrolyte abnormalities. This is particularly important in patients are partially anorexic or eating diets severely restricted in sodium.

Another option to improve diuresis is to replace furosemide with another diuretic such as torsemide (alternative spelling, torasemide). Torsemide, like furosemide, is a loop diuretic. In humans, torsemide is characterized by more reliable gastrointestinal absorption, a longer half-life, and adjunctive antialdosterone effects. In dogs, torsemide has a longer half-life and is well suited for both resolution and long-term control of CHF. Torsemide is markedly more potent than furosemide and the recommended dose range for treatment of CHF in dogs is 0.1–0.6 mg/kg SID. Dogs with mild CHF typically require 0.1–0.3 mg/kg SID and any increases in dose in response to reoccurrence of clinical signs are done in 0.1 mg/kg/day increments. In dogs with CHF refractory to existing doses of furosemide (typically >6 mg/kg/day), replacement of furosemide involves replacing the total daily dose of furosemide with 1/10th to 1/20th the dosage of torsemide. For example, if the existing furosemide dose was 25 mg BID, the equivalent torsemide dose would be 1/10th to 1/20th of 50 mg or 2.5–5 mg per day. There are limited reports of use of torsemide in cats. The dose range in cats is likely similar to that in dogs. Torsemide, like all diuretics, requires close monitoring of renal function, electrolytes, blood pressure, hydration status, and body weight.

Clinicians might wish to consult with a specialist to discuss individualized treatment and monitoring plans in patients with refractory CHF. In general, the need for diuretics in addition to or in place of furosemide in patients with refractory signs of CHF is considered a poor prognostic sign.

Volume depletion is caused by high dose and potent diuretics and affects renal excretion of other cardiac drugs, such as digoxin, and close monitoring of such drugs is needed.

Thus, the risk for digoxin toxicity increases with worsening hypovolemia. In late stages of CHF, free water retention by arginine vasopressin (antidiuretic hormone) can result in severe hyponatremia and hypochloremia. These electrolyte derangements can be difficult to treat. Occasionally, cautious addition of sodium chloride or potassium chloride to the diet, warm sodium chloride enemas, diuretic reduction, or cautious restriction of water intake can be performed. Hyponatremia is considered a poor prognostic sign in dogs with chronic CHF.

Additional Vasodilators

Patients with refractory CHF might benefit from vasodilator therapy in addition to standard administration of ACEI. In these instances, use of arterial vasodilators such as hydralazine or amlodipine is occasionally considered. Due to the perceived relationship between afterload (which is approximated by the aortic systolic blood pressure) and degree of mitral regurgitation, arterial vasodilators are often considered in dogs with refractory CHF due to MMVD, but their efficacy in reducing the degree of regurgitation is unknown. The limiting factor in the administration of additional vasodilators is systemic hypotension, and vasodilators are not prescribed if the baseline systemic systolic blood pressure is <100 mmHg. Amlodipine (0.–0.4 mg/kg PO BID in dogs and cats) is a calcium channel blocker with potent antihypertensive properties. A starting dosage of 0.1 mg/kg BID and uptitrating over two weeks to the higher dosage of 0.3–0.4 mg/kg BID is typically well tolerated. Prior to the widespread use of amlodipine as an antihypertensive agent in both dogs and cats, hydralazine was often used in dogs and continues to be an option in refractory cases of canine MMVD. Hydralazine (0.5–2 mg/kg PO BID) is a direct-acting vasodilator with a shorter half-life and more rapid onset of action than amlodipine. Thus, acute hypotension and reflex tachycardia are more common than with amlodipine. In emergency situations where acute arterial vasodilation is needed (i.e., acute life-threatening CHF or systemic hypertension), hydralazine is considered. Common adverse effects of hydralazine include hypotension and gastrointestinal signs.

Oral nitrate compounds such as sustained-release isosorbide dinitrate or mononitrate (0.5–2.0 mg/kg PO BID in dogs and cats) are infrequently used as a venous vasodilator. Administration is usually performed when signs of congestion persist despite diuretic usage or further increases in diuretic usage are hindered by concomitant azotemia or arterial hypotension. Due to rapid development of tolerance, oral nitrates are typically administered in two doses eight hours apart with a 16-hour drug-free interval. In humans who are intolerant of ACEI, hydralazine or amlodipine along with an oral nitrate is administered, albeit with less clinical benefit than ACEI.

Pulmonary hypertension (PHT) (see Chapter 23) is a common complication in patients with advanced heart failure, especially those with MMVD. Signs of PHT include right-sided heart failure, syncope, and persistent tachypnea in the absence of pulmonary edema.

Echocardiography can help confirm the diagnosis. Phosphodiesterase V inhibitors, such as sildenafil (1–3 mg/kg PO TID) or tadalafil (1 mg/kg PO SID) are variably effective. In the authors' experience, sildenafil seems to be more effective than tadalafil. Both drugs can be very expensive, especially in large-breed dogs. Both agents are well tolerated in dogs. Rarely, inguinal flushing and gastrointestinal upset are noted. Systemic hypotension is rare. Monitoring of the clinical symptoms as well as pulmonary and systemic pressures is recommended.

Positive Inotropes

In cases of refractory heart failure due to DCM or MMVD, off-label dosages of pimobendan are often utilized. The authors will increase frequency of dosing from 0.25 mg/kg BID to TID followed by a slow titration to 0.5 mg/kg TID as needed. Additional pimobendan can also be effective in cases of biventricular heart failure as well as in patients with PHT. Cats with DCM or other forms of systolic dysfunction also appear to tolerate doses of pimobendan greater than 0.25 mg/kg BID. On rare occasions, three days of dobutamine infusion in the hospital at 2.5–10 µg/kg/min can be considered as there might be some residual positive inotropic benefit for some time after the hospitalization. Oral digoxin can be added to the existing treatment regimen, especially if tachyarrhythmias such as atrial fibrillation are present. Care should be taken to monitor serum digoxin levels to avoid toxicity.

Cough Suppression

Many canine patients with chronic heart failure develop a cough secondary to bronchial compression as a result of bronchomalacia and severe atrial dilation. In the absence of CHF, a variable amount of cough suppression is achieved with hydrocodone (0.22–0.44 mg/kg PO B-QID) or butorphanol (0.55 mg/kg PO B-QID). Bronchodilators, such as aminophylline or theophylline, are typically ineffective.

Therapy of Acute Life-Threatening Heart Failure

Therapy for acute-life threatening heart failure is based on many of the same principles that guide therapy for chronic heart failure, namely diuresis to alleviate congestion, vasodilators to reduce preload and afterload, and positive inotropes to improve myocardial contractility (Table 19.2). In acute heart failure, hemodynamic abnormalities such as congestion and low cardiac output predominate and therapy is targeted towards resolution of congestion, such as pulmonary edema, pleural effusion, or ascites, and improvement of forward cardiac output and tissue perfusion. In general, more attention is given to stabilization of hemodynamics versus interruption of neurohormonal systems, such as the RAAS or sympathetic nervous systems that are so critical to treatment of chronic heart failure.

Diuretics

Diuretics are a mainstay of treatment of acute CHF. Treatment induces potent and rapid diuresis. Parameters commonly monitored during diuresis include respiratory rate and effort, body weight, urine production, electrolytes, renal function, and blood pressure. Furosemide is the most commonly used diuretic for the treatment of acute CHF. When given by IV, IM, or SC routes, diuresis begins within 5–10 minutes and reaches a peak at 30–60 minutes with duration of action between two and three hours. A typical initial dose is 2–4 mg/kg IV/IM/SC in dogs and 1–2 mg/kg IV/IM/SC in cats. Because of its relatively short duration of action, repeated bolus injections of furosemide are needed if respiratory rate and other clinical signs are not improved within 2–4 hours after initial dose. During administration, patients should produce large quantities of dilute urine, and failure to induce diuresis should alert clinicians to the possibility of underlying renal dysfunction, poor forward cardiac output, and/or reduced renal perfusion. In patients with left-sided CHF such as pulmonary edema, the simplest way to monitor response to diuretics is to monitor respiratory rate and effort. Most patients with severe pulmonary edema will exhibit respiratory rates at presentation >45 breaths/min with increased abdominal effort and orthopnea. As diuretics resolve pulmonary edema, the respiratory rate and effort should begin to decrease, signaling an ability to reduce frequency of diuretic injections to q6–8h. Continued improvement in respiratory rate and effort over the subsequent 12–24 hours leads to replacement of parenteral furosemide with oral furosemide.

Diuretic therapy for treatment of acute CHF should be personalized for individual patients depending on the severity of clinical signs, current or previous therapy with oral diuretics, co-administration of other heart failure medications, hydration status, renal function, and blood pressure. In general, patients with extreme respiratory distress or those already receiving oral diuretics will require higher initial starting doses and more frequent repeated boluses, while those with preexisting renal dysfunction, dehydration, or low blood pressure will require more conservative dosing. Renal and electrolyte bloodwork as well as blood pressure measurement are typically performed as soon as practicable after

Table 19.2 Commonly used drugs for the treatment of acute heart failure

Drug	Indications	Dose	Comments/Adverse Effects
Diuretics			
Furosemide	Relief of congestion	Dog: 2–4 mg/kg IV/IM/SC q2–4h; 0.66 mg/kg IV bolus followed by 0.66 mg/kg/h CRI Cat: 1–2 mg/kg IV/IM/SC q2–4h	Azotemia, dehydration Electrolyte disturbances Monitor renal function Repeated doses based on respiratory rate and other signs
Vasodilators			
ACE inhibitor	Anti-RAAS Hypertension	Enalapril Dog/Cat: 0.5 mg/kg q12–24h Benazepril Dog/Cat: 0.25–0.5 mg/kg q12–24h Lisinopril Dog: 0.25–0.5 mg/kg q24h Ramipril Dog: 0.25 mg/kg q24h Imidipril Dog: 0.25–0.5 mg/kg q24h	Azotemia, hypotension Monitor renal function Initiation might be delayed until acute congestion resolved
Sodium nitroprusside	Hypertension Afterload reduction Preload reduction	Dog: 1–10 µg/kg/min CRI	Hypotension, monitor blood pressure Light sensitive Typically only used for 12–48 h
Nitroglycerin	Afterload reduction Preload reduction	Dog: 1–10 µg/kg/min CRI	Hypotension, monitor blood pressure Typically only used for 12–48 h
Hydralazine	Hypertension Afterload reduction	Dog: 0.2–2.0 mg/kg q12h	Hypotension Gastrointestinal signs
Sildenafil	Pulmonary hypertension	Dog: 1–3 mg/kg q8h	Variably effective Expensive
Positive inotropes			
Dopamine	Poor contractility	Dog: 1–10 µg/kg/min CRI	Tachycardia, arrhythmias Used only for 12–48 h
Dobutamine	Poor contractility	Dog: 2.5–10 µg/kg/min CRI	Tachycardia, arrhythmias (less than dopamine) Used only for 12–48 h
Pimobendan	Poor contractility Afterload reduction	Dog: 0.25 mg/kg q12h 0.15 mg/kg IV once	Contraindicated if outflow obstruction present
Digoxin	Poor contractility Supraventricular tach	Dog: 0.005–0.0075 mg/kg q12h Cat: 0.03125 mg/cat q24–48h	Long half-life Monitor serum levels Gastrointestinal signs Typically only used if atrial fibrillation is present

ACE, angiotensin converting enzyme; CRI, constant rate infusion; IM, intramuscular; IV, intravenous; RAAS, renin-angiotensin-aldosterone system; SC, subcutaneous.

initial presentation, and can help guide the initial or subsequent dosing strategy. In the majority of instances, mild azotemia, electrolyte abnormalities, increased total protein, loss of body weight, and other signs of volume depletion will be detected after the first 18–24 hours of diuretic therapy. In many cases, mild increases in BUN or creatinine and mild clinical dehydration are noted and do not necessitate complete cessation of the diuretic therapy. The possibility of severe azotemia, electrolyte imbalances, or acute kidney injury, particularly if preexisting renal dysfunction is present, is the main limiting factor regarding the dose and frequency of diuretic administration. In cases where diuretic therapy results in these signs, temporary cessation of diuretic administration along with replacement fluids administered either SC or IV might be needed.

In treating acute CHF, clinicians continuously weigh hydration status and renal function against the degree of

respiratory compromise and prescribed dose of diuretics. There is no "one size fits all" formula for diuretic administration and clinicians should constantly reassess their therapy during the first 18–24 hours. The authors discourage the routine use of IV fluid administration at the same time diuretics are being administered. Rather, they recommend offering water *ad libitum* during treatment of acute CHF to allow patients to semi-self-regulate their hydration status. Given the potency of the loop diuretics, patients will be unable to consume enough water to replace the fluids being lost. In cases of dire CHF or instances where patients obsessively drink repeated quantities of water when offered, water restriction might be needed.

While diuretics are generally considered a highly effective means of relieving congestion, inadequate response to diuretics or the inability to administer sufficient doses due to renal disease necessitates additional strategies to improve renal perfusion and decrease intravascular pressure though positive inotropes and vasodilators.

Positive Inotropes

Acute heart failure is accompanied by decreased cardiac output. Decreased tissue perfusion, particularly to the kidneys, activates sodium- and water-retaining mechanisms, such as the RAAS and SNS, leading to signs of congestion. Poor perfusion of the proximal convoluted tubule can decrease response to furosemide as active secretion of furosemide into the nephron's intraluminal space is required for its diuretic effect. Positive inotropes increase myocardial contractility and cardiac output and are particularly indicated in instances of low-output (forward) heart failure wherein signs of cardiac shock, such as weakness, pallor, hypotension, and hypothermia, are evident. Positive inotropes are often used in dogs with DCM, and less commonly in dogs with MMVD. Because most forms of feline cardiomyopathy are diastolic in nature, positive inotropes are rarely used in cats with heart failure. Positive inotropes act via increased binding of calcium ions to the myocardial actin-myosin-troponin complex, either by increasing intracellular calcium concentration or by increasing the sensitivity of the actin-myosin-troponin complex to calcium binding.

Commonly administered positive inotropes include sympathomimetic agents such as dopamine or dobutamine, calcium sensitizers such as pimobendan, and intracellular calcium agents such as digoxin. Dopamine is a precursor of norepinephrine while dobutamine is a synthetic catecholamine, and both agents bind to myocyte beta-adrenergic receptors in order to increase myocardial contractility and heart rate. At high doses, both agents also act on peripheral alpha-1 receptors to cause unwanted arterial vasoconstriction. In dogs, dopamine (1–10 µg/kg/min) or dobutamine (2.5–10 µg/kg/min) are administered via constant rate infusion (CRI) and titrated upwards to effect. Both agents are diluted in small volumes of 5% dextrose to limit the total volume of fluids administered to dogs with acute CHF. During administration, blood pressure, mentation, muscle tone, urine output, and other indices of improved tissue perfusion such as body temperature or blood lactate guide dose titration. For both dopamine and dobutamine, the rate-limiting factor during administration is tachycardia, tachyarrhythmias, or excessive vasoconstriction. Efficacy likely is best within the first 48 hours of administration, after which the effects wane as beta-receptors are saturated or downregulated.

Pimobendan is a calcium sensitizer and phosphodieterase inhibitor. Its positive inotropic action is due to its ability to increase the binding of calcium ions to the actin-myosin-troponin complex without a substantial increase in intracellular calcium concentration. This mechanism provides improved cardiac contractility without substantial concomitant increases in myocardial oxygen or energy demands. Pimobendan (0.25 mg/kg PO BID or 0.15 mg/kg IV once in dogs followed by start of oral dosing 12 hours after injection) can used in place of either dopamine or dobutamine when constant rate infusion is not practical. Pimobendan is well tolerated in dogs with acute CHF and oral dosing continues into the chronic phase of CHF once the acute episode of CHF is resolved.

Digoxin is a digitalis glycoside with modest positive inotropic effect as well as ability to reduce or slow conduction through the AV node. Its use in acute heart failure is limited by its variable oral bioavailability, long half-life, and narrow therapeutic window. Use of digoxin for acute heart failure has been largely replaced by pimobendan except in instances of atrial fibrillation or supraventricular tachycardia wherein oral digoxin (0.005–0.0075 mg/kg PO BID) is used to help slow the ventricular heart rate. The long-half life of digoxin precludes rapid achievement of therapeutic serum levels, and digoxin therapy is usually combined with other antiarrhythmic agents such as diltiazem (see Chapter 21). Toxicity includes arrhythmias and gastrointestinal signs such as vomiting, anorexia, and diarrhea. The authors discourage the use of IV digoxin administration due to a high incidence of toxicity.

Vasodilators

Venous and arterial vasodilators reduce preload and afterload, respectively. In cases of acute CHF, venous vasodilation is often used in conjunction with diuretics to help rapidly relieve congestion. Arterial vasodilation reduces peripheral vascular resistance/afterload and encourages improved cardiac output.

Nitroprusside is a potent mixed vasodilator capable of both venous and arterial vasodilation. It acts by releasing nitric oxide, which induces vascular smooth muscle relaxation. Nitroprusside is metabolized very rapidly and is administered via CRI (1–10 µg/kg/min in dogs). Its rate-limiting factor is systemic arterial hypotension, and blood pressure monitoring is highly recommended during use. Typically, the dosage is adjusted to achieve a systolic arterial blood pressure no lower than 90 mmHg. The short half-life of nitroprusside allows clinicians to effectively make changes in infusion rates in response to blood pressure. Nitroprusside, while highly effective, is only occasionally used due to its need for CRI and sensitivity to light that requires the administration set to be covered in light-protective wrapping. Similar to dopamine or dobutamine, nitroprusside infusions are given short term, typically not longer than 48 hours. At very high doses or for extended periods of administration, accumulation of nitroprusside metabolites such as cyanogen can result in toxicity. Nitroprusside is rarely used in cats. At the time of writing, supply shortages of nitroprusside have severely curtailed its use and alternative nitric oxide donors such as IV nitroglycerin (1–10 µg/kg/min) have been used.

ACE Inhibitors

ACE inhibitors form a cornerstone of therapy of chronic CHF. Their utility in acute life-threatening CHF is less evident. Compared to hydralazine or nitroprusside, the arterial dilating effects of ACEI are modest. ACEI's ability to decrease AT II and aldosterone production appears more beneficial over longer periods of time as opposed to rapidly acting short-term effects in acute CHF. The rate-limiting factors affecting ACEI use include azotemia and systemic arterial hypotension. The authors occasionally delay initiation of ACEI until acute CHF is stabilized with diuretics, positive inotropes, and other vasodilators, and are especially cautious in patients already suffering from systemic hypotension or in those that required very high doses of diuretics to alleviate congestion and are significantly dehydrated. In these cases, ACEI administration might be delayed until the patient's hydration status and renal bloodwork are reevaluated. They are then prescribed as part of the chronic CHF therapy with close monitoring of renal bloodwork and systemic blood pressure.

Additional Therapies for Acute CHF

Oxygen supplementation is provided in cases of respiratory compromise and hypoxemia. Inspired O_2 concentration is typically increased to 40% through the use of oxygen cages or, in the case of large dogs, nasal insufflation. Manual removal of pleural, pericardial, or abdominal fluid should be performed if these effusions are a cause of respiratory compromise. In patients that are extremely anxious, mild sedation with morphine (0.1–1.0 mg/kg SC/IM in dogs), acepromazine (0.1–0.2 mg/kg SC/IM in dogs) or butorphanol (0.1–0.3 mg/kg IM/IV in dogs or cats) can be considered. Care must be taken to avoid oversedation as further compromise of respiratory function can result. Bronchodilators such as aminophylline or theophylline or cough suppressants such as hydrocodone are rarely needed in cases of acute CHF.

Further Reading

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20

Ventricular Arrhythmias

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Etiology/Pathophysiology

Ventricular arrhythmias (VA) such as single ventricular premature depolarizations (contractions) (VPCs) can be seen in normal animals in *low* numbers (less than 50 per 24-hour period on a Holter monitor). They are very commonly seen in association with noncardiac disease, possibly due to myocardial ischemia, electrolyte abnormalities or other factors surrounding the underlying disease. For example, VPCs can be seen following vehicular trauma (traumatic myocarditis), surgery, gastric dilation and volvulus, splenic disease, immune-mediated hemolytic anemia and/or polycythemia, hypoxia, the use of anesthetic agents (especially thiobarbiturates), pancreatitis, prostatitis, and neurologic disease. Thus, ventricular arrhythmias are relatively common to any number of different systemic diseases. They may also be associated with primary underlying myocardial diseases such as dilated cardiomyopathy in Doberman pinschers and arrhythmogenic right ventricular cardiomyopathy in boxers. They can also be idiopathic in origin, meaning that no underlying systemic or cardiac disorder can be identified.

The most important clinical considerations with VPCs are whether there is an underlying systemic or cardiac cause of the VPCs and whether there is the need to treat the VA. Decisions to treat VA should be based on hemodynamic consequences and the risk of degeneration of the VA into an unstable rhythm such as ventricular fibrillation. Single VPCs do not cause clinical signs as they are transient and hemodynamically not significant. What is more important is attempting to identify malignant characteristics of VPCs or patient groups that might be more susceptible to the development of an unstable rhythm that can lead to sudden death. However, our ability to predict the likelihood of sudden death associated with VPCs is poor. It appears that in dogs and cats with VPCs and no underlying heart disease, the number of VPCs is not predictive of the risk of sudden death, which in this setting is typically low. When there is underlying myocardial disease, the presence of VPCs may indicate an increased risk of sudden death or simply be a marker for the severity of the disease (for example, Doberman pinschers with dilated cardiomyopathy or cats with hypertrophic cardiomyopathy). The presence of VPCs in boxers with familial ventricular arrhythmias may indicate an increased risk of sudden death.

Signalment

Certain breeds with specific underlying cardiac diseases are predisposed to malignant VA. Doberman pinschers with dilated cardiomyopathy, boxers with arrhythmogenic right ventricular cardiomyopathy, dogs with severe subaortic stenosis, young German shepherds with inherited ventricular arrhythmias, dogs and cats with myocarditis and cats with hypertrophic cardiomyopathy represent situations where a VA may signal increased risk for clinical signs or sudden death. Other than the specific patient groups and underlying type of cardiac diseases mentioned above, there is no other specific age, breed or sex predilection

History and Clinical Signs

Dogs with VA secondary to systemic disease often do not need the VA to be treated as the arrhythmia tends to be self-limiting if the underlying disease is addressed. For example, a patient with VPCs and gastric dilation-volvulus does not necessarily require antiarrhythmic therapy for the VPCs, and instead needs relief of the dilation and volvulus. This will in turn lead to resolution of the

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arrhythmias, usually within 72 hours. Dogs with single VPCs and underlying myocardial disease may or may not need to be treated. More often, the presence of VPCs in a patient with underlying heart disease indicates the need to further investigate the arrhythmia (e.g., with 24-hour ambulatory ECG [Holter] analysis) to determine if more serious arrhythmias are occurring at other times (Figure 20.1).

An example would be a Doberman pinscher with dilated cardiomyopathy, who is already receiving therapy but is found to have a newly discovered ventricular arrhythmia. Immediate introduction of antiarrhythmic therapy in this case may or may not be appropriate and further evaluation with Holter monitoring would be recommended. Patients with VPCs do not show clinical signs associated with only single premature beats. Even with ventricular tachycardia, if the rate of the ventricular is below 200–220 bpm, no clinical signs may be present. The rate at which a ventricular tachycardia will cause clinical signs will depend on many underlying factors such as rate, underlying myocardial function, species, and/or breed. Typically, however, when the rate of the ventricular tachycardia is rapid (greater than 250 bpm), signs of poor cardiac output will be present and syncope may occur. Clinical signs will also be influenced by the degree of underlying heart disease. Thus, the patient with systolic dysfunction and ventricular arrhythmias may exhibit clinical signs at a slower ventricular rate than a patient without underlying myocardial disease and ventricular tachycardia. Patients with more serious ventricular arrhythmias (ventricular tachycardia, ventricular fibrillation) and compromised/diminished myocardial function may have a history of exercise intolerance, shortness of breath, syncope or near syncope.

Diagnosis

Two basic ECG characteristics of VPCs are that they are premature in their timing (earlier than the sinus beat) and they are wide and bizarre in morphology compared to the sinus beat (Figures 20.2 and 20.3). They appear wide and bizarre because VPCs originate below the bundle of His and therefore cannot take advantage of the specialized conduction system. They therefore must depolarize the ventricles muscle cell to muscle cell. This is relatively slow and produces a wide and bizarre complex. QRS complexes can be positive or negative in lead II, depending on the site of origin of the VPC, and they have no relationship to the P-waves. Because depolarization occurs in an abnormal fashion, repolarization is also abnormal and there is typically a large and bizarre T-wave which is opposite in polarity to the VPC.

Ventricular premature depolarizations can occur in patterns such as ventricular bigeminy (every other beat is a VPC) and ventricular trigeminy (every third beat is a VPC). This type of pattern, however, does not correlate with severity or potential malignancy of a ventricular rhythm. More important characteristics of potentially dangerous ventricular arrhythmias include the rate of firing of a VPC and the morphology of a ventricular rhythm. If a VPC fires rapidly and occurs close to the peak of the preceding T-wave (so-called R-on-T phenomenon), depolarization during this time may predispose to ventricular fibrillation (Figure 20.4).

Ventricular rhythms can be monomorphic (one morphology) or polymorphic (several different morphologies), with the polymorphism generally considered to imply multiple origins or pathways for the arrhythmia, thus increasing the potential for degeneration into a malignant arrhythmia (Figure 20.5).

A ventricular couplet is two consecutive VPCs, a ventricular triplet is three consecutive VPCs, and ventricular tachycardia is >3 consecutive VPCs occurring at a rate of >170–180 bpm. Ventricular tachycardia is considered sustained if it lasts >30 seconds and nonsustained if it lasts <30 seconds. A ventricular rhythm that is less than approximately 140–170 bpm is not truly a tachycardia and is therefore best termed an accelerated idioventricular rhythm (sometimes referred to as slow ventricular tachycardia) (Figure 20.6).

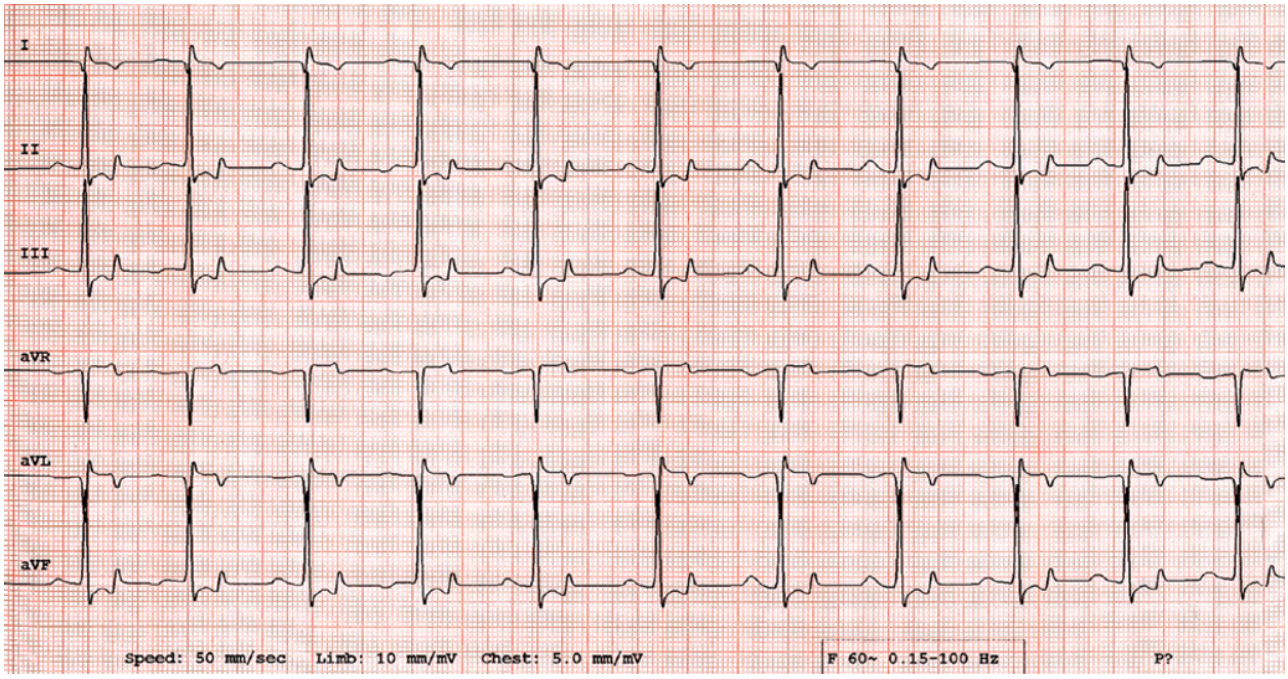
Accelerated idioventricular rhythms are seen commonly in hospitalized patients in association with noncardiac diseases as mentioned in the beginning of the chapter. These are often benign, the rate is too slow to cause clinical signs and they often do not require therapy.

Therapy

Prior to discussing specific therapeutic interventions, it is important to review the main objectives of treating a ventricular arrhythmia: (1) to improve hemodynamics in order to alleviate clinical signs and (2) to prevent sudden death.

When making the decision to treat or not, it is important to attempt to determine whether the arrhythmia is causing hemodynamic compromise. A healthy heart can tolerate many types of VA whereas a diseased heart cannot. Therefore, the presence or absence of underlying cardiac disease is an important factor in this decision. Evaluation of the peripheral pulse quality, mucous membrane color, attitude of the patient, and arterial blood pressure can be helpful in determining whether hemodynamics are being affected. Sustained ventricular tachycardia at a high rate is more likely to cause hemodynamic compromise than an idioventricular rhythm or a ventricular tachycardia firing at slower rates.

(a)



(b)



Figure 20.1 ECG and Holter tracings from a boxer dog acquired during a screening clinic for arrhythmogenic right ventricular cardiomyopathy. (a) Six-lead ECG showing a normal sinus rhythm present with a heart rate of approximately 136 bpm. (Paper speed 50 mm/s, sensitivity 10 mm/mV.) (b) A full screen shot from a 24-hour Holter worn by the same dog. There is ventricular bigeminy present throughout the ECG on this screen (VAs in red). (Paper speed 50 mm/s, sensitivity 10 mm/mV.)



Figure 20.2 Lead II ECG from a dog with single monomorphic ventricular premature contractions (*arrows*). (Paper speed 50 mm/s, sensitivity 5 mm/mV.)

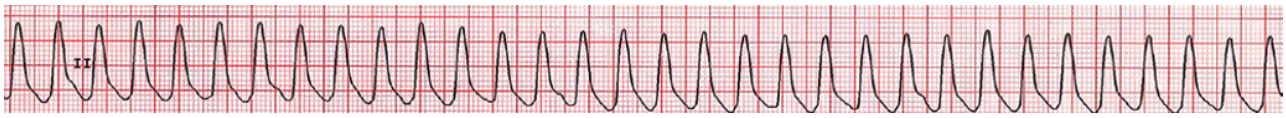


Figure 20.3 Lead II ECG from a cat with a monomorphic ventricular tachycardia at a rate of approximately 375 bpm. (Paper speed 50 mm/s, sensitivity 10 mm/mV.)



Figure 20.4 ECG strip from a dog in ventricular fibrillation. Ventricular fibrillation on the left portion of the tracing isT terminated with an external biphasic defibrillation shock, which restores a spontaneous rhythm. Note that the morphology of the two beats after defibrillation is altered (aberrant conduction) as a result of myocardial stunning from the electrical shock.

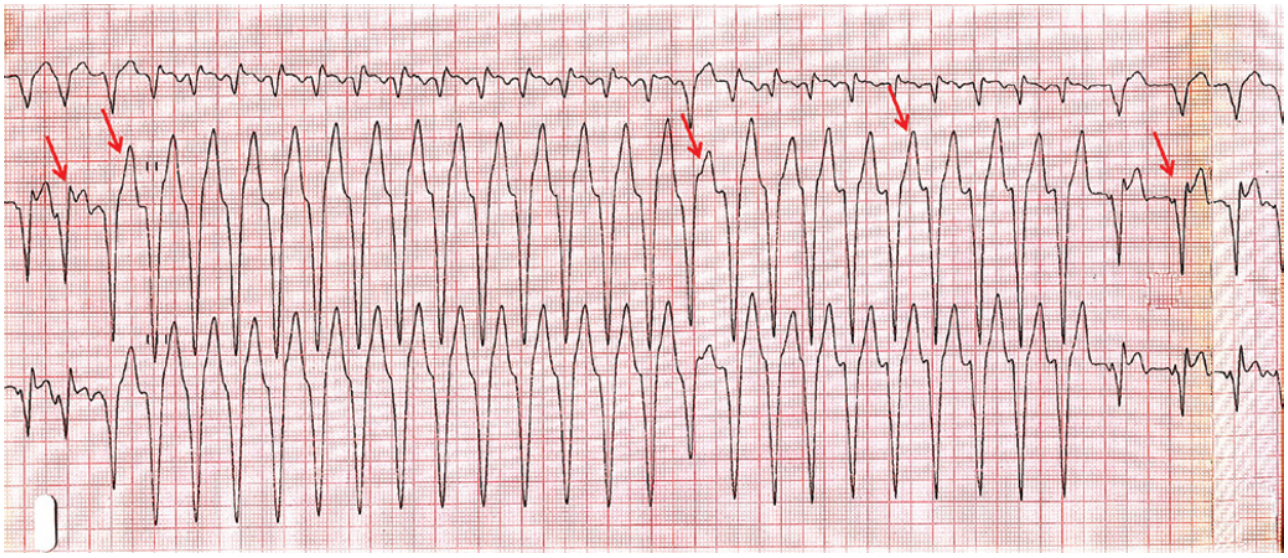


Figure 20.5 Three-lead ECG from a Doberman pinscher with polymorphic ventricular tachycardia. Note the abrupt changes in morphology of the ventricular complexes throughout the ECG (*arrows*). (Paper speed 50 mm/s, sensitivity 10 mm/mV.)

The second important consideration for decisions regarding the initiation of antiarrhythmic or other therapeutic intervention for a ventricular arrhythmia is whether the arrhythmia is likely to degenerate into ventricular fibrillation, which will cause sudden death. Again, the presence or absence of underlying cardiac disease is important since a healthy heart can tolerate more than a diseased heart. It is believed that the faster the

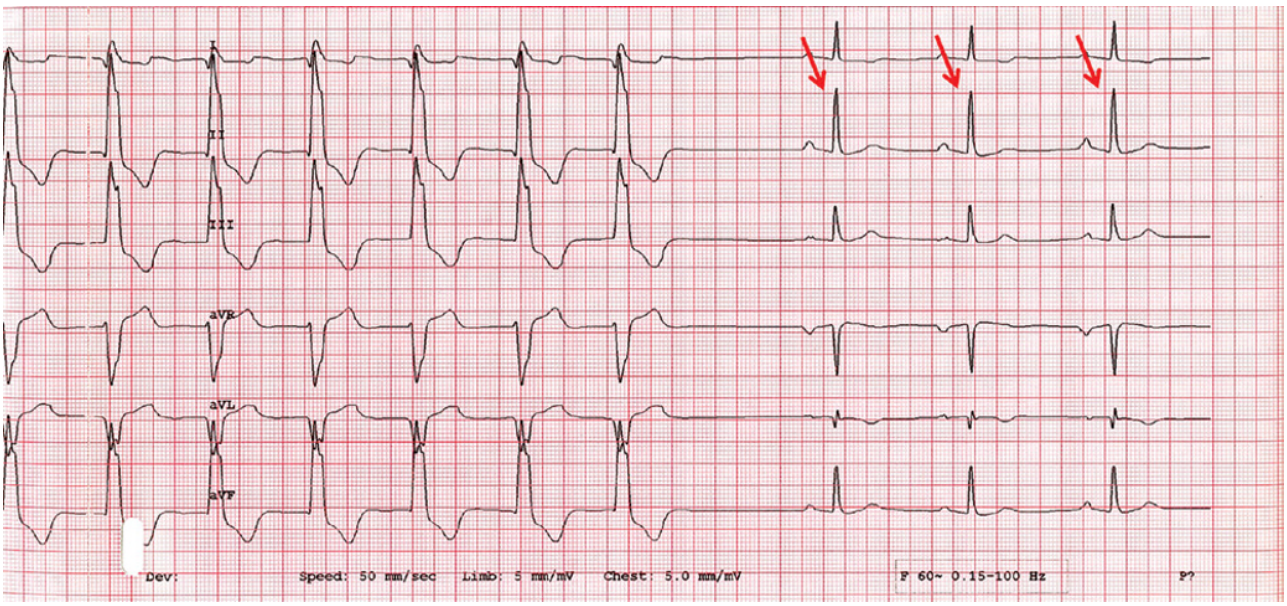


Figure 20.6 Six-lead ECG from a dog with an accelerated idioventricular rhythm. Note that the initial seven beats are wide and bizarre in morphology as typical for ventricular ectopy, but the rate is slow (approximately 125 bpm). When the idioventricular rhythm breaks spontaneously, normal sinus beats are then seen (*arrows*) at a rate of approximately 90 bpm. (Paper speed 50 mm/s, sensitivity 5 mm/mV.)

ventricular tachycardia, the more likely a beat will fall within the vulnerable period and induce ventricular fibrillation (R-on-T phenomenon). Polymorphic ventricular tachycardia is also thought to be more dangerous than monomorphic ventricular tachycardia. As mentioned above, certain patient groups appear to have an increased risk of sudden death associated with ventricular tachycardia.

Acute Therapy of Ventricular Tachycardia

Initial therapy for dogs or cats with ventricular tachycardia that is thought to be malignant and directly related to the current clinical signs is an IV bolus of lidocaine (see Table 20.1 for doses).

Lidocaine should be used with caution in cats, as they are very sensitive to its CNS effects. In both cats and dogs, it is important to determine plasma or serum potassium concentration as lidocaine will be less effective when hypokalemia is present. Thus, if lidocaine fails to convert a ventricular rhythm, assessment of a patient's electrolyte values, specifically potassium, is required. Additionally, hyperkalemia can also be a cause of supraventricular rhythms which can mimic the appearance of ventricular tachycardia in a cat.

Fortunately, most ventricular arrhythmias are responsive to therapy with lidocaine. However, some severe ventricular arrhythmias may not terminate following lidocaine injection, and in this situation, IV procainamide would be the next antiarrhythmic to administer.

Table 20.1 Typical medication doses

Drug name	Dosage
Amiodarone	Oral: 10–20 mg/kg PO q24h for 7–10 days then reduce to 3–15 mg/kg PO q24–48 h thereafter (D)
Atenolol	Oral: 0.2–1 mg/kg q12–24h (D), 6.25–12.5 mg q12–24h (C)
Esmolol	IV bolus: 0.2–0.5 mg/kg over 1 min, repeat q5min (D, C)
Lidocaine	IV bolus: 2 mg/kg over 30 s; maximum three boluses (D) 0.25–0.5 mg/kg (C) CRI 25–80 µg/kg/min (D)
Mexiletine	Oral: 4–8 mg/kg PO q8h (D)
Procainamide	IV bolus: 5–15 mg/kg over 1 min (D) 1–2 mg/kg (C) CRI 20–50 µg/kg/min (D)
Sotalol	Oral: 1–3 mg/kg q12h (D, C)

C, cat; D, dog; IV, intravenous; CRI, constant rate infusion; PO, by mouth (*per os*).

Intravenous procainamide may result in hypotension and should therefore be administered slowly. With refractory ventricular arrhythmias, magnesium sulfate supplementation can also be considered. Magnesium has primary antiarrhythmic properties similar to Class III agents, so supplementation works well in combination with lidocaine or other Class I agents. Early administration may

prevent worsening of ventricular arrhythmias and low magnesium concentrations may result in hypokalemia that is nonresponsive despite adequate supplementation. Other alternatives, such as synchronized cardioversion, esmolol or precordial thump, can be attempted if the above therapies fail to improve hemodynamic stability.

Precordial thump for control of ventricular arrhythmias was previously recommended as an initial maneuver in the treatment of ventricular tachycardia (VT) or ventricular fibrillation, but is now only considered for patients with witnessed, monitored and unstable VT resulting in cardiac arrest/asystole. A precordial thump is a very carefully aimed blow with the fist to the chest with the intent to interrupt a life-threatening rhythm. The thump is thought to produce an electrical depolarization of 2–5 joules, but is only effective if used near the onset of ventricular fibrillation. The precordial thump for VT remains controversial as precordial blows can trigger ventricular fibrillation (i.e., commotio cordis). It should only be used for asystole or ventricular fibrillation when a defibrillator is unavailable for use.

Chronic Therapy of Ventricular Tachycardia

All chronic antiarrhythmic agents have the potential to act as proarrhythmics, so their use should be monitored. This is ideally done by obtaining a 24-hour Holter recording before and 8–15 days after initiation of antiarrhythmics. If worsening arrhythmias develop, then a proarrhythmic effect should be considered as an underlying etiology. In addition, all antiarrhythmic agents have significant toxicity profiles. In both dogs and cats, the authors' first choice for chronic ventricular arrhythmia therapy is sotalol. Although not a pure beta-blocker, sotalol has significant beta-blocking effects, and should therefore be used with caution and slowly uptitrated in dogs with significant ventricular systolic dysfunction, such as those with dilated cardiomyopathy. In addition, it should not be combined with other beta-blockers. It is the first choice for boxers with arrhythmogenic right ventricular cardiomyopathy.

Amiodarone is a drug that appears to be very effective for refractory arrhythmias but it has been reported to have significant and severe side-effects. The low end of the dosage range should be used first and uptitrated only if necessary. There are many side-effects to the chronic use of amiodarone. It may cause a hepatopathy, so liver enzymes should be evaluated before starting and periodically while receiving amiodarone and any time anorexia develops. It may also cause neutropenia of unknown clinical significance and neurologic signs, and/or ataxia, especially at higher doses and with prolonged use. Amiodarone can be combined with a beta-blocker. Additionally, it does not appear to have significant negative inotropic effects and is thus safe to use in patients with ventricular dysfunction. The authors have not used this drug in cats.

Mexiletine is another useful antiarrhythmic agent, but has become increasingly more difficult to find for veterinary patients and has several times come off the market. It is often used in combination with atenolol or sotalol for refractory arrhythmias or as an initial antiarrhythmic agent for dogs with systolic dysfunction. The authors have not used mexiletine as an antiarrhythmic in cats.

Although antiarrhythmics are usually successful at controlling clinical signs in animals with ventricular arrhythmias, their ability to decrease the risk for sudden death is uncertain. Recently, the use of implantable cardioverter defibrillators (ICD) has been investigated in dogs. These devices, which have similarities with pacemakers, are extensively used in people to terminate life-threatening episodes of ventricular tachycardia or fibrillation with high-energy electrical shocks. Accurate detection of arrhythmias amenable to electrical therapy is, however, still challenging in dogs. Advances in ICD technology and programmability may help to expand their use in veterinary medicine.

21

Supraventricular Arrhythmias

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Arrhythmias are classified as supraventricular or ventricular based upon the location of the cardiac tissues responsible for their occurrence. Supraventricular anatomic structures include the sinus and atrioventricular (AV) nodes, the His bundle, the atrial myocardium, the ostia of the coronary sinus, pulmonary veins and venae cavae (Figure 21.1).

Arrhythmias can be further divided into bradyarrhythmias (heart rate <60 bpm in dogs; <100 bpm in cats) or tachyarrhythmias (heart rate typically >180–200 bpm in dogs; >220–240 bpm in cats). Major bradyarrhythmias include sinus bradycardia, sick sinus syndrome (sinus node dysfunction), atrial standstill and atrioventricular (AV) blocks. Among tachyarrhythmias, atrial fibrillation (AF) is by far the most common. Other forms of supraventricular tachycardia (SVT) are less commonly encountered in clinical practice (Table 21.1).

Sinus Bradycardia

Etiology/Pathophysiology

Sinus bradycardia (or exaggerated sinus arrhythmia) is rarely a primary disorder and is usually benign in small animal patients. It results from an underlying disease responsible for excessive vagal tone, particularly gastrointestinal, respiratory, neurologic, and ocular diseases. Drugs (digoxin, opioids, calcium channel blockers, beta-blockers), hypothermia, and hypothyroidism are other extrinsic causes of sinus bradycardia. Though rare, sinus bradycardia, when diagnosed in an animal with impaired consciousness, should raise the suspicion of elevated intracranial pressure leading to brainstem compression. The clinical picture of this physiologic response, known as the Cushing's reflex, combines bradycardia, systemic hypertension and an abnormal respiratory pattern, characterized by periods of apnea.

Signalment

There is no breed or age predisposition. These animals are usually free of any underlying cardiac disease.

History and Clinical Signs

Most dogs and cats do not display clinical signs that can solely be attributed to sinus bradycardia. However, extreme cases of sinus bradycardia may cause lethargy and collapse.

Diagnosis

On the surface ECG, P-waves are accompanied by QRS complexes and the QRS complexes are in direct association with the preceding P-wave, such that the PR interval is relatively constant. The P-waves are typically positive in leads II, III, and aVF. When markedly elevated vagal tone is the cause for the bradycardia in dogs, a wandering pacemaker, which corresponds to a variation in the amplitude of the P-wave usually in relation to the respiratory cycle, may be present. The QRS complexes are usually narrow (duration <60 ms in dogs; 40 ms in cats) (Figure 21.2).

Therapy

Treatment is usually not necessary. However, vagally induced bradyarrhythmias respond to the administration of parasympatholytic medications. An increase in heart rate following the intravenous administration of atropine or glycopyrrolate confirms the contribution of excessive vagal tone to the bradycardia. Transient AV block frequently occurs following parenteral administration of atropine, most likely because of an initial blockade

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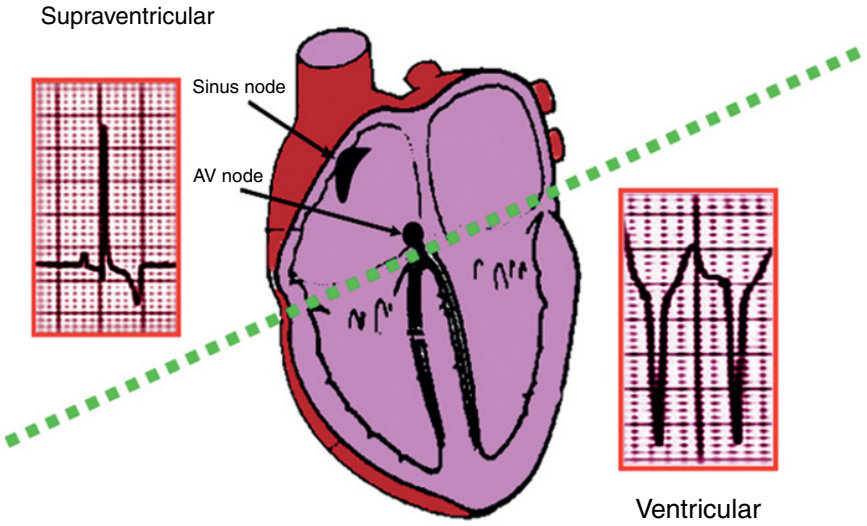


Figure 21.1 Supraventricular structures include the sinus node, the atrial myocardium, the atrioventricular node (AV node), the His bundle and the ostia of the veins entering the atria. Supraventricular rhythms are characterized by a narrow QRS complex, while ventricular rhythms are characterized by a wide and "bizarre" QRS complex.

Table 21.1 Differential diagnosis of supraventricular arrhythmias

	Rate (beats/min)	P-waves (II,III,aVF)	QRS complexes	P:QRS relationship	Regularity
Sinus bradycardia	<60 (D) <100 (C)	Positive Wandering pacemaker	Narrow	P before QRS 1:1	Regular, or regularly irregular (sinus arrhythmia)
Sick sinus syndrome	Variable pauses >3 s	Positive Negative Occasionally absent	Narrow Wide (VEB)	P before QRS	Irregular
Atrial standstill	20–60 (D)	Absent	Wide(VEB)	None	Regular
First-degree AV block	WNL	Positive Wandering pacemaker	Narrow	P before QRS 1:1	Regular, or regularly irregular (sinus arrhythmia
Second-degree AV block	WNL pauses	Positive	Narrow Wide(BBB)	P before QRS Isolated P	Irregular
Third-degree AV block	20–60 (D) 80–140 (C)	Positive	Narrow (JEB) Wide (VEB)	None	Regular
Atrial fibrillation	100–120 Lone AF 150–180 No CHF >180 CHF	Absent Fibrillation waves	Narrow Rarely wide(BBB)	None	Irregular
Focal atrial tachycardia	210–230	Positive Negative	Narrow Rarely wide(BBB)	P before QRS	Regular or irregular
Atrial flutter	180–350	Absent Flutter waves	Narrow Rarely wide(BBB)	None	regular or irregular
Junctional tachycardia	120–200	Negative	Narrow Rarely wide(BBB)	P during or after QRS	Regular
AV reciprocating tachycardia	190–300	Negative	Narrow Rarely wide(BBB)	P after QRS	Regular

AF, atrial fibrillation; AV, atrioventricular; BBB, bundle branch block; C, cat; CHF, congestive heart failure; D, dog; JEB, junctional escape beat; VEB, ventricular escape beat.

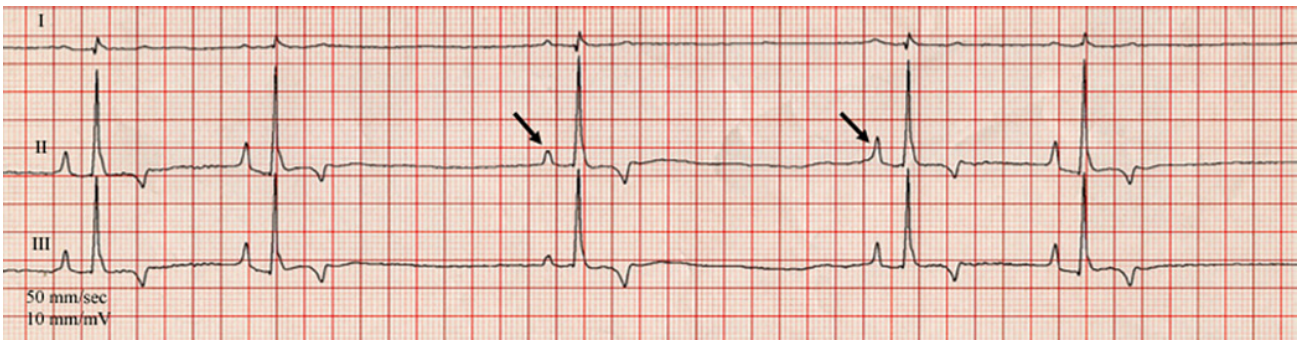


Figure 21.2 ECG of a healthy dog illustrating respiratory sinus arrhythmia with a wandering pacemaker (*arrows*).

of presynaptic muscarinic receptors that normally inhibit acetylcholine release. Once postsynaptic muscarinic blockade is established, this transient bradycardia resolves. The bradycardia subsides sooner after intravenous administration, due to a more intense chronotropic response than seen with subcutaneous and intramuscular injections. Side-effects associated with repeated injections of parasympatholytic agents, such as mydriasis, dry mouth, constipation, urinary retention, and on occasion neurologic signs, limit their chronic use.

Prognosis

In most cases, resolution of the extrinsic cause will be accompanied by a return to normal heart rate.

Sick Sinus Syndrome (Sinus Node Dysfunction)

Etiology/Pathophysiology

Sick sinus syndrome is a disease of the tissues of the conduction system characterized by periods of normal sinus rhythm or sinus bradycardia, interspersed with long periods of sinus arrest and a failure of the AV and ventricular pacemakers to initiate an escape rhythm. Lack of cardiac output resulting from a pause of approximately 6–8 seconds can lead to syncope. Histopathologic examination of the sinus node reveals degenerative changes characterized by the extensive replacement of nodal cells by fibrous and fibro-fatty tissue.

Epidemiology

Sick sinus syndrome is the indication for 15–25% of permanent pacemaker implantation in dogs. It has not been reported in cats.

Signalment

It affects older dogs with a higher prevalence in miniature schnauzers. It is also reported in pugs, cocker spaniels, dachshunds, West Highland white terriers, and other small terrier breeds. Females are at higher risk of developing sick sinus syndrome than male dogs.

History and Clinical Signs

Initially, dogs show signs of confusion, stumbling or episodic weakness, during which they become recumbent with no alteration of consciousness. These signs then progress to syncope, sometimes triggered by exercise or excitement. However, in the early stages of the disease, signs may be absent or limited to a decrease in activity level.

Diagnosis

Physical Examination

Physical examination frequently reveals periods of bradycardia, asystole or short runs of tachycardia followed by long pauses (Figure 21.3).

The presence of an apical systolic left-sided murmur on auscultation is common as these dogs are also predisposed to degenerative mitral valve disease.

Electrocardiography

Sinus arrest and sinus block cannot be differentiated, and are identified as a prolonged pause without a P-wave on the ECG. A variant of the disease, sometimes called bradycardia-tachycardia syndrome, is characterized by periods of paroxysmal SVT followed by a period of asystole, caused by the temporary failure of the sinus rhythm to resume when the tachycardia abruptly terminates.

A partial or adequate increase in heart rate in response to atropine is common in these dogs and does not rule out the presence of sick sinus syndrome, particularly when there are ECG findings compatible with the syndrome in the face of syncopal episodes. However, the use of opioids and other sedatives frequently results in a worsening of the periods of asystole. It is not uncommon that dogs which were asymptomatic while awake become hemodynamically unstable after sedation or while under anesthesia.

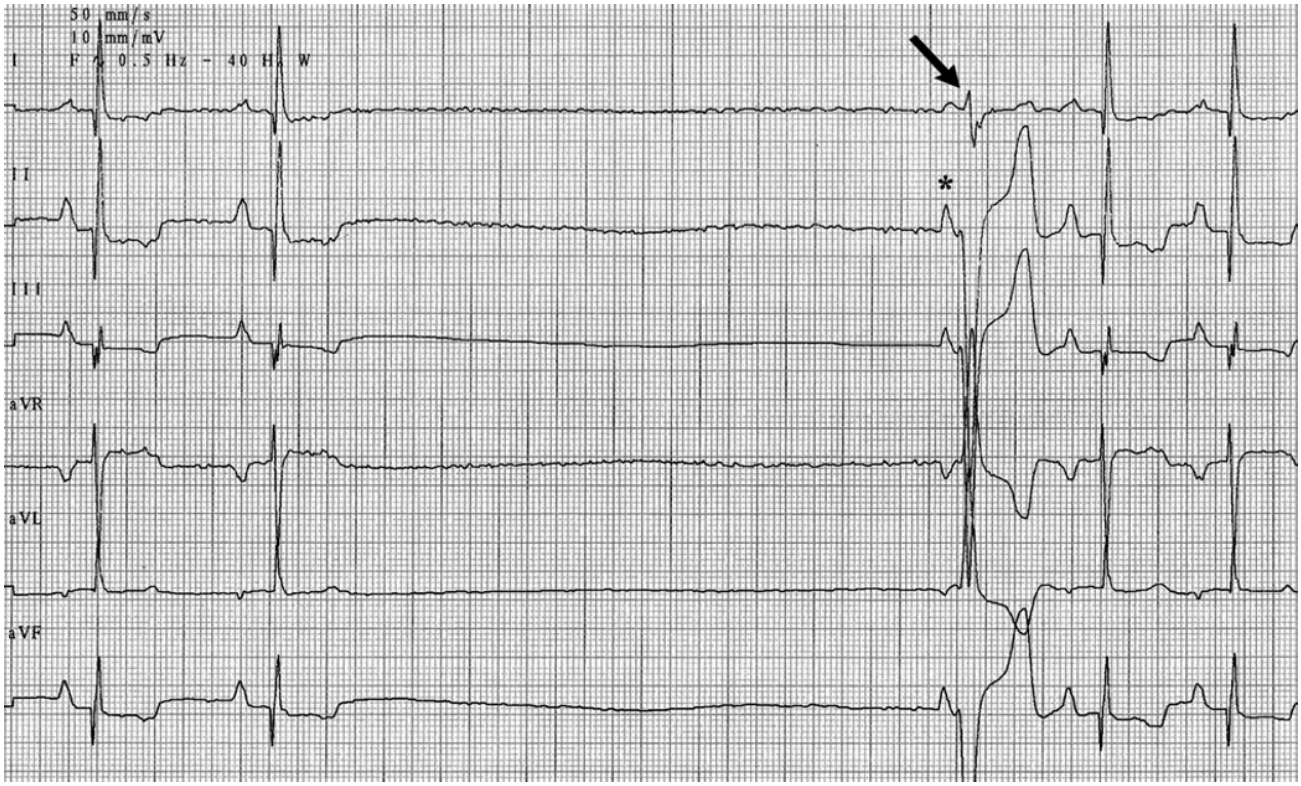


Figure 21.3 Six-lead ECG of a dog with sick sinus syndrome. After the first two sinus complexes, there is an unexpected 2.3-second pause that is terminated by a ventricular escape beat (*arrow*). Note that the propagation to the ventricles of a P-wave (*) is prevented by the occurrence of the escape beat.

Therapy

Medical Therapy

Two drugs are occasionally successful at temporarily increasing heart rate and alleviating clinical signs in dogs with sick sinus syndrome. Terbutaline is a selective beta-2-agonist commonly used as a bronchodilator. Aminophylline or theophylline is a phosphodiesterase inhibitor and bronchodilator with mild chronotropic effects. See Table 21.2 for drug dosages.

Pacemaker Therapy

Long-term management of sick sinus syndrome requires permanent pacemaker implantation. The goal of pacemaker therapy is to stimulate a heartbeat when necessary in order to maintain the heart rate within a predetermined range that optimizes cardiac output. The basic function of a pacemaker is to deliver an electric current to the heart that triggers contraction. Modern pacemakers also sense the intrinsic cardiac electrical activity, only delivering an impulse if the native conduction system fails to depolarize (Figure 21.4).

For optimal cardiac performance, the pacing system should mimic normal physiology as closely as possible. Therefore, atrial pacing when AV nodal function is unaffected by disease may be preferred in order to maintain synchrony between atrial and ventricular activity. However, the simplest and most commonly used type of pacing in veterinary patients involves a single lead placed in the right ventricle via the jugular vein.

Prognosis

Sudden death is rare in dogs with sick sinus syndrome. However, long-term quality of life is typically diminished with medical therapy alone. Conversely, permanent transvenous pacemaker implantation alleviates clinical signs in the majority of dogs with sick sinus syndrome.

Persistent Atrial Standstill

Etiology/Pathophysiology

Persistent atrial standstill, or "silent atrium," corresponds to the absence of atrial tissue depolarization and contraction, despite normal sinus nodal activity. Histologically, extensive fibrosis extends throughout the atria. It may occur secondary to the progression of

Table 21.2 Drug dosages and indications

Drug name	Dosage	Indications
Atropine	SC, IM, IV: 0.02–0.04 mg/kg (D, C)	Sinus bradycardia Sick sinus syndrome, First- and second-degree AV block
Glycopyrrolate	SC, IM, IV: 0.005–0.01 mg/kg (D, C)	Sinus bradycardia Sick sinus syndrome, First- and second-degree AV block
Terbutaline	Oral: 0.2 mg/kg q8–12h (D) 0.625 mg q8–12h (C) IV: 0.01 mg/kg IV (D, C)	Sinus bradycardia Sick sinus syndrome
Isoproterenol	CRI: 0.04–0.09 µg/kg/min, to effect (D,C)	Second- and third-degree AV block
Aminophylline/ Theophylline	Oral: 10 mg/kg q12h (extended release) (D, C) IV: 10 mg/kg (D)	Sick sinus syndrome
Digoxin	Oral: 0.005 mg/kg q12h (D)	AF (rate control)
Diltiazem	IV bolus: 0.1–0.4 mg/kg over 5 min (D, C) CRI: 0.05–0.15 mg/kg/h (D, C) Oral: 1–2 mg/kg q8h (D, C) 3 mg/kg q12h (extended release) (D) 15–30 mg q12–24h (extended release) (C)	SVT (rate control or conversion) AF (rate control)
Atenolol	Oral: 0.2–1 mg/kg q12-24h (D) 6.25–12.5 mg q12–24h (C)	SVT (rate control or conversion) AF (rate control)
Esmolol	IV bolus: 0.2–0.5 mg/kg over 1 min, repeat q5min (D, C)	SVT conversion
Procainamide	IV bolus: 5–15 mg/kg over 1 min (D) 1–2 mg/kg (C) CRI: 20–50 µg/kg/min (D)	SVT conversion
Lidocaine	IV bolus: 2 mg/kg over 30 s. Maximum 3 boluses (D) 0.25–0.5 mg/kg (C)	SVT conversion Vagally mediated AF conversion
Sotalol	Oral: 1–3 mg/kg q12h (D, C)	SVT conversion SR maintenance

AF, atrial fibrillation; AV, atrioventricular; C, cat; CRI, constant rate infusion; D, dog; IM, intramuscular; IV, intravenous; SC, subcutaneous; SR, sinus rhythm; SVT, supraventricular tachycardia.

primary cardiac disease, myocarditis, or as a manifestation of a neuromuscular disorder. However, the etiology often remains unknown.

Hyperkalemia is described as a cause for transient atrial standstill. Other possibilities include quinidine or digoxin toxicity, myocardial infarction, hypoxia, and hypothermia.

In the presence of persistent atrial standstill, the combination of chronic bradycardia, lack of atrial contribution to ventricular filling and decreased atrial natriuretic peptide production results in low cardiac output, increased circulating blood volume, and ultimately heart failure.

Epidemiology

It is a rare arrhythmia in dogs, and there are only a few documented cases in cats.

Signalment

Atrial standstill has been identified in various dog breeds, with a possible higher prevalence in English springer spaniels. It usually affects young adults, but can be diagnosed as early as 4–6 months of age. Most cats diagnosed with atrial standstill have echocardiographic changes consistent with hypertrophic cardiomyopathy.

History and Clinical Signs

Most animals show signs of low cardiac output, including profound lethargy and syncope, in addition to evidence of left- or right-sided congestive heart failure. In rare cases of muscular dystrophies, progressive skeletal muscle wasting may occur.

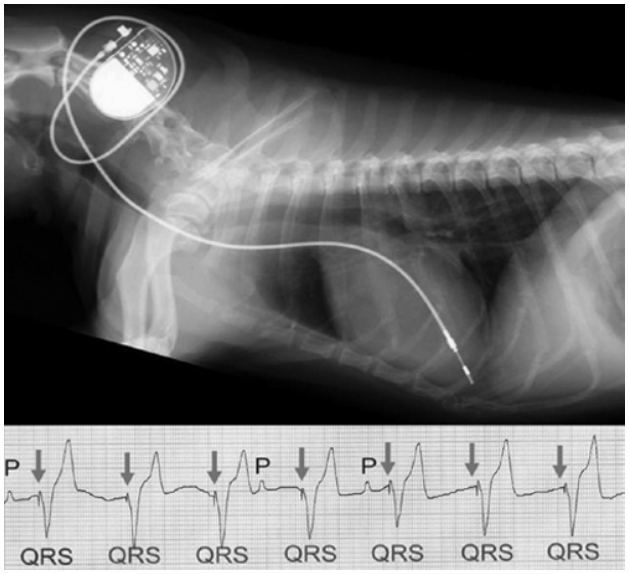


Figure 21.4 Permanent transvenous pacemaker in a dog with third-degree atrioventricular block. The upper panel is a lateral radiographic view of the thorax showing a transvenous lead implanted in the right ventricular apex and connected to a pacemaker generator secured subcutaneously in the region of the neck. The ECG tracing in the lower panel shows regular right ventricular pacing (*arrows*) and occasional P-waves that are dissociated from the ventricular complexes. Note that the QRS complexes are wide and "bizarre" and preceded by a pacing spike.

Diagnosis

Electrocardiography

The ECG of persistent atrial standstill is characterized by a lack of P-waves with a regular ventricular or AV nodal escape rhythm, at a rate of 20–60 bpm in dogs. In cases of transient atrial standstill from hyperkalemia, a narrowing of the T-wave and an increase in its amplitude occur when plasma potassium concentration increases above 5.5–6 mmol/L. As potassium concentration continues to rise, it leads to bradycardia associated with reduced P-wave amplitude and a widening of the QRS complexes. The P-waves then disappear, mimicking the ECG of persistent atrial standstill (Figure 21.5). Another term used to describe this rhythm disturbance associated with hyperkalemia is sinoventricular rhythm.

Echocardiography

On echocardiogram, mild to severe atrial dilation is present with no evidence of atrial contraction. Some degree of ventricular dilation is usually visible.

Therapy

Treatment relies on permanent transvenous ventricular pacemaker implantation.

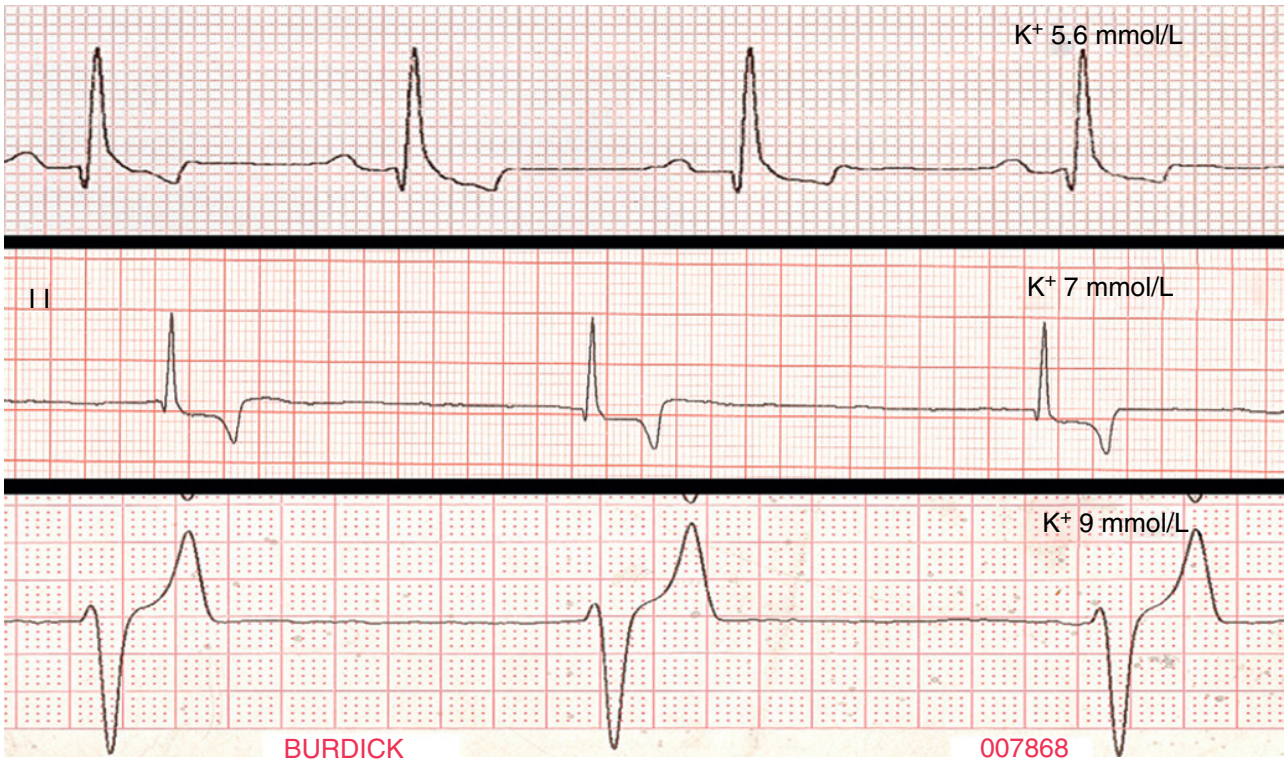


Figure 21.5 ECG strips of a dog with hyperkalemia. As serum potassium increases (top to bottom panel), heart rate decreases, QRS complexes widen, T-waves become tall and peaked, and P-wave amplitude decreases.

Prognosis

Myocardial damage usually progresses, extending to the ventricles. Most animals succumb within 12–18 months after initial diagnosis, despite pacemaker implantation.

Atrioventricular Block

Etiology/Pathophysiology

Causes of AV block include excessive vagal tone, AV node fibrosis, inflammation or infiltration, and potentially drug toxicity (calcium channel blockers, beta-blockers, or digoxin). Age-related fibrodegenerative changes in the AV node is the most common cause of AV block in dogs.

Epidemiology

Atrioventricular block represents between 60% and 80% of the indications for permanent pacemaker implantation in dogs. The prevalence of clinically significant AV block is much lower in cats than dogs. When AV block does occur in cats, it is typically associated with cardiomyopathy. Fortunately, feline escape rhythms are typically faster than canine (80–120 bpm) and pacing therapy is usually not required.

Signalment

Atrioventricular block is more common in geriatric pets. Most dogs are above 10 years of age at the time of diagnosis. Labradors, cocker spaniels, West Highland white terriers, beagles, German shepherds, springer spaniels, Cavalier King Charles spaniels, and dachshunds are overrepresented. Cats with high-degree second-degree and complete AV block are typically older than 10 years of age. There is no evidence of breed or sex predisposition in this species.

History and Clinical Signs

The hemodynamic effect of AV block depends on the rate of ventricular contraction. However, one-third of cats, and occasionally dogs, with advanced AV block may show no apparent signs, and bradycardia is detected on physical examination. More commonly, animals show signs of anorexia, lethargy, exercise intolerance, disorientation, episodic weakness, and syncopal episodes. Some animals develop right-sided congestive heart failure and, less commonly, left-sided congestive heart failure if the bradycardia is left untreated.

Syncopal episodes are rarely witnessed in cats with AV block and dyspnea is a more frequent chief complaint by owners of cats presented with AV block, whether congestive heart failure is present or not.

Diagnosis

Electrocardiography

There are three types of AV block. With first-degree AV block, all the atrial impulses are conducted to the ventricles, but the PR interval is prolonged on the ECG (PR >130 ms in dogs, >90 ms in cats). Second-degree AV block is diagnosed when some P-waves are not followed by a QRS complex on the surface ECG. Second-degree AV block is said to be high grade when the number of atrial impulses that fail to be conducted (P-waves not followed by a QRS complex) to the ventricles are more than the number of impulses that are conducted (P-waves followed by a QRS complex). Third-degree or complete AV block is characterized by an absence of conducted P-waves to the ventricles. The ECG displays independent atrial and ventricular activities (Figure 21.6).

Cardiac output is dramatically reduced. In response, the atrial rate, which is under adrenergic tone, is elevated. Electrical activation of the ventricles is dependent on an escape rhythm beyond the site of block. In dogs, the QRS complexes are generally wide and bizarre at rates around 20–60 bpm. In cats, the escape rhythm is usually seen as narrow QRS complexes, indicating their origin in the area of the His bundle, and it occurs at a rate of 80–140 bpm.

Finally, the ventricular rate is regular, unless ventricular premature beats originating from ischemic areas of myocardium are present.

Echocardiography

An echocardiogram is indicated to identify concomitant structural cardiac disease, which is frequent in cats with complete AV block. It is also essential to identify cardiac neoplasia that can infiltrate and disrupt the AV nodal tissue, to assess systolic function in the presence of myocarditis, and to determine the degree of volume overload secondary to chronic bradycardia.

Other Methods

Serum cardiac troponin I can be used to assess the degree of myocardial damage and raise a suspicion of myocarditis. Although a mild elevation of plasma cardiac troponin I level is common in dogs with complete AV block, marked increases suggest myocarditis as the cause for the AV block.

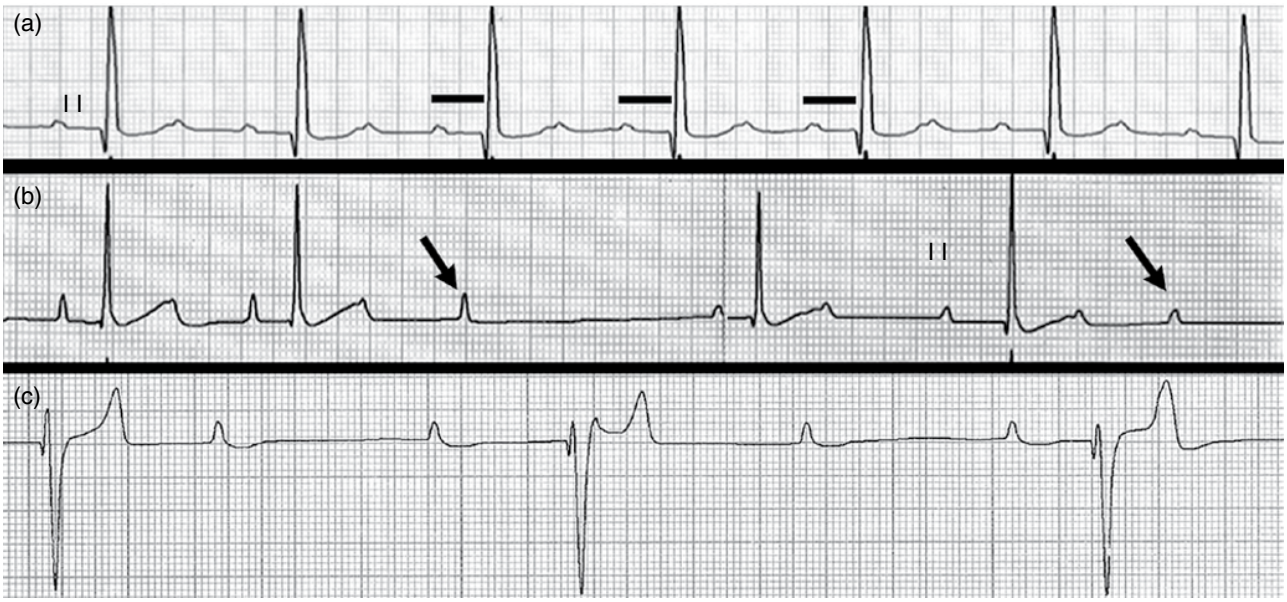


Figure 21.6 ECG strips of dogs with atrioventricular block. (a) First-degree atrioventricular block: there is a prolongation of the PR interval (180 ms, recording speed at 50 mm/s) and all the P-waves are associated with a QRS complex. (b) Second-degree atrioventricular block: the third and sixth P-waves (*arrows*) are not followed by a QRS complex, indicating an intermittent failure of the impulse to propagate to the ventricles. (c) Third-degree atrioventricular block: there is complete dissociation between the P-waves and the QRS complexes. The ventricles are activated by an escape rhythm at a rate of 37 bpm (recording speed at 50 mm/s).

Therapy

Medical Therapy

Sympathomimetic chronotropes increase heart rate by beta-adrenergic stimulation. Agents with beta-2 effects cause systemic vasodilation, whereas drugs with associated alpha stimulation cause vasoconstriction. Dopamine (5–10 µg/kg/min IV) and dobutamine (2–10 µg/kg/min IV) may contribute to an increase in heart rate and systolic function. They are usually administered as a continuous rate infusion and the dose is increased to effect. They are particularly indicated in the management of beta-blocker overdose. Isoproterenol, a pure beta-agonist, improves conduction in the AV node and the His–Purkinje system, which may result in the partial or complete resolution of AV block. It may also increase the rate of a ventricular escape rhythm in complete AV block, but usually with limited success. It is administered as a continuous rate infusion and its dose adjusted to effect. However, it causes a significant decrease in diastolic blood pressure via beta-2 stimulation. Finally, respiratory and metabolic acidosis decrease its effectiveness.

Pacemaker Therapy

Permanent ventricular pacemaker implantation is the treatment of choice for dogs and cats with clinical AV block.

Prognosis

In dogs, following permanent pacemaker implantation, estimated survival at one year is approximately 85%. Most dogs will usually die of noncardiac-related causes, unless concurrent progressive degenerative valvular disease or cardiomyopathy is present.

Pacemaker implantation may not be required in the vast majority of cats with complete AV block. Indeed, these animals have a median survival greater than one year without pacemaker therapy. Finally, the presence of underlying structural heart disease or congestive heart failure at the time of diagnosis may not significantly alter their prognosis.

Atrial Fibrillation

Etiology/Pathophysiology

Atrial fibrillation is characterized by uncoordinated atrial activation from multiple simultaneous electrical wavelets resulting in inadequate mechanical contraction and an irregular ventricular response rate. Atrial dilation is a risk factor for developing AF. However, it commonly occurs in large-breed dogs with only mild to moderate atrial dilation, and it is rarely present in small-breed dogs with degenerative mitral valve disease despite extreme atrial dilation. It is also rarely diagnosed in cats. Fibrosis, inflammation, and autonomic imbalances are other important contributors to the initiation of AF.

Epidemiology

In dogs, AF is one of the most common types of tachyarrhythmias that require treatment. Most dogs with AF

have underlying primary cardiac disease, in the form of dilated cardiomyopathy or degenerative mitral valve disease. Less commonly, "lone atrial fibrillation" occurs in giant-breed dogs with structurally normal hearts. Atrial fibrillation is rarely identified in cats but most cats with AF have underlying structural cardiac disease with atrial enlargement. Many of these cats also show signs of congestive heart failure.

Signalment

The vast majority of dogs with AF are giant- and large-breed dogs. In the giant-breed group, Irish wolfhounds, mastiffs, Newfoundlands, rottweilers, and Great Danes are overrepresented, with a male predisposition. Cats with AF are usually older males.

History and Clinical Signs

Most dogs with "lone" atrial fibrillation are asymptomatic. Conversely, some dogs with compensated cardiac disease and AF show signs of lethargy, exercise intolerance, and rarely anorexia, cough or syncope. When AF occurs in the presence of congestive heart failure, generalized weakness, dyspnea, cough, and abdominal distension from ascites are usually present. Cats frequently show signs of an underlying cardiac disease, including dyspnea and arterial thromboembolism. However, AF can also be an incidental finding on auscultation in this species.

Diagnosis

Physical Examination

On physical examination, AF is identified as a sustained and irregularly irregular rhythm accompanied with pulse deficits. A murmur may be ausculted, as severe underlying cardiac disease is common in dogs with AF.

Electrocardiography

On the surface ECG, AF is an irregular tachyarrhythmia, with usually narrow QRS complexes and no P-waves that can be replaced by an undulation of the baseline, or F-waves. It is also permanent, indicating that sinus rhythm never spontaneously resumes following initiation of AF. The average heart rate is typically above 180–200 bpm (Figure 21.7).

The rate is much lower with "lone" AF, usually approaching 100–120 bpm at rest. Although atrial fibrillation is a SVT, concurrent lesions of the ventricular conduction system (bundle branch block) may result in widening of the QRS complexes that may resemble those of ventricular tachycardia.

Ambulatory 24-Hour Holter Recording

Determination of the average ventricular rate during AF is critical information in deciding upon a treatment strategy. Unfortunately, brief ECG recordings obtained in an unfamiliar environment do not adequately reflect the daily variations of heart rate. Heart rate is therefore better assessed from a 24-hour Holter recording. For reference, the average heart rate of healthy dogs varies between 85 and 100 bpm. Conversely, it is approximately 120 bpm in dogs with "lone" AF, 155 bpm in dogs with underlying cardiac and 200 bpm in dogs with congestive heart failure.

Therapy

Treatment Strategy

A rate-control strategy is usually applied to the treatment of AF. This approach aims at slowing ventricular rate in response to the rapid supraventricular impulses which are bombarding the AV node. Control of the number of impulses, which are able to conduct through the AV node, will help in alleviation of clinical signs and prevention of further deterioration of ventricular function. However, it does not terminate the arrhythmia.

Rate-control is based on using drugs to decrease the ability of the AV node to conduct impulses. The need for pharmacologic control of the heart rate is determined from the heart rate distribution obtained from a baseline 24-hour Holter recording. The effect of rate-control drugs is then assessed on a follow-up Holter two weeks after treatment initiation. What constitutes adequate rate control has not been precisely defined and may depend on the animal's underlying myocardial function. Usually, an average heart rate of no greater than 120–140 bpm is considered adequate to observe clinical improvement. If the average heart rate is considered too high, drug dosages are increased by small increments with close monitoring of the animal's clinical status, as response to antiarrhythmics varies between patients. In contrast, medical therapy is usually not needed in dogs with "lone" AF. "Lone" AF can be successfully terminated via DC electrical cardioversion. However, there does not appear to be any benefit in converting the rhythm when adequate/appropriate rate-control therapy is effective.

Medical Therapy

Calcium Channel Blockers

Diltiazem is widely used for the management of AF. A graded dose of diltiazem results in a decrease in ventricular response rate, because of slower action potential propagation in the AV node. Oral formulations include an extended-release form. When evaluated for long-term management of AF, a dose of 3–5 mg/kg q12h PO of the extended-release formulation usually achieves satisfactory rate-control. Better rate-control, especially during periods associated with high adrenergic tone, can be obtained by adding digoxin to the treatment regimen. Calcium channel blockers decrease ventricular

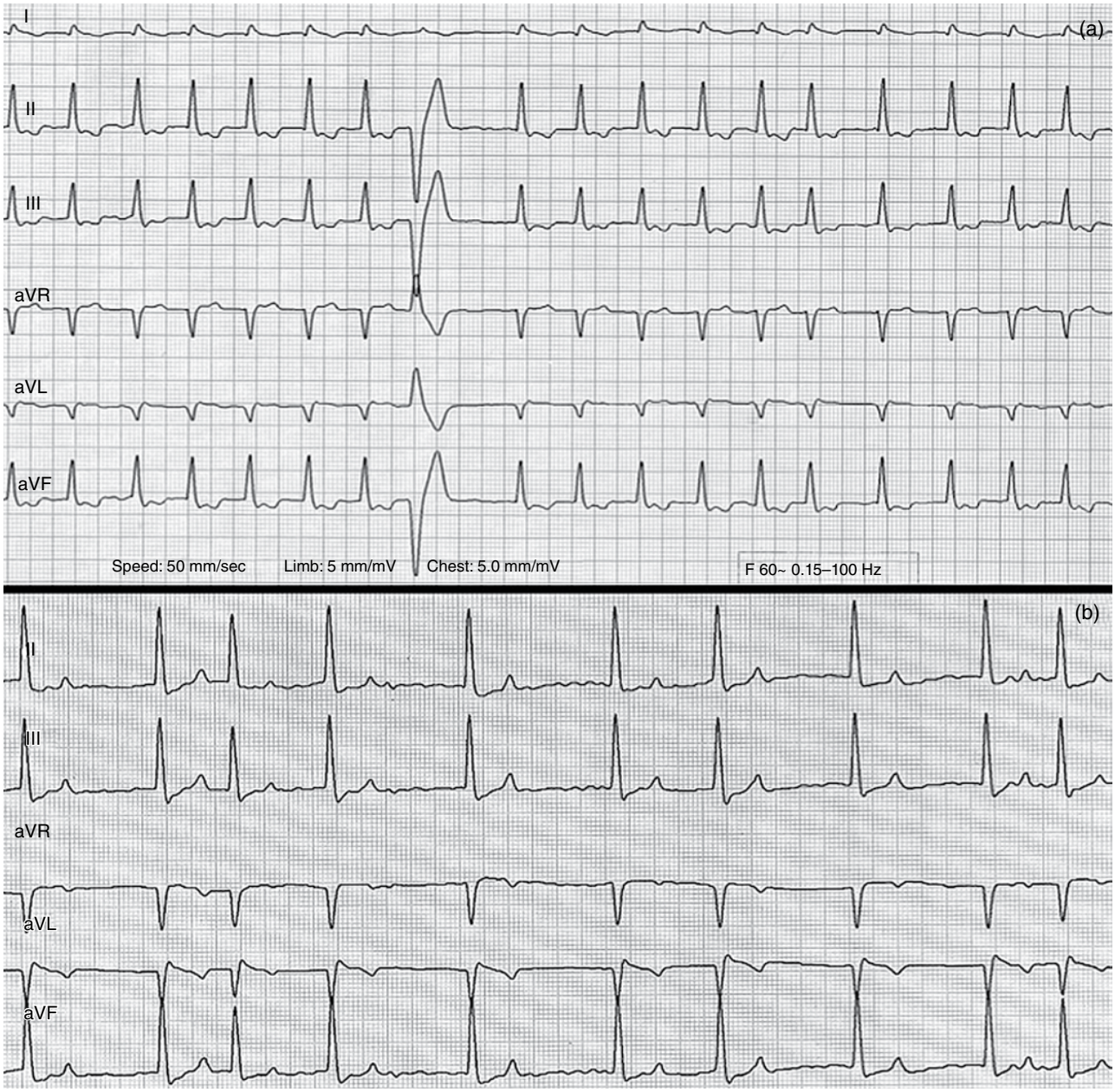


Figure 21.7 Six-lead ECG of a dog with atrial fibrillation (speed: 50 mm/s). (a) Atrial fibrillation appears as an irregular and narrow QRS complex tachycardia at a rate of 220 beats. Note that the eighty complex has a wide and "bizarre" morphology, suggesting it is a ventricular premature contraction (VPC). (b) Following administration of rate-control medications, atrial fibrillation is still present but the heart rate has decreased to 140 bpm.

contractility and may cause hypotension when used in animals with severely depressed cardiac function.

Beta-Blockers

The range of indications and side-effects for beta-blockers is very similar to that of calcium channel blockers. Beta-1-selective agents, such as atenolol, are preferred to nonselective agents that can cause bronchospasm.

Prognosis

Long-term prognosis is good for dogs with "lone" AF. However, in some breeds, in particular Irish wolfhounds, it may be considered an early sign of dilated cardiomyopathy. In AF dogs with heart disease, median survival has been reported to be 32 months. However, it was only five months when congestive heart failure was present. In cats, treatment targeted at AF is rarely required as their

ventricular response rate usually approaches the heart rate recorded in cats with sinus rhythm and heart failure.

Other Forms of Supraventricular Tachyarrhythmia

Etiology/Pathophysiology

Initiation of tachyarrhythmias requires a suitable substrate and precipitating factors. Interstitial fibrosis, inflammation, ischemia or atrial chamber dilation, combined with adrenergic stimulation and electrolyte abnormalities promote the risk for tachyarrhythmia. It is therefore expected that SVTs are commonly diagnosed in pets with heart failure.

Supraventricular tachyarrhythmias encompass focal atrial tachycardia, atrial flutter, focal junctional tachycardia, and atrioventricular reciprocating tachycardia. Focal atrial tachycardia is caused by the rapid and repeated activation of a small area of diseased atrial myocytes. Atrial flutter results from an electrical impulse circling rapidly and continuously around a large area of myocardium. Focal junctional tachycardia is caused by the rapid discharge of cells in the area of the AV node. Finally, atrioventricular reciprocating tachycardias result from the presence of an accessory pathway, which is a small strand of muscle tissue bridging the atria and ventricles through the cardiac skeleton and forming an alternative route of atrioventricular or ventriculoatrial electrical conduction besides the atrioventricular node. When conduction is also possible from atrium to ventricle, preexcitation may be identified during periods of sinus rhythm as short PR intervals and a widening of the initial portion of the QRS complexes (Figure 21.8). This finding confirms the existence of an accessory pathway. During episodes of atrioventricular reciprocating tachycardia, the impulse typically descends along the atrioventricular node to the ventricles and returns to the atrium using the accessory pathway.

Sustained tachyarrhythmias can lead to the development of heart failure, a phenomenon known as tachycardiomyopathy. It is likely that a sustained rate above

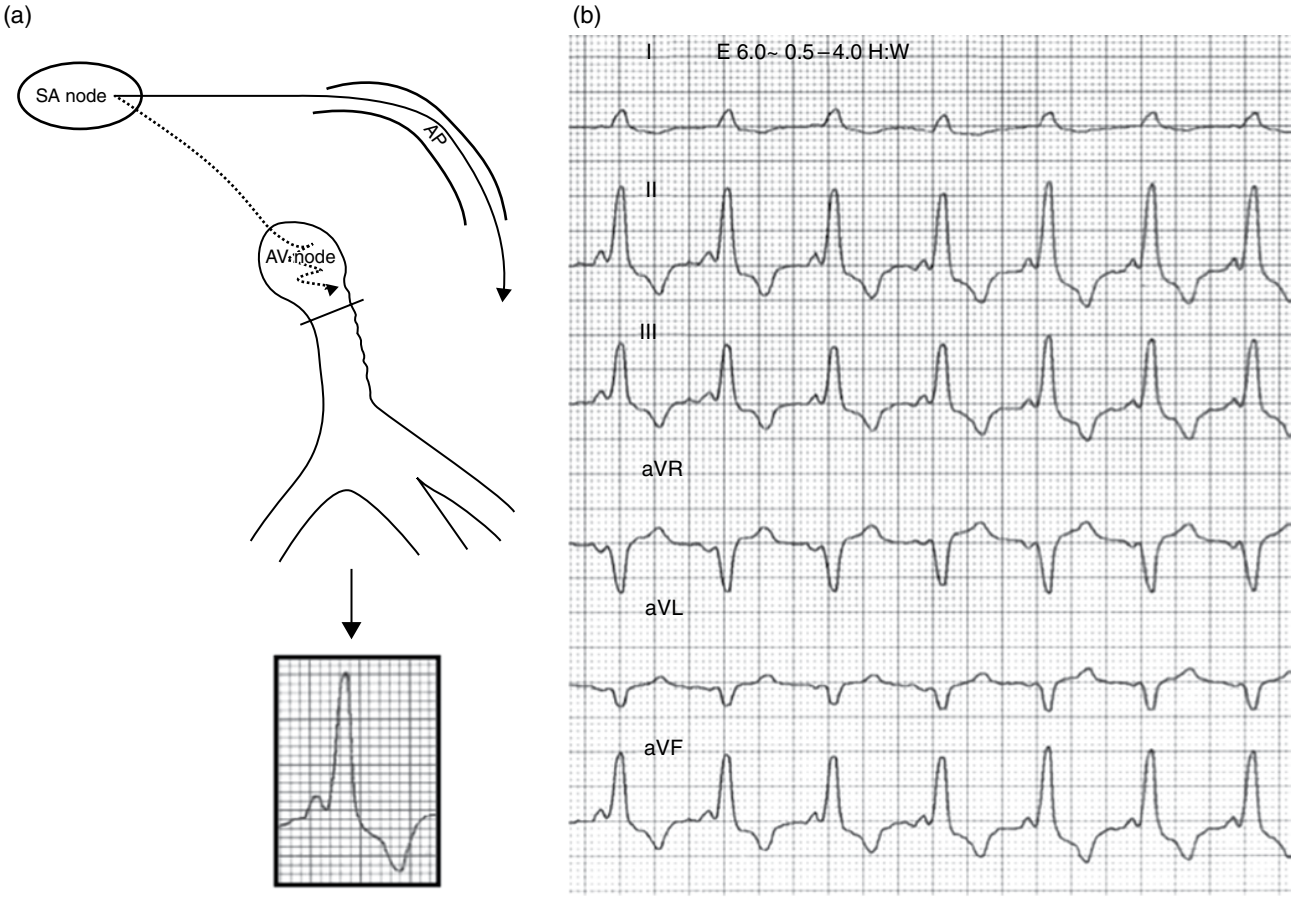


Figure 21.8 Ventricular preexcitation. (a) When a dog has an accessory pathway (AP), the sinus impulse may conduct simultaneously through the atrioventricular node and the abnormal muscle bundle. Ventricular activation is initiated without delay from the accessory pathway, resulting in a short PR interval and widening of the QRS complex. (b) Six-lead ECG of a dog with ventricular preexcitation.

250 bpm can induce severe myocardial dysfunction within 3–4 weeks in dogs.

Epidemiology

Supraventricular tachycardias other than AF are rare in both dogs and cats.

Signalment

Large- and giant-breed dogs, in addition to brachycephalic breeds, are more commonly diagnosed with SVTs. Tachyarrhythmias associated with an accessory pathway have more frequently been reported in Labradors.

History and Clinical Signs

Signs of SVTs include weight loss, lethargy, exercise intolerance, excessive panting, and dyspnea. However, it is not uncommon for dogs to be perceived as being nonclinical. Owners of dogs with SVTs may report "seeing" their pet's heart pounding in the chest during episodes of tachycardia. Weakness and transient loss of consciousness are less common with SVT. Additionally, SVTs may only be recognized at the time of physical examination in dogs with signs of congestive heart failure.

Diagnosis

Physical Examination

Cardiac auscultation is a useful diagnostic tool to calculate heart rate, detect occasional ectopic beats, and distinguish between paroxysmal and sustained arrhythmias. While paroxysmal SVTs are usually regular, SVTs may also be irregular. Some dogs experiencing episodes of paroxysmal SVT will be in sinus rhythm at the time of presentation. Femoral pulses may be weaker during bouts of tachycardia.

Electrocardiography

It is critical to differentiate supraventricular from ventricular tachycardia. However, treatment can be initiated without identifying the exact mechanism of an SVT.

The first step in the diagnosis of tachyarrhythmias is recognizing that an uninterrupted and irregular (a variation >100 ms between RR intervals) tachycardia is typically AF. Once AF is ruled out, SVTs must be differentiated from ventricular tachycardia by looking at the morphology of the QRS complexes. Ventricular tachycardias have wide QRS complexes (>0.06 s in dogs; >0.04 s in cats) followed by a large T-wave directed opposite to the QRS complex, whereas the main characteristic of SVTs is narrow QRS complexes, indicating that electrical impulses, once they reach the ventricles, propagate within specialized muscular bundles of the His–Purkinje conduction system, similar to normal sinus beats. However, on occasion, SVTs can display wide QRS complexes if a bundle branch block is present. In these challenging cases, the identification of P-waves associated with QRS complexes confirms the origin of the arrhythmia above the His bundle. P-waves can occur before, during or after the QRS complexes. They can be positive or negative. Oftentimes, P-waves are buried within the T-waves. Although rarely effective, vagal maneuvers can be done to slow AV conduction, revealing hidden P-waves associated to QRS complexes.

It is important to consider that ventricular tachycardias are much more frequent than SVTs. Following careful examination of the ECG, if uncertainty persists about the origin of a wide QRS complex tachycardia, it should be first treated as if it were ventricular tachycardia.

Ambulatory 24-Hour Holter Recording

The information collected from Holter recordings includes the number of episodes and their duration, the modes of arrhythmia onset and termination, and information about the overall heart rate, especially when the animal is in a familiar environment. Evaluation of heart rate distribution over 24 hours in the light of an activity log completed by the owner during the period of recording is a source of valuable information on the circadian pattern of the arrhythmia and on the contribution of adrenergic tone to the initiation and rate of the arrhythmia.

Echocardiography

An echocardiogram is useful to assess for the presence of structural cardiac disease and tachycardia-induced cardiomyopathy.

Therapy

Decision to Treat

Treatment is justified when SVTs cause clinical signs, which are directly related to their rate and duration, as well as ventricular performance. In the absence of obvious clinical signs, treatment should be considered if tachycardia-induced cardiomyopathy is suspected. When SVTs are intermittent, relating the clinical signs to the arrhythmia may be challenging. In that situation, long-term recording of the cardiac rhythm via ambulatory 24-hour Holter recording, or preferably with a wearable or an implantable loop event recorder, is indicated.

A rate-control or rhythm-control strategy, which consists of restoring sinus rhythm, can be applied to the treatment of SVTs. Drug selection is based on the type of arrhythmia, the risk of adverse reactions, and the degree of cardiac dysfunction. Other factors to take into account include decreased oral medication absorption, drug

metabolism and elimination in the presence of ascites, as well as decreased hepatic and renal blood flow that accompany heart failure. Moreover, drug selection may depend on the level of certainty regarding the nature of the arrhythmia. Indeed, it may be challenging to determine the origin of wide-complex tachycardias, which are characteristic of ventricular tachyarrhythmias but on occasion correspond to SVTs with aberrant intraventricular conduction. For example, drugs used for rate-control management of SVTs, in particular calcium channel blockers, may cause hemodynamic collapse if given in the presence of rapid ventricular tachycardia and would persist at a fast rate despite treatment. Besides the drugs used for chronic management, paroxysmal SVTs may require emergency intervention when they cause hemodynamic instability.

Acute Management

Antiarrhythmic drug administration should always be preceded by attempts to identify and eliminate potential triggers for the arrhythmia. This includes correcting electrolyte disturbances, hypoxemia, hypovolemia, and acidosis.

Common drugs used for the management of SVTs include calcium channel blockers (diltiazem), beta-blockers (esmolol), sodium channel blockers (procainamide, lidocaine), and drugs that combine several antiarrhythmic properties (sotalol).

Diltiazem

On occasion, diltiazem terminates SVTs if the arrhythmia mechanism is dependent on the AV node. Diltiazem can be administered as intravenous boluses and constant rate infusion for acute management of tachyarrhythmias.

Esmolol

Esmolol is a short-acting intravenous beta-1-selective blocker that is rapidly metabolized by blood esterases. It is used for rate-control and termination of AV node-dependent SVTs. However, it may be less effective than intravenous diltiazem.

Procainamide

Procainamide has been used for the management of SVTs. It is also indicated for acute management of broad-complex tachycardias, when discrimination between SVT and ventricular tachycardia is difficult, as it is also very effective in terminating ventricular arrhythmias. Unfortunately, it is no longer available in an oral formulation and the IV formulation has limited availability outside the United States.

Lidocaine

While lidocaine is extensively used as first-line therapy for acute termination of ventricular tachycardia, its use for treatment of SVT has only been reported recently. It has been shown to terminate episodes of SVTs in the presence or absence of an accessory pathway. Lidocaine has also been used successfully to terminate recent onset of paroxysmal atrial fibrillation initiated by elevated vagal tone in large-breed dogs with normal cardiac function. One to two boluses of lidocaine restored sinus rhythm within 30–90 seconds, while causing mild self-limited hypotension following the intravenous bolus.

Sotalol

Although availability of the IV formulation of sotalol is limited, the oral formulation can be used for acute management of SVTs, as most of them are not immediately life-threatening. Sotalol has potassium channel and mild beta-blocking properties, which make it a good option to terminate and prevent/decrease the recurrence of focal atrial tachycardias, atrial flutter, and AV reciprocating tachycardia. Conversion of those arrhythmias back to sinus rhythm usually occurs 2–4 hours after oral administration of the drug.

Long-Term Management

Termination of the arrhythmia and maintenance of sinus rhythm is the preferred approach for the long-term management of SVTs (rhythm-control strategy). It is more likely to succeed when limited structural cardiac changes are present. However, rate-control strategies used for the management of atrial fibrillation can also safely be applied to the control of most sustained SVTs.

Among various antiarrhythmic medications, sotalol has proven to be the most effective rhythm-control drug. Conversion to sinus rhythm usually occurs just a few hours after oral administration, but it can take up to a few days to observe a response. Sotalol is also effective at preventing arrhythmia recurrence. The negative inotropic effect of sotalol is modest compared to other beta-blockers. Nonetheless, dogs with myocardial failure should be closely monitored while receiving sotalol. Atrioventricular reciprocating tachycardia usually responds well to sotalol, which alters the electrophysiologic properties of all the cardiac structures necessary for the maintenance of this arrhythmia, including the accessory pathway, the atrial myocardium, the AV node, and the ventricular myocardium. In dogs that fail to respond to monotherapy, sotalol can be combined with mexiletine (5–7 mg/kg q8h) with better results.

Nonpharmacologic Treatment of Supraventricular Arrhythmias

Synchronized DC cardioversion and radiofrequency catheter ablation have been successfully used to treat supraventricular arrhythmias. In particular, dogs with AV reciprocating tachycardia show the best results with

radiofrequency ablation. The technique consists in identifying the location of the accessory pathway, usually around the tricuspid valve annulus, and delivering radiofrequency energy to permanently damage the tissue and block electrical conduction along the abnormal muscle bundle. However, the necessary equipment is available in only a few specialized veterinary centers.

Prognosis

Adequate rhythm or rate-control prevents complications, such as tachycardia-induced cardiomyopathy. When the arrhythmia terminates following the administration of antiarrhythmic medications, it is critical to monitor with frequent 24-hour Holter recordings for any signs of arrhythmia recurrence.

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22

Systemic Hypertension

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Etiology/Pathophysiology

Systemic hypertension (HT) describes a situation of sustained elevation of blood pressure (BP). Systemic hypertension is a clinical condition and should be considered a clinical complication of certain diseases rather than a disease in itself. In veterinary medicine, systolic blood pressure (SBP) is the value most often used to assess BP status in the conscious clinical patient, and systemic hypertension is typically diagnosed when reliable measures of SBP deliver values ≥160 mmHg. Clinically detectable damage caused by HT may be noted in the eyes, central nervous system, heart, and kidneys. Injury related to HT in these organ systems is often collectively termed "target organ damage" (TOD). Target organ damage may be clinically obvious, especially in the ocular or nervous systems. In other cases, TOD may be subtle and result in accelerated progression of deterioration of damaged organs (e.g., accelerated deterioration of renal function) rather than overt clinical signs.

In veterinary patients, systemic hypertension has typically been identified as one of three types: situational (so-called "white coat") hypertension, systemic hypertension secondary to systemic disease, and idiopathic systemic hypertension. Once situational hypertension has been ruled out, systemic hypertension secondary to systemic disease is more common than idiopathic hypertension. The designation of HT as "idiopathic" in a given patient is dependent on a thorough search for common diseases associated with HT.

Pathophysiology of Systemic Hypertension

The pathophysiologic mechanism(s) of any individual's elevated BP is likely related to the cause of the HT, but the specific pathways leading to sustained elevations in BP are poorly understood for most diseases. Blood pressure in health is modulated by interaction of diverse physiologic systems affecting the heart, kidney, brain, and vasculature. These systems rely on neural modulation (via the sympathetic nervous system [SNS]), hormonal modulation (e.g., renin-angiotensin-aldosterone system [RAAS], natriuretic peptides), vascular resistance modulation by circulating or local vasoactive mediators (e.g., endothelin, thromboxane, prostaglandins, etc.) and any structural changes (e.g., arteriosclerosis) that may be present. Abnormalities in any of these contributing factors or the interaction among these factors may alter arterial BP.

In health, increased BP typically leads to natriuresis in the normal kidney and lowering of systemic BP. No matter what the mechanism by which the initial elevation in BP occurs (e.g., catecholamine excess or alterations in RAAS activity), if "normalization" of elevated BP via natriuresis does not occur or is inadequate, abnormality in renal sodium handling is implied, and this may be the final common pathway for many etiologies of HT.

The fact that multiple and complicated pathophysiologic pathways are involved in modulation of BP and development of HT has three clinical repercussions. First, HT due to different diseases is likely to respond to different medications, based on the pathophysiologic pathway of the development of HT in an individual patient. Second, lack of complete understanding of these pathways limits our ability to apply specific physiologic blocks to lower BP, and nonspecific vasodilation becomes the treatment of choice for many cases of HT. Last, because any decrease in BP below the individual's current set point (normal or abnormal) is likely to stimulate reactive, BP-increasing responses from modulating systems like the SNS and RAAS, simultaneous blockade of these systems may be required when direct vasodilators are used in order to optimize response.

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Pathophysiology of Target Organ Damage

Arterial blood flow is maintained at relatively constant levels in the brain, kidneys, and eyes through a process of vascular autoregulation, wherein small resistance vessels constrict when BP is elevated and dilate when BP is decreased to maintain flow. Hypertensive damage in these organs occurs when these autoregulatory mechanisms fail. Elevated BP without adequate resistance vessel constriction causes overdistension of vessels, which leads to damage to endothelial tight junctions and allows protein and plasma leakage into interstitial tissue in affected tissue beds (i.e., tissue edema). If excessive vascular resistance vessel constriction occurs, ischemia of local tissues may result in focal hemorrhage and necrosis. Permanent structural changes such as arteriosclerosis may develop, decreasing vascular distensibility. Any combination of these mechanisms may result in clinical signs of TOD (Table 22.1).

Epidemiology

The most common diseases associated with HT in dogs include acute or chronic renal disease, especially protein-losing renal disease, hyperadrenocorticism, adrenal tumors, including pheochromocytomas and aldosterone-secreting tumors, and diabetes mellitus. The most common diseases associated with feline HT include chronic renal disease, feline hyperthyroidism, hyperaldosteronism, and diabetes mellitus. In both species, the suspected association (medical or age group related) between subclinical renal dysfunction and both diabetes mellitus and hyperthyroidism may partially account for the occurrence of HT in affected animals. Ten to 15% of hyperthyroid cats that are normotensive at the time of diagnosis may become hypertensive after successful therapy for hyperthyroidism, indicating other mechanisms of HT at work in these patients. The prevalence of idiopathic and situational HT remains unclear for both species.

Signalment

Systemic hypertension is associated with many diseases that are more common in older animals, but aging itself is not a cause of HT. In the case of secondary HT, the signalment of affected animals reflects groups at risk for the underlying disease. In cats, because two common

Table 22.1 Evidence of target organ damage. Clinical signs of target organ damage and additional recommended testing

Organ system affected	Associated clinical findings	Recommended diagnostic testing
Eyes	Acute blindness due to retinal detachment or severe hyphema Retinal hemorrhage Retinal vascular narrowing or tortuosity Focal retinal transudates Focal retinal ischemic degeneration Partial or complete retinal detachment Papilledema	Fundoscopic examination Coagulation/platelet assessment if hyphema or retinal hemorrhage
Brain	Seizures (focal facial or grand mal) "Stroke-like" intracranial neurologic deficits Decreased mentation/obtundation Photophobia Nystagmus	Complete neurologic examination Additional imaging (e.g., MRI)
Kidneys	Proteinuria Microalbuminuria Progressive decrease in renal function	Serum BUN and creatinine Complete urinalysis Urine culture Quantitation of proteinuria or albuminuria Advanced renal testing (e.g., GFR)
Heart	Left ventricular concentric hypertrophy Arrhythmia Gallop rhythm Systolic heart murmur Increased sensitivity to fluid loading (unexpected acute heart failure after fluid administration) Epistaxis	Auscultation Thoracic radiographs Echocardiography Doppler echocardiography may be required to rule out other causes of LV hypertrophy (e.g., subaortic stenosis) Assessment for coagulation/platelet abnormalities if epistaxis

Note: recommended testing list is not exhaustive, additional testing may be indicated in individual patients.
BUN, blood urea nitrogen; GFR, glomerular filtration rate; LV, left ventricle; MRI, magnetic resonance imaging.

diseases associated with HT are diseases of older cats (chronic kidney disease [CKD] and hyperthyroidism), the age distribution of hypertensive cats tends to include a greater proportion of older than younger patients.

History and Clinical Signs

Patients with HT are typically identified by BP measurements taken when a suspicious underlying disease or condition (e.g., proteinuria, hyperadrenocorticism) is diagnosed or suspected. Blood pressure should also be monitored in any patient receiving drugs that can cause vasoconstriction, such as phenylpropanolamine, a common medication for urinary incontinence that is responsible for BP elevations in some dogs. Additional HT patients are recognized when evidence of TOD (e.g., ocular hemorrhage, neurologic signs, gallop heart sound) is identified. In these patients, further evaluation (see Table 22.1) after diagnosis of HT may reveal the underlying cause. The clinical history of hypertensive patients may be consistent with the underlying disease (e.g., polyuria/polydypsia with renal disease), reflect TOD (e.g., acute blindness due to retinal detachment or obtundation due to increased intracranial pressure) or reveal use of hypertensive medications (e.g., phenylpropanolamine). Because of the high variability of clinical signs, and because changes in mentation and behavior due to HT may be subtle or attributed to aging changes, a high level of suspicion for HT should be maintained regarding possible reasons for and signs of HT in clinical patients.

Diagnosis

Patient Selection and Set-Up

Blood pressure should be measured in dogs and cats with diseases known to be associated with HT, and in those animals showing evidence of TOD. In both species, diagnosis or suspicion of renal disease (acute or chronic, proteinuric or nonproteinuric), adrenal neoplasias (e.g., pheochromcytoma or aldosterone-secreting tumors) and diabetes mellitus should lead to BP assessment. In cats, evaluation of hyperthyroidism should include BP assessment and BP should be reevaluated after successful therapy for hyperthyroidism. Similarly, suspicion of or diagnosis of hyperadenocorticism in dogs should include evaluation of blood pressure.

Animals with evidence of TOD (see Table 22.1) should have BP measured at the earliest opportunity regardless of underlying disease, so that intervention may ease or prevent further damage. If an animal with TOD is diagnosed as HT, antihypertensive therapy should begin immediately.

Nonspecific screening of patients for HT is not recommended. The prevalence of HT in healthy-appearing animals without causative disease is low, so many positive diagnoses of HT in this patient group will be false positives due to situational hypertension. Normal animals may be tentatively diagnosed with HT when elevated BP is a result of agitation or anxiety during BP evaluation. These animals may be identified as anxious during measurement, and repeat measurements later in the day or the following day after a period of acclimation may render more accurate results. Animals without causative disease or evidence of TOD may be accepted as normotensive if a confirmatory BP measurement after an initial HT measurement is within normal range. In most cases, animals with known causative disease or TOD and initially elevated BP are confirmed as "true" HT if confirmatory measurement is performed.

Commonly available methods to assess BP in dogs and cats include direct measurement (via arterial puncture or arterial cannulation) or indirect (noninvasive) methods, including Doppler sphygmomanometry and oscillometry. Although high-definition oscillometry (HDO) is now available, results may not be comparable to other methods and repeatable measurements may be difficult to obtain in awake cats. "Standard" oscillometry (widely available in stand-alone monitors or anesthesia monitors) or Doppler sphygmomanometry is currently recommended for clinical use.

Prior to BP measurement, the patient should be allowed to relax with minimal restraint for 5–10 minutes in a quiet area. The owner may help calm the animal during the measurement if appropriate. Systolic BP is typically used for clinical decision making and heart rate should be recorded in all patients. Notation of heart rate and any rhythm abnormalities may assist with full evaluation of the patient; tachycardia during BP measurement may signal increased patient anxiety, or provide additional information regarding underlying disease status (e.g., sinus tachycardia or arrhythmias in thyrotoxic cats). A gradually decreasing heart rate during measurement repetitions may occur in a patient that is slowly relaxing, and additional measurements at the lower heart rate may provide more accurate results than the initial measurements at a higher heart rate.

Methods of Measurement

Direct Blood Pressure Measurement

Direct arterial BP measurement is performed by inserting a needle or catheter attached to a pressure transducer into a peripheral artery in a clinical patient to obtain a pressure trace. Arterial cannulation using the dorsal

pedal artery is most frequently used for anesthesia and postanesthesia monitoring, but is typically impractical for clinical use on conscious patients for diagnostic purposes. Direct femoral puncture may be used for acute measurement of BP in conscious animals with local anesthesia, but is time-consuming and cumbersome in clinical practice.

Doppler Sphygmomanometry

Doppler sphygmomanometry (DS) is the most common method of measuring BP in cats and is also used commonly in dogs. A piezoelectric crystal attached to an audio amplifier is applied to the skin overlying a peripheral artery and an occlusion cuff inflated with a pressure bulb is positioned proximally on the same limb. The BP cuff is premeasured and sized such that the width of the cuff is approximately 40% of the circumference of the limb at the level of cuff placement.

In dogs and cats, the forelimb is the most common measurement site with the animal in lateral recumbency or sitting and the limb held at the level of the right atrium. The cuff is placed at mid-antebrachium and attached to the sphygmomanometer. The probe (with coupling gel) is held or taped in place over an artery distal to the cuff (usually the palmar arterial arch) and the position is adjusted until a clear pulsatile audio signal can be detected. The cuff is inflated to approximately 20–40 mmHg past the point at which the sound of blood flow is occluded and then slowly deflated. The pressure at which the sound signal reappears is recorded as the systolic BP. As the cuff is further deflated, the audio signal will become muffled – this pressure may be recorded as diastolic BP but is less reliable than the systolic BP by this method. Three to five repeated measurements taken approximately 30 seconds to one minute apart can be averaged to render a representative SBP.

Oscillometry (OSC)

Oscillometric BP devices deliver systolic, diastolic, and mean BP values as well as heart rate. These systems are most reliable in cats when a tailhead cuff is used in unrestrained sternal recumbency, but forelimb (radial level), hindlimb (metatarsal level or proximal to hock in recumbent animal) or tailhead (in standing or recumbent animals) cuffs may be used in dogs.

The cuff width is chosen similarly to the DS technique. The cuff is positioned with the bladder of the cuff (usually identified on the cuff by a small arrow) centered squarely over the artery and secured. The OSC machine is set to read BP at approximately one-minute intervals. The arithmetic mean of 3–5 SBP replicates is used as a representative value, with any obvious erroneous or outlying values discarded. OSC equipment may be unable to read BP accurately at high heart rates (>180 bpm) or if an arrhythmia is present, and a Doppler or invasive measurement system should be used in these patients. Doppler and OSC devices may not deliver the exact same results in a given patient, nor will different measurements sites in the same patient deliver the exact same results for SBP. Therefore, the same technique and the same cuff site should be used consistently in a given patient when monitoring BP over time.

Therapy

Acute or chronic HT may result in life-altering or life-limiting TOD and may affect the quality and therefore length of life in an affected patient. The goals of HT therapy are to stop or limit the extent of TOD in affected animals and to improve the quality of life in all patients. This may be accomplished by use of medications that decrease SBP and concurrent therapy of underlying causative disease. In all cases, control or resolution of the underlying condition is an important part of HT management.

Medical Therapy

The goal of therapy of HT is reduction of SBP to <160 mmHg, and ideally to 120–140 mmHg. Optimal therapy of HT usually involves use of a direct vasodilating agent (e.g., amlodipine or hydralazine) along with an agent to prevent reactive stimulation of the RAAS (usually an angiotensin-converting enzyme inhibitor [ACEI] or more recently, angiotensin receptor blockers [ARBs], e.g., telmisartan).

In *cats*, amlodipine (0.625–1.25 mg per cat PO q24h) is often successful as a single agent to control HT, with minimal side-effects in most patients. In *dogs*, ACEIs (enalapril or benazepril 0.25–0.5 mg/kg PO q12–24h) are useful in decreasing proteinuria commonly associated with HT and are typically considered a first-line agent to treat HT of any etiology. Angiotensin-converting enzyme inhibitors alone may not bring BP into the desired range in dogs and amlodipine (0.2–0.4 mg/kg PO q24h) or hydralazine (0.5–2.0 mg/kg PO q12h) may be added. The once-daily dosing regimen of amlodipine makes use of this drug more appealing than twice-daily dosing with hydralazine in most patients. Telmisartan has recently been approved for therapy of HT due to CRD in cats and expected decreases in SBP are similar to those expected with amlodipine therapy. Spironolactone (1–2 mg/kg PO q12h) has theoretical benefits in limiting RAAS activation in chronic HT, but studies supporting improved quality of life or survival outcomes with this medication are lacking at this time. Beta-blocking medications like

atenolol do not appear to provide reliable BP control, but may be useful to limit tachycardia in thyrotoxic cats. Alpha-blocking (e.g., prazosin) or mixed adrenergic-blocking medications (e.g., labetolol) have not been systematically evaluated in clinical veterinary patients.

In patients with evidence of acute TOD (e.g., intracranial neurologic signs or acute blindness due to retinal detachment), medications with quick onset of action should be used, with a goal of reducing the SBP by ~25% in the first few hours. The most commonly used rapid-onset medication for this purpose is hydralazine, which may have onset of action within 1–2 hours. Acutely, furosemide 1–2 mg/kg IV can be administered to nonazotemic patients, but this medication is not suitable for long-term therapy of HT. If continuous intravenous infusion is possible, sodium nitroprusside (typically diluted in 0.9% saline) can be administered beginning at a rate of 1–2 µg/kg/min with upward titration as needed to attain the goal of 25% reduction of SBP in the first few hours. Alternatively, fenoldopam, a selective dopamine-1 receptor agonist, can be delivered as a constant rate infusion (CRI) at an initial dose of 0.1 µg/kg/min, with doses titrated upward by 0.1 µg/kg/min at 15-minute intervals until the 25% reduction in SBP is reached, with a maximal infusion rate of 1.6 µg/kg/min. Constant BP monitoring is required when using sodium nitroprusside or fenoldopam due to the rapid onset of action and potent BP-lowering effects of these medications.

Some diseases (hyperadrenocorticism in dogs, hyperthyroidism in cats) may contribute to systemic hypertension through mechanisms that may be at least partially reversible with therapy for the underlying disease. In dogs with hyperadrenocorticism, successful medical or surgical therapy may be associated with decreased but not always normalized BP. Similarly, hyperthyroid cats that are hypertensive prior to therapy for hyperthyroidism may have normal BP after successful therapy for hyperthyroidism or maintain elevated BP. Additionally, cats successfully treated for hyperthyroidism may develop HT post treatment. In order to manage these complicated canine and feline HT cases, close monitoring of BP is recommended both before and after therapy of the underlying disease.

While no specific treatment protocols have been published, a reasonable approach to these patients follows the general approach to management of HT with some modification of follow-up decision making. Patients with these diseases and BP ≥180 mmHg may be considered to be at increased risk for TOD and despite plans to modify the underlying disease state, should be treated for their HT as other therapies commence. Once underlying disease therapy starts, the BP should be monitored periodically throughout the course of treatment until the underlying disease is alleviated or resolved. Blood pressure should be assessed again at this point, and consideration given to discontinuing the antihypertensive medication on a trial basis in normotensive patients (this should only be attempted in patients with no co-morbid risks factors and no evidence of TOD). In patients with pretreatment BP <180 mmHg, therapy of the underlying disease can commence without concurrent therapy of HT as long as no evidence of TOD is present, with post-treatment monitoring of BP recommended. Rechecking BP post therapy for feline hyperthyroidism should be performed regardless of pretreatment BP, since late-developing HT (i.e., 3–6 months post normalization of thyroid status) has been documented in these patients.

Monitoring

Use of higher doses of amlodipine or hydralazine or use of "normal" doses in debilitated animals may result in hypotension, which may be discernible as weakness, lethargy or mental dullness and prerenal azotemia. In most cases, discontinuing the medication for 1–2 doses and then decreasing the subsequent dosage administered will result in clinical improvement, but cautious fluid administration may be required to resolve azotemia. Amlodipine may cause gingival hyperplasia in some animals; discontinuation of this medication and substitution of hydralazine or telmisartan is recommended in affected animals. Use of ACEI in dehydrated animals may result in prerenal azotemia and occasionally hyperkalemia. Again, temporary discontinuation of ACEI and reinstitution when hydration is normalized should improve renal function.

Once target blood pressure has been achieved with therapy, routine monitoring at least every three months is recommended. Body weight and condition may change over time, requiring adjustment of BP medication dosing. In dogs, dosage increases may be necessary over time to maintain BP in the target range. In patients in whom improvement of SBP into target range is difficult, partial reduction of SBP should still be sought. The risk of TOD increases with increasing SBP, so even some degree of improvement may be beneficial.

Prognosis

Prognosis for improvement in HT and decreased incidence and degree of TOD is good in patients treated promptly and monitored closely. Animals with retinal detachment may regain some amount of vision but may not attain complete normality. Decreased proteinuria may be noted in

animals receiving ACEIs or ARBs. In many patients, improvement may be subtle, but noted by the patient's owner as improvements in wakefulness, interest in eating and interaction, and increased activity. Improvement in general quality of life is reported in many patients.

Proof of improved survival in treated veterinary HT patients is lacking, but because untreated TOD contributes to decreased quality of life, untreated HT may lead to euthanasia.

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23

Pulmonary Hypertension

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Etiology/Pathophysiology

Pulmonary hypertension (PH) is an elevation in systolic pulmonary arterial pressure greater than 30 mmHgI. Typically, PH is a complication of other primary diseases and occasionally occurs as an idiopathic process. Pulmonary arterial pressure is influenced by pulmonary blood flow, pulmonary vascular resistance, and pulmonary venous pressure. Ultimately, PH can be considered an umbrella term encompassing pulmonary arterial hypertension (precapillary PH) and pulmonary venous hypertension (postcapillary PH) (Figure 23.1).

Normally, the pulmonary vasculature is composed of thin-walled, low-pressure, high-capacitance, and low-resistance vessels. The pulmonary vasculature receives the complete cardiac output from the right heart with every contraction. Pulmonary hypertension results when there is an imbalance in pulmonary vascular mediators favoring vasoconstriction and muscularization of pulmonary arteries.

The three main components involved in PH development are the endothelin pathway, the prostacyclin pathway, and the nitric oxide pathway. In the presence of PH, the endothelin pathway contributes to the release of the potent vasoconstrictor, endothelin-1 from endothelial cells, resulting in pulmonary artery vasoconstriction, smooth muscle cell proliferation, and increased collagen synthesis. Prostacyclins, released by the pulmonary artery endothelium, normally mediates vasodilation, yet with PH, the vasodilatory effects are negated and the result is pulmonary artery vasoconstriction, cellular proliferation, and thrombosis. In the normal setting, nitric oxide release from vascular endothelium leads to an increase in vasodilatory cGMP. In the presence of PH, the nitric oxide pathway is deranged and results in vasoconstriction, smooth muscle cell proliferation and hypertrophy, platelet aggregation, and adhesion.

In addition to alterations in pulmonary vascular mediators contributing to PH, hypoxia also directly affects pulmonary vascular tone. Hypoxia (globally or locally) results in pulmonary artery vasoconstriction, which is in contrast to the systemic vasculature which vasodilates in response to hypoxia. Pulmonary artery vasoconstriction, in response to hypoxia, is a compensatory mechanism to divert blood away from hypoxic lung. Unfortunately, in the setting of PH, hypoxia from respiratory disease and left-sided congestive heart failure will worsen preexisting PH severity.

The vascular changes that result from the imbalance of these pathways promote muscularization of normally nonmuscular peripheral pulmonary arteries, medial hypertrophy, loss of peripheral pulmonary arteries, intimal proliferation, and vascular thrombosis. Ultimately, these vascular changes result in an increase in pulmonary vascular resistance leading to right ventricular hypertrophy that can result in congestive heart failure and death.

Epidemiology

Since PH usually occurs secondary to another disease process, the presence of PH in the population is potentially extensive. In reports of PH in dogs, the majority of cases result from left-sided heart disease (53%), pulmonary disease (28%), pulmonary thromboembolism (4%), heartworm disease (4%), congenital heart disease (i.e., left-to-right shunts) (3%), and miscellaneous causes (7%).

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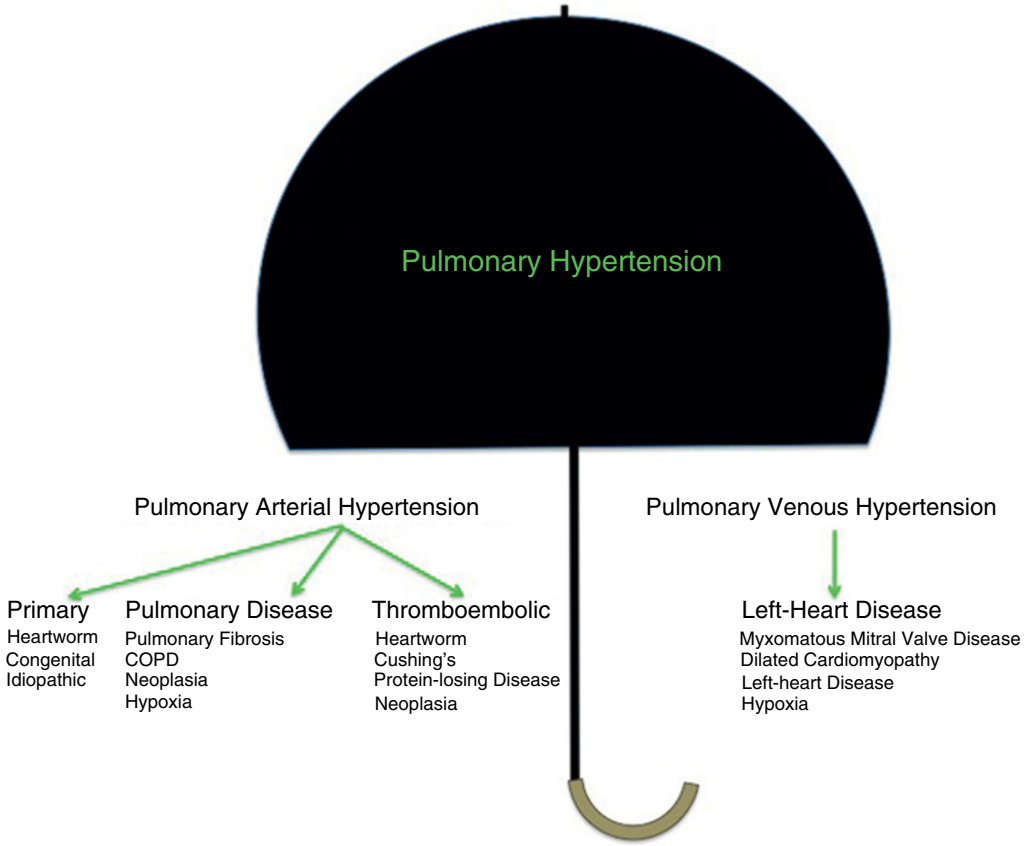


Figure 23.1 Pulmonary hypertension classification (see text for details). COPD, chronic obstructive pulmonary disease.

Signalment

The typical signalment of the patient with PH is a middle-aged to older small-breed dog, which reflects the population of dogs that are predisposed to myxomatous mitral valve disease and chronic pulmonary disease. The exceptions to this typical signalment include the young heartworm-infected dog and the dog with congenital heart disease that results in a reverse patent ductus arteriosus, reverse ventricular septal defect or reverse atrial septal defect.

History and Clinical Signs

The clinical history of the dog with symptomatic PH typically includes a combination of cough, dyspnea, lethargy, exercise intolerance, reported heart murmurs, ascites, and syncope. Because PH is often a consequence of underlying cardiac and pulmonary disease, it may be difficult to determine if the etiology of the clinical sign is a direct result of the PH or the underlying disease process.

Physical Examination

Dogs with PH often have abnormal physical examination findings that could be directly associated with increased pulmonary artery pressure or may be present secondary to the underlying disease process that resulted in the PH. These findings may include mitral and/or tricuspid insufficiency, heart murmurs, split or prominent second heart sounds, pulmonary crackles, cyanosis, and ascites. In most cases, detection of these abnormal physical examination findings in combination with typical clinical signs leads the clinician to suspect a diagnosis of PH.

Diagnosis

The goals of diagnosing PH include defining the underlying etiology of the PH, determining the severity of PH, assessing for evidence of right heart impairment, and to obtain information that may aid in patient prognostication.

Right Heart Catheterization

Right heart catheterization is the gold standard in diagnosing PH. Unfortunately, in veterinary medicine right heart catheterization is usually prohibitive due to the need for sedation and the unacceptable level of invasiveness required. Right heart catheterization provides true measurements of pulmonary artery pressure, right ventricular pressure, right atrial pressure, and pulmonary capillary wedge pressure. In addition, cardiac output measurements can be obtained to calculate pulmonary vascular resistance. Pulmonary vascular resistance (PVR) can be calculated by the following equation and expressed as dynes*sec*cm^{-5}.

$$PVR = \left[\left(mPAP - PCWP\right) \times 80\right]/CO$$

where mPAP indicates mean pulmonary artery pressure, PCWP is pulmonary capillary wedge pressure, and CO is cardiac output. Measuring and calculating mPAP, PCWP, and PVR help to determine the etiology of the PH. Based on these measurements, PH can be further classified as pulmonary arterial or venous hypertension. Pulmonary arterial hypertension can be diagnosed if the mPAP is increased, the PVR is elevated, and the PCWP is normal. Pulmonary venous hypertension can be diagnosed if the mPAP is increased, the PVR is normal, and the PCWP is elevated.

Thoracic Radiography

Pulmonary hypertension cannot be diagnosed by thoracic radiographs but there are specific changes associated with PH that, when present, would support the diagnosis of PH. Right heart enlargement, pulmonary artery enlargement, and pulmonary artery tortuosity are abnormalities that may suggest the presence of PH (Figure 23.2).

On the other hand, thoracic radiographs may only show changes that represent the underlying disease process that results in PH development (i.e., left-sided heart disease, left-sided congestive heart failure, primary pulmonary disease, patent ductus arteriosus). Noncardiogenic pulmonary edema can form as a direct result of PH and is typically in a patchy, diffuse alveolar lung pattern.

Electrocardiogram

The electrocardiogram is of limited use in contributing to PH diagnosis. If there are findings of a right axis deviation or evidence of right heart enlargement, this would help support the diagnosis of PH (Figure 23.3).

Echocardiogram

Echocardiography is the standard, noninvasive method for quantifying and diagnosing PH in veterinary medicine. Tricuspid regurgitation enables the clinician to estimate the systolic pulmonary artery pressure (Figure 23.4) and pulmonic insufficiency provides estimation of the mean and diastolic pulmonary artery pressures (Figure 23.5).

Based on tricuspid regurgitation, PH can be classified as mild (≥2.8 to <3.5 m/s, ≥31 to <50 mmHg), moderate (3.5–4.3 m/s, 50–75 mmHg) or severe (>4.3 m/s, >75 mmHg). Multiple two-dimensional, M-mode, and Doppler echocardiographic findings support the diagnosis of PH when tricuspid regurgitation is or is not present, and they include interventricular septal flattening (Figure 23.6), right ventricular hypertrophy, right ventricular dilation, decreased tricuspid annular plane systolic excursion, main pulmonary artery enlargement, abnormal pulmonary artery flow profiles, and decreased relative area change (a.k.a. distensibility index) of the right pulmonary artery.

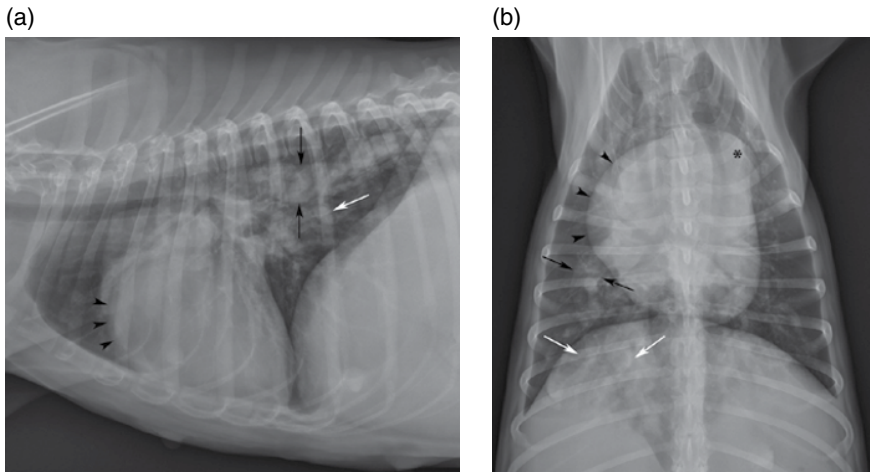


Figure 23.2 Thoracic radiographs from a dog with severe pulmonary hypertension from heartworm infection. (a) Lateral view. (b) Ventrodorsal view. Black arrowheads show the borders of the enlarged right atrium. * shows the enlarged main pulmonary artery. Black arrows show the borders of the severely dilated and tortuous right pulmonary artery. White arrows indicate the region of interstitial to alveolar pulmonary infiltrates.

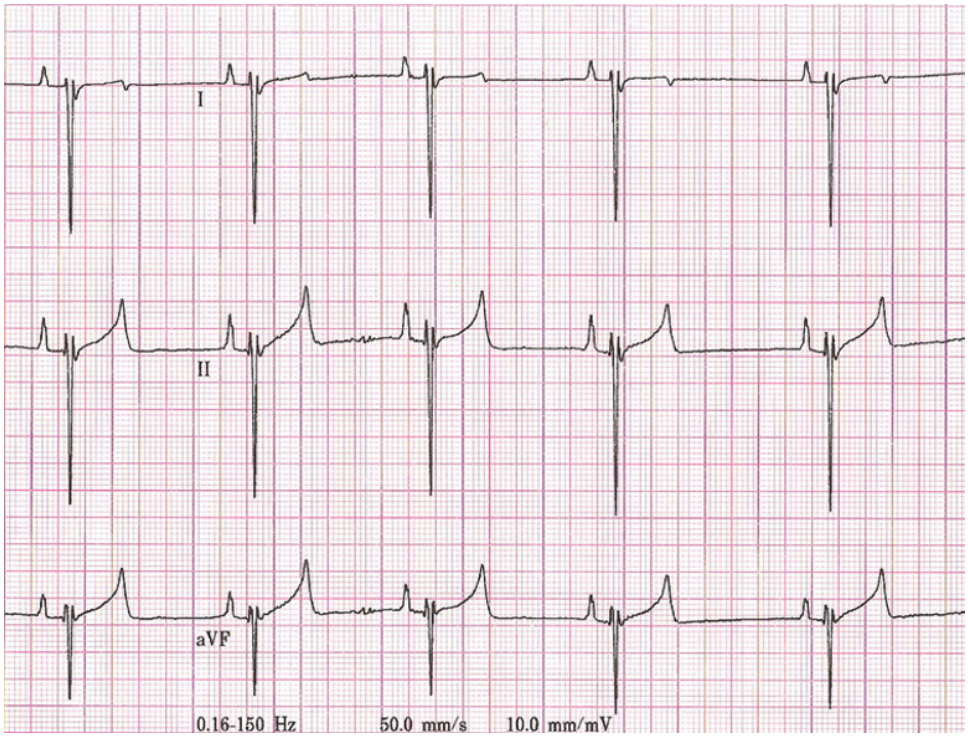


Figure 23.3 Electrocardiogram from a dog with severe pulmonary hypertension secondary to a reverse patent ductus arteriosus. Leads I, II, and aVF. 50 mm/s with a sensitivity of 10 mm/mV. Heart rate is 85 bpm. Sinus rhythm with evidence of right heart enlargement (deep S-waves in leads I, II, and aVF) and a right axis deviation.

(a) (b)

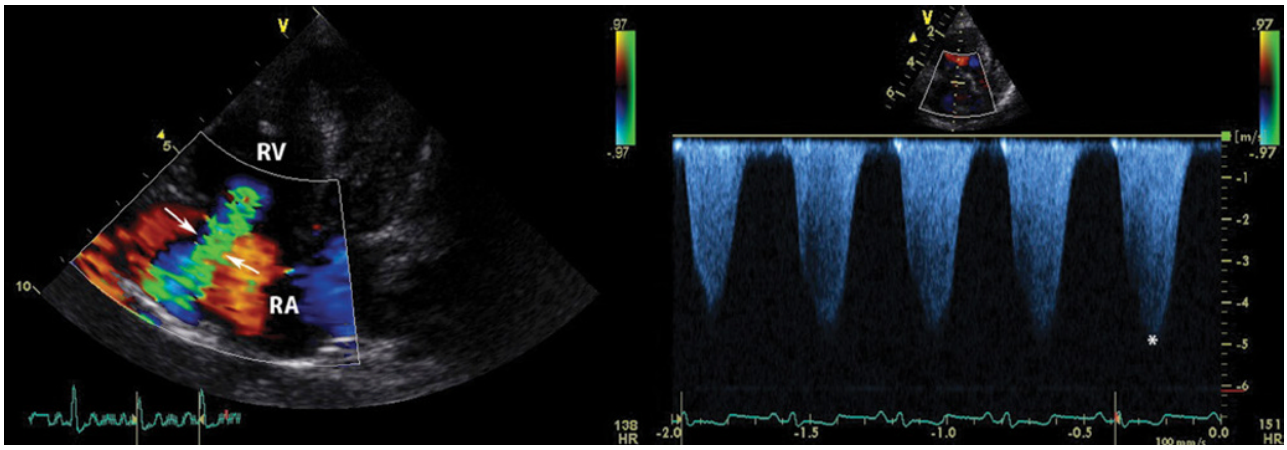


Figure 23.4 Tricuspid regurgitation in a dog with severe pulmonary hypertension secondary to intersitial lung disease. (a) Color Doppler showing tricuspid regurgitation. White arrows show the borders of the tricuspid regurgitation jet. RA, right atrium; RV, right ventricle. (b) Spectral Doppler of the tricuspid regurgitation jet. * indicates the peak velocity (4.8 m/s, 92 mmHg).

Therapy

The goals of treatment for patients with PH are to treat the underlying disease, improve clinical signs (i.e., exercise intolerance, cough, syncope, congestive heart failure), lower pulmonary artery pressure, improve right ventricular function, prolong survival, and improve quality of life. Since PH is a sequela of an underlying disease in many patients, treating the underlying problem is often the first step. Targeting the primary disease (i.e., medications for

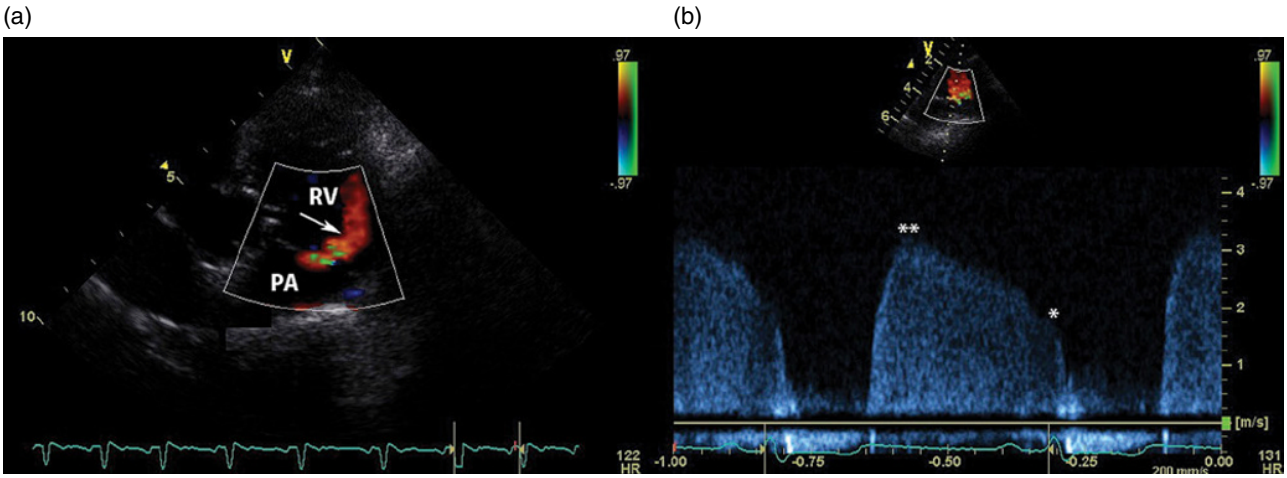


Figure 23.5 Pulmonic insufficiency in a dog with severe pulmonary hypertension secondary to interstitial lung disease. (a) Color Doppler showing pulmonic insufficiency. White arrow shows the pulmonic insufficiency jet. PA, pulmonary artery; RV, right ventricle. (b) Spectral Doppler of the pulmonic insufficiency jet. ** shows the peak velocity (estimated mean pulmonary artery pressure, 3.4 m/s, 46 mmHg) and * shows the end-diastolic velocity (estimated diastolic pulmonary artery pressure, 2 m/s, 16 mmHg).

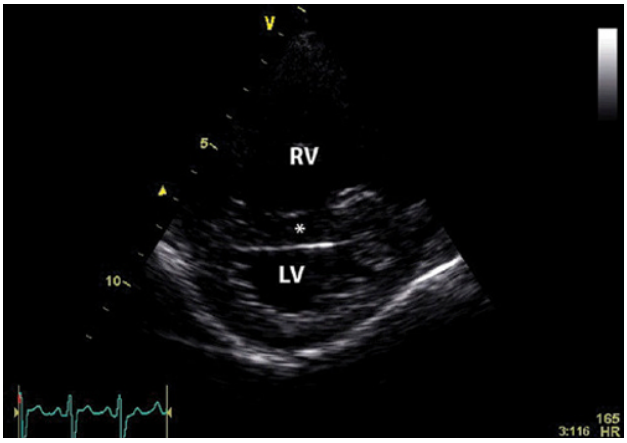


Figure 23.6 Septal flattening in a dog with severe pulmonary hypertension secondary to pulmonary neoplasia. Severe septal flattening at end-diastole indicating high right ventricular pressures. * shows the flat interventricular septum bowing over to the left side. LV, left ventricular lumen; RV, right ventricular lumen.

congestive heart failure, anticoagulants for pulmonary thromboembolism, oxygen for respiratory disease) in conjunction with directly lowering PA pressures is often necessary.

There are multiple treatment options that target the different pathways involved in PH. Unfortunately, in veterinary medicine many are extremely cost prohibitive (i.e., endothelin antagonists cost ~$50 000/year) or require frequent and impractical administration of medication (i.e., prostacyclins require a continuous rate infusion or 6–12 times daily dosing).

Sildenafil

Sildenafil (Viagra® and Revatio®) is a selective phosphodiesterase-5 inhibitor that specifically targets receptors in the pulmonary vasculature and results in pulmonary artery vasodilation. In dogs with PH, sildenafil is administered at a dose of 1–2 mg/kg orally q8h. Sildenafil has been shown to lower the estimated pulmonary artery pressures in dogs and to improve clinical signs, survival times and quality of life. For the most part, sildenafil has minimal side-effects (i.e., gastrointestinal upset) in most cases of PH, with the exception of left-sided heart disease. Sildenafil can lower the pulmonary artery pressure to a dangerous level in dogs with elevated pulmonary venous pressure, resulting in flooding of the pulmonary capillaries and subsequent congestive heart failure. In dogs with left-sided heart disease, sildenafil is indicated only if the patient is syncopal or in right-sided congestive heart failure and pimobendan should be considered a viable alternative treatment option in these cases as a pulmonary artery vasodilator.

Prognosis

The prognosis for patients with PH is variable and dependent on the underlying disease process. With the advent of sildenafil, the prognosis for PH in dogs has improved. Now that there is a viable treatment option, clinicians are more readily recognizing PH as a clinical syndrome in patients with clinical signs, physical examinations findings, and diagnostic testing results consistent with PH.

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24

Congenital Heart Disease

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Congenital heart disease (CHD) accounts for a small subset of dogs and cats presenting for veterinary care, estimated to account for less than 10% of cardiac disease in these species. However, the spectrum of CHD is broad and complex – making the diagnosis, treatment, and prognosis for these animals more challenging. Successful diagnosis and treatment of CHD provides great potential impact on patient survival – e.g., correctly diagnosing and closing a patent ductus arteriosus (PDA) can give an animal an additional decade or more of life. Since some forms of CHD are curable, it is imperative that animals with CHD not be missed during pediatric general examination.

Etiology

Causes of CHD

The precise etiology of CHD in nearly all veterinary species is not known. In humans, both genetic and environmental factors (drug use, toxin exposure, or infectious diseases during pregnancy) have been implicated in the genesis of CHD. In some breeds of dog there is a clear familial component, though the genetics have not been fully elucidated for any defect. Examples of diseases with a well-recognized inheritable component include patent ductus arteriosus (PDA) in the poodle, atrial septal defect (ASD) in the standard poodle and Doberman pinscher, subaortic stenosis (SAS) in the Newfoundland, pulmonary valve stenosis (PS) in the beagle, tetralogy of Fallot and related defects in the keeshond, ventricular septal defect (VSD) in the beagle and English springer spaniel, and tricuspid valve dysplasia (TVD) in the Labrador retriever.

The following paragraphs define some of the more common congenital heart malformations seen in animals as well as briefly describing the pathophysiology of such lesions. Figure 24.1 provides gross postmortem examples of several of these defects.

Left-to-Right Shunting Lesions

A shunt is defined as an abnormal mixing of blood in the heart or great vessels. The consequences of mixing between the left and right heart (shunting) vary depending on their magnitude and direction. In a left-to-right shunt (meaning from the systemic circulation to the pulmonary circulation) the signs are principally of volume overload to the lungs and the left heart because the normal amount of blood flowing to the lungs is augmented by the amount added from the shunt before returning to the left heart. Conversely, right-to-left shunts (where blood is diverted from the venous system to the systemic arterial system) result in poor oxygenation and cyanosis.

Patent Ductus Arteriosus

The ductus arteriosus is a normal structure in the fetus derived from the left sixth aortic arch and allows for the diversion of blood away from the lungs *in utero* when the lungs are not expanded by air. Within the first 12–24 hours after birth, the ductus begins to constrict in response to increased oxygen tension and is closed within the first week of life. If the ductus remains open, the fall in pulmonary vascular resistance allows flow from the aorta to the pulmonary artery. Persistent patency of the ductus arteriosus is the most common CHD of the dog and appears to be the second most common defect of the cat. Definitive therapy is an option for animals with PDA (via either interventional closure or surgical ligation) and long-term survival is excellent after closure if heart failure or frequent arrhythmias have not yet developed.

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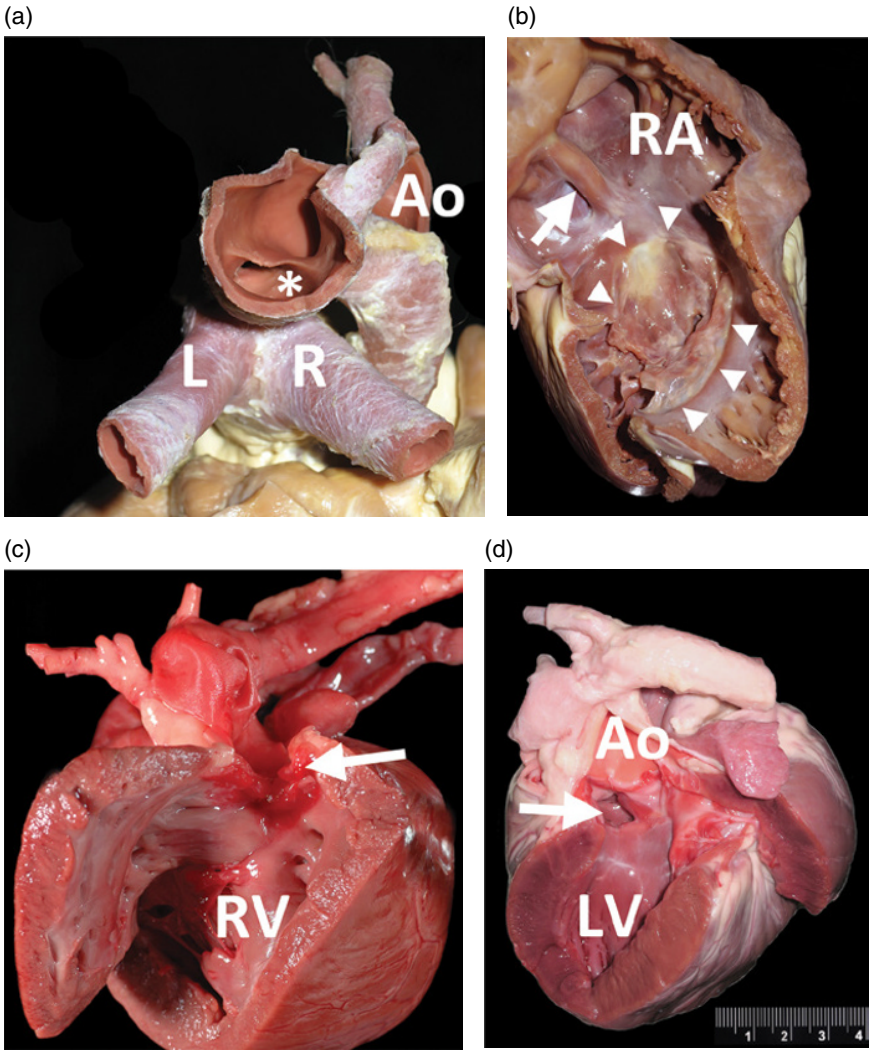


Figure 24.1 Gross postmortem specimens of common congenital heart defects. (a) A dog with patent ductus arteriosus; the image is taken from a caudal perspective with the descending aorta (Ao) coming toward the viewer. The origin of the ductus (*asterisk*) within the aorta can be seen traversing ventral toward the pulmonary artery, which is seen below as the left (L) and right (R) branches. (b) A dog with tricuspid valve dysplasia showing severe right atrial (RA) enlargement, a sheet-like tricuspid valve with fused, thick leaflets (*arrowheads*), and the ostium of a patent foramen ovale (*arrow*). (c) A dog with pulmonary valve stenosis showing moderate right ventricular (RV) hypertrophy and thickened pulmonary valve leaflets (*arrow*). (d) A dog with a large ventricular septal defect (*arrow*), seen in the membranous septum at the junction of the left ventricle (LV) and aorta (Ao).

Ventricular Septal Defects

Ventricular septal defects are the most common form of CHD in cats, and are also seen in ~9% of dogs with CHD. The pathophysiology of VSD is such that small defects (restrictive) may be well tolerated and not result in overt signs of cardiac dysfunction. Larger defects, however, result in the shunting of large volumes of blood from the left ventricle to the pulmonary circulation. The result of this increased pulmonary flow is damage to the lung vasculature and volume overload as the blood returns to the left heart. VSDs can occur in several different areas along the interventricular septum and numerous classification schemes have been developed to characterize the location of the defect. Exact confirmation of the size of the defect and secondary cardiac changes (e.g., aortic insufficiency or left ventricular enlargement) carry prognostic information for the clients. Additionally, some defects may be in a location amenable to catheter-based closure.

Atrial Septal Defects

As with a VSD, an atrial septal defect is a hole in the intracardiac septum separating the left and right heart. ASD is a rare defect in small animals, accounting for 2–6% of cases. In addition, it is often seen in association with other defects.

The degree of shunting depends on the size of the defect and the relative resistance of the pulmonary versus the systemic circulation. Typically, flow is driven from the left atrium across the ASD to the right, thereby increasing blood flow through the lungs. In contrast to left-to-right shunts such as PDA and VSD that result in left heart enlargement, atrial-level shunts cause right heart enlargement as the increased pulmonary venous return is shunted to the right atrium. With profound shunting, pulmonary hypertension and shunt reversal (Eisenmenger's physiology) may occur. Flow across the atrial septum may also develop if right atrial pressure becomes elevated, even in the presence of a normally formed atrial septum. This develops because the atrial septum is composed of two membranes that are closed during the first week of life as left atrial pressure exceeds right atrial pressure. If the animal has right-sided heart disease that elevates right atrial pressure (pulmonary stenosis, tricuspid dysplasia, tetralogy of Fallot), then the membranes may remain separate and allow flow across the atrial septum from right to left, referred to as a patent foramen ovale (PFO).

In the setting of a large ASD or concurrent defects, presenting signs will be an asymptomatic heart murmur, pulmonary overcirculation, or weakness, lethargy, or cyanosis associated with pulmonary hypertension and shunt reversal.

Atrioventricular Septal Defects

Defects of the atrioventricular septum (AVSD) may be considered separate from ASD or VSD. The atrioventricular septum is composed of centrally located tissue derived from the endocardial cushions. With an AVSD, defects may occur in the interatrial septum above the atrioventricular valves (a primum defect) or the interventricular septum just below the atrioventricular valves (inlet VSD), and may cause concurrent malformations of the atrioventricular valves. These defects were formerly referred to as endocardial cushion defects or defects in the atrioventricular canal. Signs vary depending on the relative size of each defect, but both congestive heart failure and cyanosis are common. AVSDs are relatively uncommon in dogs, but are seen in roughly 10% of cats with CHD.

The diagnosis is made by demonstration of the atrioventricular valves in the same imaging plane and variably sized defects in the ventral interatrial septum, inlet interventricular septum, and septal leaflets of the atrioventricular valves. There are also partial forms of AVSD recognized, depending on the presence/absence of atrial and ventricular septal defects as well as the degree of development of distinct mitral and tricuspid annuli.

Stenotic Valve Lesions

Subaortic Stenosis

Aortic stenosis occurs almost exclusively in the dog and is very rare in the cat. In almost all cases, obstruction is the result of subaortic tissue that narrows the left ventricular outflow tract. The tissue may be a discrete fibrous ridge or a tunnel-like narrowing. Rarely, valvar aortic stenosis is seen with fusion and/or thickening of the valve leaflets. In order to maintain forward stroke volume, such that the same volume of blood is pumped out of the left ventricle with each heartbeat, the blood must accelerate through the narrowing at a higher velocity. This requires that a greater left ventricular pressure be generated. The elevated left ventricular pressure leads to increased left ventricular wall stress and the development of concentric left ventricular hypertrophy.

The natural history of SAS includes a near normal lifespan for patients with mild disease; those with moderate to severe disease may experience exercise intolerance, syncope, left-sided congestive heart failure, or sudden cardiac death. All patients with SAS are believed to be at higher risk for development of bacterial endocarditis due to damage of aortic valve integrity from the turbulent, high-velocity jet. As such, antibiotic prophylaxis is advised for surgical or dental procedures, or in cases of potential bacteremia (e.g., skin laceration).

Screening young dogs for SAS bears some mention. First, SAS may progress as the dog grows because the subvalvar ridge does not change in size while the heart and stroke volume increase with the patient's development. Therefore, the final assessment of severity can only be made when the patient is full grown or nearly so. Second, screening breeding dogs for mild disease is a very real clinical problem as some breeds (boxer, greyhound, etc.) have aortic flow velocities that, with excitement, may be considered mild stenosis. This creates a gray zone between normal and mildly affected that can make breeding recommendations challenging.

Pulmonary Valve Stenosis

Pulmonary valve stenosis (PS) is principally a disease of the valve leaflets and/or annulus, rather than the subvalvar region as in SAS. PS comes in varying forms – fusion of the valve leaflets resulting in a narrowed orifice and doming valves, valvular thickening and dysplasia resulting in thick immobile valves that do not open normally, and annular hypoplasia where the valve annulus is abnormally small. The same hemodynamic derangements described above for SAS apply to the right ventricle in patients with PS. Right ventricular concentric hypertrophy is common and at times can be so severe as to create a dynamic and muscular subvalvar obstruction. In these instances, the right ventricle (RV) hypertrophies to such

an extent that it obstructs blood flow from getting out of the right heart during contraction.

The natural history of PS is more benign than for SAS, although patients may similarly suffer exercise intolerance, syncope, sudden cardiac death, and right-sided congestive heart failure if the disease is severe. Dogs with PS do not appear to be at an increased risk for endocarditis. Elevated right atrial pressure in the presence of a PFO may allow shunting of blood across the atrial septum from right to left and the development of cyanosis and secondary erythrocytosis. PFO is seen in ~30% of dogs with PS as the atrial septum does not close normally at birth due to elevated right atrial pressure. If flow from the right atrium to left atrium is substantial across a PFO, the animal may have significant mixing of poorly oxygenated blood from the right atrium to the left and clinical cyanosis.

Mitral and Tricuspid Valve Stenosis

Mitral valve dysplasia (MVD) and TVD may result in stenosis of these valves. Atrioventricular valve stenosis is rare in small animals, but both mitral stenosis and tricuspid stenosis are occasionally encountered in dogs and cats. These lesions lead to progressive atrial enlargement, atrial arrhythmias, and congestive heart failure if left untreated.

Regurgitant Valve Lesions

Mitral and Tricuspid Valve Dysplasia

Congenital malformations of the atrioventricular valves are considered rare in dogs, but account for a greater proportion of congenital heart disease in cats. Mitral valve dysplasia or TVD is a developmental abnormality of valve formation, resulting in abnormal leaflet shape, attachment, and/or function. Animals with MVD or TVD have pathology that typically results in regurgitation of the affected valve; however, a combination of stenosis and regurgitation may be encountered. Chronic mitral valve regurgitation leads to left ventricular and left atrial volume overload and dilation in the setting of MVD, which may lead to left-sided congestive heart failure. Similar progression may be seen in the right heart for TVD. Postmortem findings of dysplastic atrioventricular valves display fused and malformed leaflets with shortened chordae tendineae. Direct attachment from the papillary muscle to the valve is common.

Aortic and Pulmonary Valve Dysplasia

Congenital defects of the semilunar valves typically result in stenosis, as described above. In both SAS and PS, regurgitation, or insufficiency, of the affected valve is commonly observed by color Doppler imaging. Pulmonary valve insufficiency can even be seen in the majority of otherwise apparently healthy dogs when screened by Doppler echocardiography. However, aortic or pulmonary insufficiency is typically well tolerated and seldom of clinical significance. Rarely, cases of aortic or pulmonary valve dysplasia resulting in a predominantly regurgitant valve with severe insufficiency are detected, which may progress to cardiac decompensation.

Malformations of the Great Vessels

Vascular Ring Anomalies

Several malformations of the arterial system have been described in animals; the most common clinical presentation is a pediatric animal with dysphagia. The basic pathophysiology of these malformations is an embryologic defect resulting from abnormal persistence or regression of fetal vascular structures (aortic arches), ultimately leading to an abnormal spatial arrangement of the major intrathoracic arteries relative to the trachea and esophagus. Clinical signs are the direct result of extraluminal compression of the esophagus (resulting in megaesophagus, regurgitation, or aspiration pneumonia) and/or trachea (resulting in inspiratory stridor, coughing, or dyspnea). Persistence of the right aortic arch is the most common vascular ring observed in small animals. Therapy is directed at surgical decompression and transection of the offending structure, though esophageal dysfunction may persist if not corrected at a young age.

Cyanotic Heart Disease

Tetralogy of Fallot

Cyanotic heart disease is not common in small animals, but tetralogy of Fallot (ToF) is recognized in 2–6% of cases of CHD. ToF is the most common cyanotic CHD of humans and the four components of the tetralogy are right ventricular outflow tract obstruction, right ventricular hypertrophy, VSD, and dextroposition of the aorta. The underlying pathophysiology of this defect is believed to result from incomplete rotation and faulty partitioning of the developmental outflow tracts (comprising the distal portions of the left and right ventricles and the proximal portion of the great vessels). In simple terms, the aorta receives more of the embryologic tissue and aortic development occurs at the expense of the pulmonary trunk. Therefore, the ventricular septum cannot close because the aorta is enlarged and deviated to the right. The result of right ventricular outflow obstruction with a VSD is that deoxygenated blood is diverted to the systemic circulation, causing cyanosis, weakness, and collapse. Long-standing sequelae include erythrocytosis and blood hyperviscosity due to increased erythropoiesis.

Epidemiology

The prevalence of CHD in the dog and cat is difficult to quantify due to a lack of routine perinatal care, occurrence of conditions that are not apparent on routine physical examination, and hospital biases in published reports. The work of Detweiler and Patterson in the Philadelphia area suggested a CHD prevalence rate of 0.56% among 5000 dogs surveyed in the mid-twentieth century, while Buchanan found a rate of 0.67% for all dogs presented to the University of Pennsylvania between 1987 and 1989.

While the true prevalence of CHD in dogs and cats is unknown, there are data available evaluating the relative incidence of specific malformations in each species. The author compiled data from several studies in an attempt to summarize the relative prevalence of CHD in small animals. Ten applicable studies of CHD prevalence in dogs were found in the veterinary literature, comprising a sum of 4694 defects. When totaled, PDA (26%), SAS (24%), and PS (22%) were the most common and of nearly equal incidence. As such, these three diseases should be highest on a practitioner's differential list when listening to a puppy with a loud heart murmur; other congenital malformations of the heart are less common.

There are fewer data available about CHD prevalence in the cat. When evaluating several studies of CHD prevalence in cats, five studies covering 435 defects can be found. Ventricular septal defect appears to be the most common defect in the cat, comprising over 18% of cases. PDA is not generally considered a common disease in the cat, compared to the dog, but was noted in over 11% of defects. Dysplasia of the atrioventricular valves (mitral or tricuspid) each accounted for an additional 10% of defects. Feline CHD, therefore, should be considered distinct from and with a different incidence of common defects than canine CHD. Semilunar valve disease (PS and SAS) is exceedingly rare in cats.

Signalment

Age

Most animals with CHD present at a young age. However, adult animals with undiagnosed CHD may present later in life and often as a result of complications (heart failure, syncope, or cyanosis) from their cardiovascular disorder if it was not detected at an earlier age.

Sex

Both sexes are commonly afflicted with CHD, though sex predilections for some specific conditions have been identified. PDA has been reported to occur more commonly in female dogs, with a 3:1 female predominance. Pulmonary valve stenosis has not been recognized as having gender predominance except in the English bulldog, where males are more commonly afflicted than females. A male predominance for TVD has also been reported in the veterinary literature. In the cat, a male predominance has been suggested for atrioventricular valve malformation, aortic stenosis, and tricuspid valve dysplasia.

Breed

Numerous breed predilections have been reported for animals with CHD, particularly dogs. Table 24.1 shows a listing of common defects and the breeds known or suspected to have an increased prevalence of each defect. This table should not be considered authoritative or exhaustive, as spontaneous defects can occur in any breed at any time. Additionally, the incidence of CHD will likely change as breed populations continue to evolve. In the cat, few breed predilections are recognized other than endocardial fibroelastosis, which is reported to have a higher prevalence in Burmese and Siamese breeds.

History and Clinical Signs

Animals with complex defects or severe CHD may present within the first days to weeks of life due to failure to thrive, dyspnea, cyanosis, or syncope. It is likely that most puppies and kittens with severe cardiac malformations die early in life and prior to veterinary examination. The common history for dogs and cats with CHD is that of an asymptomatic pet with an appointment for a wellness exam, deworming, and vaccination. Auscultation during the physical examination of these patients is often the first and earliest clue that CHD may be present – as such, careful and thorough examination of all young animals is advised.

Diagnosis

Auscultation

Screening for congenital cardiac disease typically begins with a thorough physical examination performed at the first general health examination. Auscultation is imperative for screening of CHD as the most common forms of CHD typically present with a systolic (SAS, PS, VSD, TVD) or continuous (PDA) murmur. Auscultation in puppies and kittens should be performed in a quiet room with appropriate restraint and sufficient time devoted to a thorough examination.

Table 24.1 Breed predilection of common congenital heart defects in the dog

PDA	SAS/AS	PS	VSD	ASD	MVD	TVD	ToF	Vasc Ring
Australian shepherd	Bouvier de Flandres	Airedale terrier	Beagle	Boxer	Bull terrier	Boxer	English bulldog	Cocker spaniel
Bichon frise	Boxer	American Staffordshire terrier	Brittany spaniel	Doberman pinscher	German shepherd	German shepherd	Keeshond	German shepherd
Cavalier King Charles spaniel	Bull terrier	Beagle	Chow chow	Standard poodle	Golden retriever	Golden retriever	Wire-haired fox terrier	Great Dane
Chihuahua	Dogue de Bordeaux	Boxer	English bulldog		Great Dane	Great Dane		Irish setter
Cocker spaniel	English bulldog	Boykin spaniel	English springer spaniel		Mastiff	Labrador retriever		
Collie	German shepherd	Bull mastiff	French bulldog		Newfoundland	Old English sheepdog		
English springer spaniel	Golden retriever	Cavalier King Charles spaniel	German shepherd		Rottweiler	Weimeraner		
German shepherd	Great Dane	Chihuahua	Keeshond					
Keeshond	Newfoundland	Cocker spaniel	Newfoundland					
Kerry blue terrier	Rottweiler	English bulldog	Samoyed					
Labrador retriever	Samoyed	French bulldog						
Maltese		Miniature schnauzer						
Miniature poodle		Pittbull terrier						
Newfoundland		Samoyed						
Pomeranian		Terrier crosses						
Rottweiler		West Highland white terrier						
Shetland sheepdog		Yorkshire errier						
Toy poodle								
Yorkshire terrier								

AS, valvar aortic stenosis; ASD, atrial septal defect; MVD, mitral valve dysplasia; PDA, patent ductus arteriosus; PS, pulmonary valve stenosis; SAS, subaortic stenosis; ToF, tetralogy of Fallot; TVD, tricuspid valve dysplasia; Vasc Ring, vascular ring anomaly; VSD, ventricular septal defect.

For dogs, all valve areas should be evaluated, including the mitral valve area on the left thoracic wall where the apical impulse is felt most strongly, the semilunar valve area (aortic and pulmonary valves) at the left heart base (the ventral 2nd–4th intercostal spaces), the area of the great vessels just dorsal to the left heart base, and the tricuspid valve area on the right thoracic wall. In the cat, localization of individual valve areas is more problematic and auscultation is usually directed along the left and right sternal border, moving from caudal to cranial on either side.

Murmur location and intensity are useful in differentiating between types of CHD as well as for distinguishing a physiologic or innocent murmur from that caused by CHD. Left and right apical systolic murmurs are commonly due to atrioventricular valve regurgitation and, in a young animal, if an apical systolic murmur is heard, defects of MVD and TVD should be considered most strongly. The murmur of a typical membranous VSD is harsh and systolic at the right sternal boarder. Left basilar systolic murmurs can be more problematic as they can indicate either an innocent murmur or CHD such as SAS, PS, or ASD. High-intensity murmurs (grade IV–VI or louder) usually indicate the presence of significant CHD regardless of location and are an indication for more advanced diagnostics. However, less intense murmurs (grade III–VI or less) may originate either from CHD or an innocent cause.

Evaluating left basilar systolic murmurs with a rubric of the 6 Ss (Table 24.2) can be useful to try and guide the need for additional diagnostic testing. In general, a soft left basilar systolic murmur heard in a young puppy or kitten that decreases in intensity over the first months of life and/or disappears by 6 months of age is likely to be innocent. If the murmur is loud or harsh, continuous or diastolic in duration, or associated with concurrent cardiac signs (arrhythmia, cough, syncope), then CHD should be considered more likely and further testing should be advised.

Other aspects of a cardiac physical examination include evaluation of the mucous membranes, jugular veins, and pulse quality. Mucous membranes should be evaluated for evidence of cyanosis, which may be indicative of a right-to-left intracardiac shunt. Very poor peripheral perfusion can be suggested by pale mucous membranes and/or a prolonged capillary refill time even in the absence of an obvious heart murmur. Hypokinetic femoral pulses are commonly detected in moderate to severe SAS, while a hyperkinetic pulse quality is suggestive of a wide pulse pressure from PDA or severe aortic insufficiency. Jugular pulsation with or without distension can suggest tricuspid regurgitation or elevated right-sided pressures due to tricuspid valve dysplasia, PS, or pulmonary hypertension from severe left-to-right shunting defects.

Additional Diagnostic Tests

While the physical examination is an important aspect of screening for the presence of CHD, it is difficult to make a definitive diagnosis from signalment and physical examination alone. Ancillary diagnostic tests, like thoracic radiography and electrocardiography (ECG), may be useful in narrowing the differential diagnostic list and determining disease severity, but can also add cost to the initial evaluation without providing definitive diagnostic information. In current veterinary practice, echocardiography with Doppler is considered the gold standard diagnostic test for confirmation of CHD.

Table 24.2 An auscultation rubric, the six Ss, for evaluation of a left basilar systolic murmur in a young animal to help determine the likelihood that the murmur is physiologic or innocent versus pathologic

Descriptor	An innocent or physiologic murmur is more likely	Significant congenital heart disease is more likely
Sensitive	The murmur is absent or much softer at rest; it changes with position or phase of respiration	The murmur is present at rest or with activity; it can be heard at all times
Short	The murmur is of short duration, predominantly early systolic	The murmur remains loud throughout nearly all of systole
Single	There are no other associated abnormal heart sounds or physical exam abnormalities; no clicks, gallops, or arrhythmias are heard	Additional auscultatory abnormalities are present and/or there are other physical exam abnormalities
Small	The murmur is localized to the left base or one single location, it does not radiate	The murmur radiates from the point of maximal intensity
Soft	The murmur is soft or quiet; generally grade I or II out of VI	The murmur is loud, generally grade III–VI or louder
Systolic	The murmur duration is limited to systole	The murmur is continuous or a diastolic component can also be appreciated

Source: Adapted from Bronzetti and Corzani (2010) with permission of SAGE Publications.

Electrocardiography

Electrocardiography may be beneficial in detecting cardiac changes related to CHD, though is most useful for characterizing dysrhythmias heard on auscultation. CHDs that cause ventricular enlargement, such as PS and SAS, may provide a substrate for ventricular arrhythmias secondary to myocardial ischemia. However, ECG is a more specific rather than sensitive test as animals with CHD may have a normal ECG. Figure 24.2 shows examples of rhythm disturbances that may be seen in the setting of CHD. Again, it should be noted that such findings are supportive of a diagnosis, but not definitive.

Thoracic Radiography

Similar to ECG, thoracic radiographs provide useful supplementary information in the evaluation of a patient with suspected CHD. However, thoracic radiography is most useful when the veterinarian suspects an animal's heart disease has decompensated and resulted in pulmonary edema or pleural effusion. If signs of respiratory compromise or cough are apparent on examination, thoracic radiographs are strongly advised. In the asymptomatic animal with a murmur, however, they are less specific than echocardiography in confirming a diagnosis. Figure 24.3 provides examples of radiographic evidence of decompensated heart failure secondary to CHD.

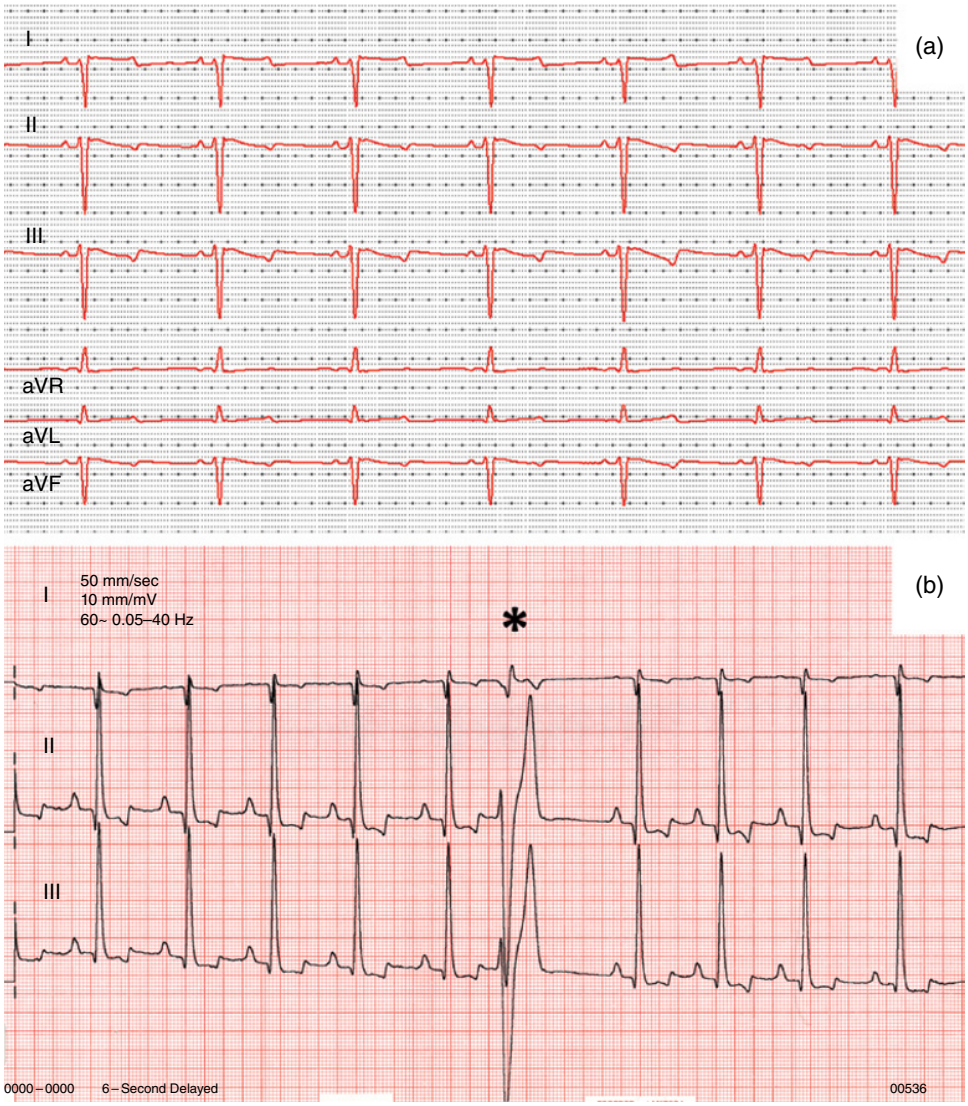


Figure 24.2 Example ECG traces from two dogs with congenital heart disease, recorded at 50 mm/s paper speed, calibration of 1 cm/mV. (a) Six-lead ECG from a 1.5-year-old miniature pinscher with pulmonary valve stenosis. A regular rhythm with right axis deviation, characterized by prominent S-waves in leads I, II, and III, is seen. (b) A three-lead ECG trace from a 1-year-old golden retriever with subaortic stenosis. An underlying sinus arrhythmia is seen with one premature ventricular complex (*asterisk*). The R-wave amplitude is tall, consistent with left ventricular hypertrophy, and the ST segment is mildly depressed, consistent with subendocardial ischemia – both findings common in dogs with subaortic stenosis.

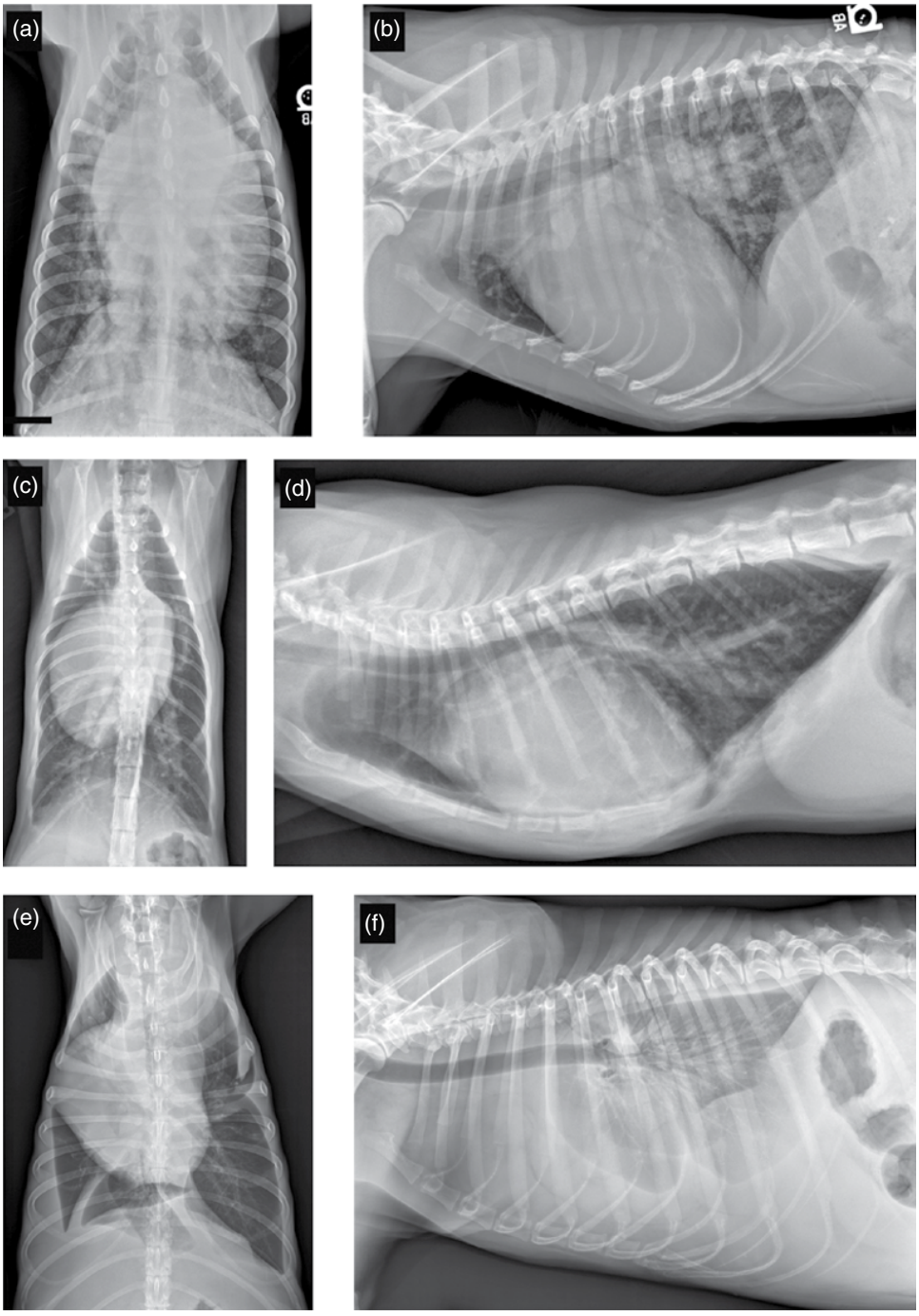


Figure 24.3 Compilation of thoracic radiographs from two dogs and a cat with congenital heart disease and decompensated heart failure. (a,b) A 1.5-year-old mixed-breed dog with a PDA. Severe left heart enlargement, dilation of the aortic arch, pulmonary venous distension and tortuosity, and perihilar interstitial densities are apparent. (c,d) A 5-month-old Angora cat with a large atrial septal defect. Severe cardiac enlargement, pulmonary overcirculation, and mild pulmonary interstitial infiltrates are apparent. (e,f) A 3-year-old German shepherd dog with tricuspid valve dysplasia and right-sided congestive heart failure. Right atrial and ventricular enlargement is evident in the dorsoventral view (e). In the lateral view (f), the thoracic structures, including the cardiac silhouette, are obscured by severe pleural effusion.

Cardiac Biomarkers: Troponin and NT-proBNP

In recent years, the use of cardiac biomarkers to screen animals for the presence of acquired cardiovascular disease has gained in popularity. The biomarkers receiving the most attention in veterinary cardiology include cardiac troponin I (cTnI) and the amino terminus of the prohormone B-type natriuretic peptide (NT-proBNP). There have been no comprehensive studies looking at the utility

of these tests in animals with CHD, though evidence in human cardiology suggests that these markers are often elevated in children with severe CHD. At this time, no guidance can be given for or against the utility of cardiac biomarkers in screening animals for CHD.

Echocardiography

History, physical examination, thoracic radiography, and ECG are all useful diagnostic tests for determining the presence of CHD, but are less capable of making a definitive diagnosis, assessing disease severity, or ruling out the presence of multiple or complex congenital lesions. In veterinary medicine, echocardiography with Doppler is the noninvasive gold standard for definitive diagnosis of CHD. All animals with a high suspicion of CHD should ideally have a detailed echocardiogram performed by a veterinarian trained in the diagnosis of CHD. Echocardiography allows for the detection of specific types of CHD, the presence of concomitant defects, and assessment of disease severity, risk for complications, direction of cardiac shunting, estimate of intracardiac pressures, and likelihood of congestive heart failure. Echocardiography is also necessary in assessing the need for therapy as well as for planning interventional or surgical options. Figure 24.4 provides representative two-dimensional images of common CHD seen in the dog and cat by echocardiography.

Angiography

Nonselective or selective angiography with fluoroscopic visualization of cardiac structures was historically the definitive test for CHD prior to the advent of echocardiography. For some defects, angiography is still utilized, particularly for lesions of the great vessels that are not easily appreciated by ultrasound. Figure 24.5 shows a nonselective, digitally subtracted angiogram of a right-to-left shunting PDA in a cat, while Figure 24.6 shows a right ventriculogram from a dog with PS. In practice, angiography is used most commonly at the time of interventional therapy to confirm the diagnosis, visualize the defect to be addressed, and guide intervention with balloon or device, as discussed in the interventional therapy section.

Cross-Sectional Imaging

Cardiac computed tomography and magnetic resonance imaging allow three-dimensional reconstructions of the heart and great vessels. Such imaging modalities are commonly employed in human medicine to evaluate children with CHD and case reports of their use in veterinary medicine are present in the literature. Figure 24.7 shows a three-dimensional reconstruction of a computed tomographic angiogram in a dog with PS. The benefit of cross-sectional imaging is likely greatest in instances of complex CHD where the cardiac anatomy can be viewed from multiple perspectives *in situ*.

Therapy

Medical Therapy

Asymptomatic Disease

Treatment of asymptomatic CHD depends on the specific underlying disease and its severity, so definitive diagnosis is essential. In general, diseases of moderate to severe outflow tract obstruction causing concentric hypertrophy (e.g., SAS and PS) are treated by the author with beta-blockers such as atenolol. Atenolol is typically uptitrated in dose over 4–8 weeks, starting at 0.2–0.5 mg/kg (0.1–0.2 mg/lb) q12h PO and increasing to a target dose of 1–1.5 mg/kg (0.4–0.7 mg/lb) q12h PO. The rationale for such therapy is that beta-blockers help to reduce the force of myocardial contraction, thereby reducing myocardial oxygen demand and protecting the diseased/hypertrophied myocardium. The antiarrhythmic properties of atenolol are also believed to be of benefit as these patients are at risk for life-threatening arrhythmias. Atenolol is often chosen given its low cost, appropriate size tablets, and ease of administration.

Therapy for asymptomatic diseases of volume overload such as moderate to severe mitral or tricuspid regurgitation and left-to-right shunting defects like PDA, prior to development of CHF, is controversial. However, the addition of angiotensin converting enzyme (ACE) inhibitors such as enalapril at 0.5 mg/kg (0.2 mg/lb) q12h PO is common if there is severe ventricular dilation, impaired cardiac output, and atrial enlargement suggesting high risk for development of CHF.

Symptomatic Disease

Medical therapy of symptomatic CHD depends on the type of lesion and developing clinical signs. Diseases of outflow tract obstruction (SAS, PS) commonly cause exercise intolerance and syncope related to reduced cardiac output, inappropriate baroreceptor activation, and/or ventricular arrhythmias. Life-threatening or symptomatic ventricular arrhythmias are treated with antiarrhythmic agents. Sotalol at a dose of 1–2 mg/kg (0.4–0.9 mg/lb) q12h PO is typically the first-line antiarrhythmic of choice so long as ventricular function is not severely depressed. Syncope that occurs without ventricular arrhythmias (presumed to be reflex-mediated syncope whereby the cardiac hypertrophy stimulates an exaggerated baroreceptor response) is typically treated with beta-blockade. Modification of exercise level with avoidance of high-level intense or burst activity will also commonly reduce this clinical sign.

Diseases of left-sided volume overload will commonly cause symptoms of cough in the dog prior to the onset of CHF due to severe left atrial enlargement and resultant left bronchial compression. Bronchial compression in the absence of CHF may be treated with

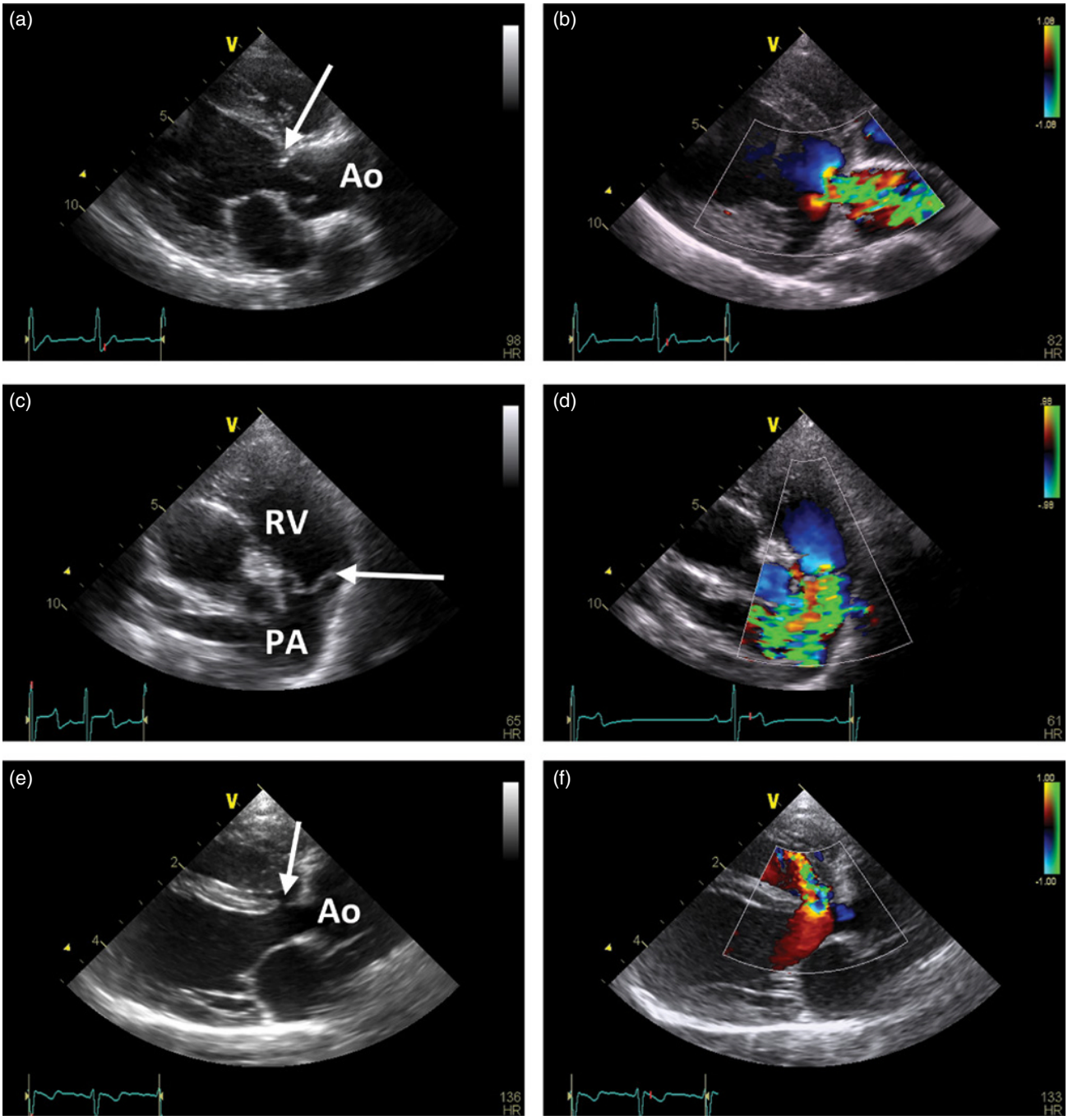


Figure 24.4 Representative two-dimensional echocardiographic images of common congenital heart defects in two dogs and a cat. (a,b) Long-axis images from a 6-month-old Newfoundland with subaortic stenosis. The ascending aorta (Ao) is dilated and there is a ring of hyperechoic tissue (*arrow*) immediately below the aortic valve. Turbulent flow is seen originating at this location in (b). (c,d) Short-axis images of pulmonary valve stenosis in a 9-month-old mixed-breed dog. The right ventricle (RV) is hypertrophied, the pulmonary trunk (PA) is dilated, and the pulmonary valve leaflets are thickened and fused together at their tips (*arrow*). Turbulence begins at the level of the stenosed valve in (d). (e,f) Long-axis images of a membranous ventricular septal defect (VSD) in a cat. Immediately below the aorta (Ao) there is a drop-out in the ventricular septum consistent with a VSD (*arrow*). Color Doppler shows the direction of the turbulent flow across the VSD from left to right in (f).

ACE inhibitors and low-dose furosemide (1 mg/kg [0.5 mg/lb] q12h PO) to decrease preload and left atrial pressure, thereby reducing bronchial compression and minimizing symptoms.

Pulmonary hypertension can develop in CHD secondary to left-to-right shunting lesions such as PDA, VSD, and ASD or secondary to chronic, severe elevations in left atrial pressure. Pulmonary hypertension therapy is

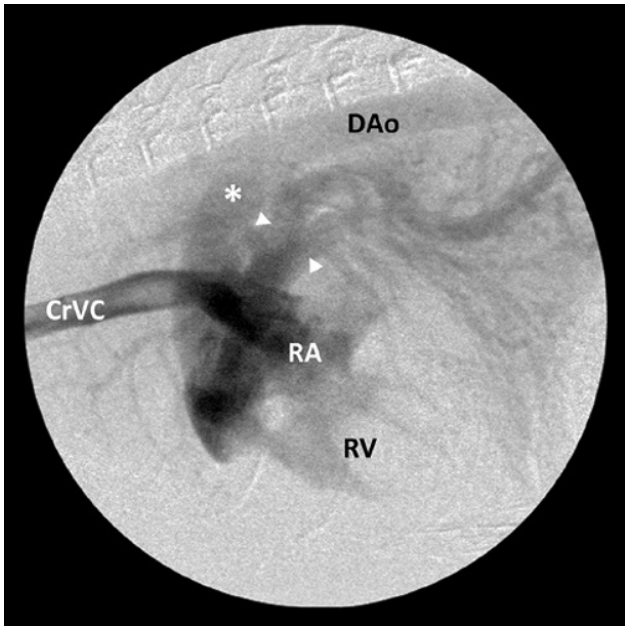


Figure 24.5 Lateral nonselective digitally subtracted angiogram of a right-to-left shunting PDA in a 1-year-old cat. The injection was made into a cephalic vein and contrast can be seen in the cranial vena cava (CrVC), right atrium (RA), right ventricle (RV), and pulmonary arteries (*arrowheads*). Contrast can be seen to communicate from the pulmonary artery through the ductus (*asterisk*) and into the descending aorta (DAo).

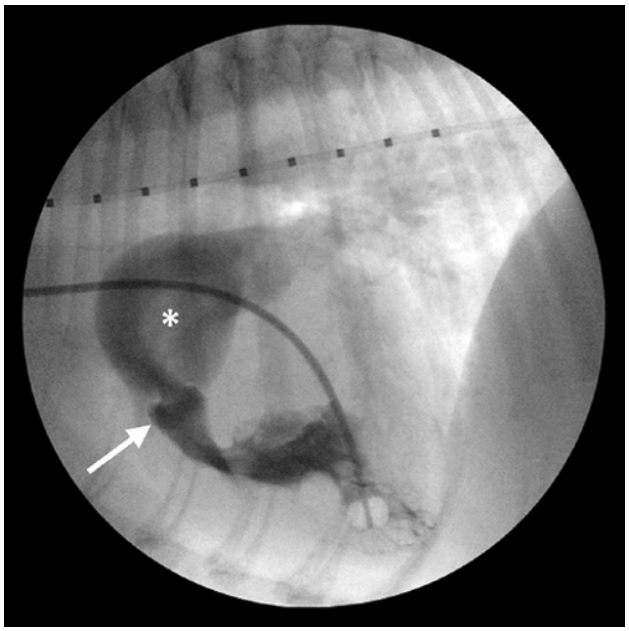


Figure 24.6 Selective right ventriculogram from a 6-month-old English bulldog with pulmonary valve stenosis. An angiographic catheter is present in the right ventricle and contrast is injected, highlighting thickened and doming pulmonary valve leaflets (*arrow*), muscular hypertrophy and narrowing of the right ventricular outflow tract below the valve, and a dilated pulmonary trunk (*asterisk*). A calibration catheter is present in the esophagus.

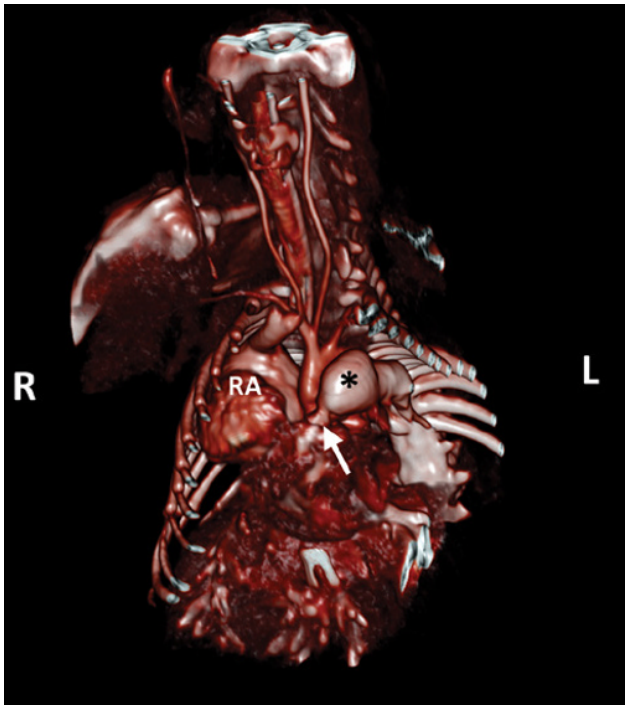


Figure 24.7 Three-dimensional reconstruction of a computed tomographic angiogram in a 2-year-old English bulldog with pulmonary valve stenosis. The thorax is viewed from a ventral perspective and the narrowed pulmonary valve annulus can be seen (*arrow*) with poststenotic dilation of the pulmonary trunk (*asterisk*) and a severely dilated right atrium (RA).

instituted with the development of secondary symptoms such as severe exercise intolerance, syncope, right-sided CHF, and shunt reversal causing right-to-left shunting, hypoxemia, and erythrocytosis. Therapy is aimed at pulmonary vasodilation, most commonly with phosphodiesterase-V inhibitors like sildenafil (usual dose 2 mg/kg [1 mg/lb] q8–12h PO).

Defects leading to pulmonary hypertension and shunt reversal (so-called Eisenmenger's physiology) lead to cyanosis and secondary erythrocytosis (packed cell volume >55%) and are treated with periodic phlebotomy or chemotherapeutic agents causing reduction in RBC production, such as hydroxyurea. The aim of phlebotomy or hydroxyurea therapy for cyanotic heart disease is a packed cell volume of approximately 55–60% as this level of erythrocytosis balances increased oxygen-carrying capacity without hyperviscosity.

Severe congenital cardiac disease due to either pressure or volume overload will commonly lead to development of left- or right-sided CHF. Left-sided CHF presents with coughing, tachypnea, and respiratory distress secondary to pulmonary edema, whereas right-sided CHF presents with signs of jugular distension, hepatomegaly, ascites, and/or pleural effusion. CHF, regardless of cause, is treated with diuretics and ACE inhibitors.

In the author's experience, right-sided CHF will commonly need higher doses of oral furosemide or an alternative diuretic such as torsemide due to the potential for intestinal edema causing decreased gastrointestinal absorption. ACE inhibitors should always be used in the treatment of chronic CHF to decrease RAAS activation associated with advanced heart failure and diuretic administration.

Pimobendan has become standard of care in the treatment of CHF secondary to acquired cardiac diseases, such as dilated cardiomyopathy and chronic degenerative valve disease. While no definitive data are available on the use of pimobendan in congenital cardiac disease, most cardiologists advocate its use with CHF due to diseases of volume overload such as PDA or mitral valve dysplasia. The administration of pimobendan as a treatment for CHF secondary to diseases of pressure overload like SAS and PS is becoming more commonplace. However, extralabel use of pimobendan should be done cautiously in the setting of outflow tract obstruction due to potential for increase in pressure gradient, wall stress, and myocardial oxygen consumption. Consultation with a veterinary cardiologist is advised prior to pimobendan use in cases of SAS and PS with CHF.

Surgical and Interventional Therapy

Congenital heart disease can be palliated medically, as noted above, but also may be treated by minimally invasive (interventional) or traditional surgical techniques whenever possible. An accurate diagnosis of CHD is critical to appropriately guide therapy as some animals can go on to live a normal life if treated early.

The decision to operate or pursue transcatheter therapy relates to the expertise of the veterinarian performing the procedure, anatomy of the defect, and client preference. Prospective comparison studies are lacking in veterinary medicine, though retrospective data on PDA closure suggest comparable to improved outcomes from a transcatheter approach compared to surgery. Novel devices, such as the Amplatz™ canine ductal occluder, have greatly improved the ease with which PDA occlusion can be performed from a transarterial approach (Figure 24.8). Gordon *et al*. showed complete PDA occlusion in 40 of 41 dogs treated by a transarterial canine-specific device with no perioperative mortality compared to a reported perioperative mortality of 2–8% in the surgical literature during open PDA ligation [1].

The CHD conditions which currently have a well-established surgical or interventional treatment option include PDA, persistent right aortic arch (PRAA), and PS. Dogs with VSD or ASD have been successfully treated by both surgical and interventional techniques and, though costly, open surgical repair and newer transcatheter devices for closure of these defects may be considered for the motivated client. Cyanotic ToF dogs can be palliated by surgical construction of a systemic-to-pulmonary anastamosis, typically a modified Blalock–Taussig shunt, which improves pulmonary blood flow and lessens central cyanosis. Open-heart repair of ToF has also been described in the dog. Atrioventricular valve dysplasia is seldom treated by surgical or interventional techniques but if a stenotic component is present, balloon valvuloplasty of the tricuspid or mitral valve may be considered. Open surgical repair of a dysplastic valve may also be considered for the motivated client.

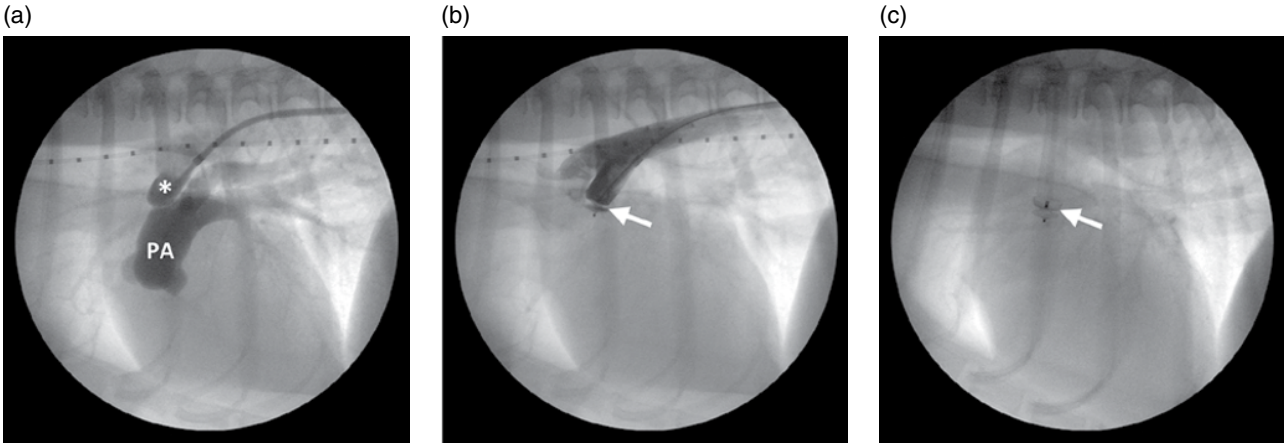


Figure 24.8 Fluoroscopic images obtained during transcatheter occlusion of PDA in a 2-year-old mixed-breed dog. (a) A sheath has been advanced from the femoral artery to the thoracic aorta and injected contrast agent defines the ductus (*asterisk*) and the pulmonary trunk (PA). (b) The Amplatz™ canine ductal occluder (*arrow*) has been advanced through the same sheath and deployed across the ductus, with contrast showing complete ductal occlusion. (c) The wire attached to the Amplatz™ canine ductal occluder has been removed as well as the sheath, and the device (*arrow*) is left permanently in place.

Prognosis

The prognosis for the animal with CHD is heavily dependent on the underlying condition and the severity of the defect. Mild stenosis of the semilunar valves (PS, SAS) rarely causes morbidity or altered survival. Conversely, dogs with severe SAS have been reported to have median survival of only 1.5–4 years. For left-to-right shunting lesions, prognosis is highly dependent on the volume of shunt flow. Small shunts (e.g., restrictive VSDs) are often well tolerated and can be associated with a normal lifespan. Large PDAs, however, are known to result in mortality of 60% or more within a year of diagnosis if they are not closed by surgery or intervention.

For most CHD, there is a paucity of literature on prognosis and survival. Experienced cardiologists have seen animals with severe disease live a near-normal lifespan, while other animals with moderate disease die from the defect prematurely. At the present time, predicting the precise prognosis for an individual animal with CHD is very difficult. Serial evaluations to detect asymptomatic cardiac dysfunction or dysrhythmias, as well as the development of clinical signs (cough, lethargy, collapse, etc.), are currently the methods used to monitor these animals.

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25

Valvular Heart Disease

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Canine Degenerative Myxomatous Mitral Valve Disease

Etiology and Pathophysiology

Canine chronic myxomatous mitral valve disease (MMVD) is the result of a progressive myxomatous degeneration of mitral valve leaflets and chordae tendinae. Pathologic changes include excessive deposition of mucopolysaccharide, fragmentation of elastin, and disorganization and disruption of collagen.

The exact etiology of the disease has not been established. Because the disease has a high prevalence in some breeds, such as Cavalier King Charles spaniel (CKCS), a genetic predisposition has been hypothesized. Swenson and co-workers provided the first evidence of a genetic predisposition in 1996. These authors reported that CKCS dogs with a more severe disease status produced more offspring with murmurs and with murmurs of higher intensity than dogs with a low-intensity status. They concluded that MMVD is inherited as a polygenic trait. The same etiology has been reported for other breeds. It has also been reported that the threshold for the expression of the disease is lower in males than in females. This would explain why males present with the disease at a younger age.

Recently, using a genome-wide association study, two specific loci associated with development of MMVD in CKCS have been identified. It is likely that other factors might contribute to the development of the disease, including the anatomy of the mitral valve, obesity, and exercise. Recently, serotonin has been hypothesized as playing a role in the pathogenesis of MMVD. However, despite similarities in the myxomatous pathology of serotoninergic and degenerative mitral valves, a direct cause–effect relationship between serotonin and the pathogenesis of MMVD has not been established.

Activation of valvular interstitial cells (VICs) is likely to play an important role in the pathogenesis of the disease. VICs represent the most common cell type in the cardiac valves and are responsible for extracellular matrix synthesis, valvular repair, and remodeling. VICs are commonly present in a quiescent state but can be activated by endothelial damage or valvular stress. Activated VICs are able to synthesize collagen, fibronectin, elastin, and growth factors and are responsible for extracellular matrix remodeling through production of matrix metalloproteinases and their inhibitors (tissue inhibitors of metalloproteinases [TIMPs]). Eventually, this process leads to decreases in collagen content and deposition of proteoglycan, typical of the myxomatous degenerative process. In summary, it can be hypothesized that in dogs with a genetic predisposition for the disease, mechanic stimuli can activate VICs with valvular remodeling and myxomatous degeneration. This hypothesis would support the theory that myxomatous degeneration is the end-result of a continuous process of damage and repair as a result of mitral valve stress.

The myxomatous degeneration of the valve leaflets eventually leads to prolapse and valvular insufficiency. Accordingly, mitral valve prolapse usually precedes mitral valve insufficiency. Mild mitral valve insufficiency is generally well tolerated by dogs and is not associated with any compensatory response because it is not associated with decreased cardiac output. However, if the disease progresses and regurgitation through the mitral valve into the left atrial becomes more severe, cardiac output decreases and activation of compensatory mechanisms occurs. These mechanisms include activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system, and increased release of endothelin, vasopressin, and natriuretic hormones. Due to the chronic nature of the disease, these mechanisms are not necessarily activated in the early stages of MMVD. This consideration has important therapeutic

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implications. In particular, when the RAAS becomes activated in dogs with natural occurring MMVD has been the source of much controversy. Some studies suggest that the RAAS might be activated relatively early in the history of the disease, whereas other studies suggest otherwise. Further complicating the picture is the observation that in dogs, alternative pathways for angiotensin II production, such as the chymase pathway, may be particularly active. Moreover, it is possible that release of natriuretic hormones from the dilated left atrium and ventricle might balance RAAS and sympathetic activation.

Moderate to severe mitral valve regurgitation leads to left ventricular volume overload, left atrial and left ventricular enlargement. Mitral valve insufficiency due to MMVD represents a unique hemodynamic condition with increased preload and decreased afterload. This is because a significant volume of left ventricular preload is ejected into the left atrium at the beginning of systole. Because the left atrium is a low-pressure chamber, there is no increase in cardiac work. This is likely the reason why many dogs with severe mitral valve regurgitation can tolerate this situation for a long time without presenting clinical signs.

Left ventricular eccentric hypertrophy, decreased afterload, and increased sympathetic activation produce hyperkinetic left ventricular function. Therefore, the recognition of normal values for fractional shortening or ejection fraction during an echocardiographic exam in dogs with left ventricular enlargement suggests the presence of a systolic dysfunction. Systolic dysfunction has been recognized to play an important role in disease progression and it is independent of clinical status. It has been hypothesized that systolic dysfunction in dogs with MMVD is the consequence of inadequate hypertrophy. Wall stress imposed by pure volume overload might not be a very potent stimulus for cardiac hypertrophy, and experimental canine models of MMVD systolic dysfunction were associated with inadequate left ventricular hypertrophy. Systolic dysfunction is more apparent in large-breed dogs affected by MMVD.

Left atrial function also plays an important role in the pathophysiology of the disease. Slowly progressing mitral valve regurgitation is associated with a progressive dilation of the left atrium. If left atrial compliance is maintained, filling pressure is also maintained close to normal limits. Accordingly, patients with severe mitral regurgitation do not develop pulmonary edema. However, chronic dilation of the left atrium is associated with left atrial hypertrophy and remodeling that, with time, decreases compliance and leads to development of pulmonary edema. In dogs with rupture of a major chorda tendinea, there is an acute worsening of mitral regurgitation. In this condition, the left atrium has no time to enlarge and there is a sudden increase of left atrial pressure with development of acute pulmonary edema.

Epidemiology

Myxomatous mitral valve disease is the most common heart disease in dogs and the most frequent cause of congestive heart failure in this species. MMVD in dogs represents 75% of all cardiovascular disease in this species. The prevalence of the disease varies with age and whether the study is based on necropsy, echocardiographic or clinical findings. The prevalence of MMVD has also been correlated with breed. In some breeds, such as the CKCS, the prevalence of the disease in animals older than 10 years is greater than 90%. Males are also reported to develop the disease at a younger age than females. Although the disease is more commonly diagnosed in small-breed dogs, it can occur in large-breed dogs.

History and Clinical Signs

Myxomatous mitral valve disease is a chronic disease in which the clinical presentation is variable. Some patients remain asymptomatic for all their lives, whereas others develop life-threating pulmonary edema and chronic congestive heart failure (CHF). Most dogs with mild to moderate MMVD are generally free of clinical signs.

The presence of clinical signs is generally related to the severity of the disease. Dogs with pulmonary edema have tachypnea and dyspnea. It has been reported that the normal respiratory rate at rest for dogs should be less than 30 breaths per minute. Accordingly, an increased respiratory rate at rest might represent the first clinical sign of worsening of the disease. Dogs with pulmonary edema are often anxious and have difficulties sleeping. They often cannot lie in lateral recumbency and prefer a sternal position (orthopnea). Weight loss is common in dogs with advanced stages of MMVD and CHF. Patients that develop right-sided heart failure have abdominal distension due to ascites. Syncope is occasionally reported in dogs with MMVD. Arrhythmias, pulmonary hypertension, vasovagal syncope, and coughing can cause syncope in these patients.

Cough represents the most common complaint for dogs affected by MMVD, especially in small breeds. It should be stressed that cough is a general clinical sign of respiratory disease and its presence in a dog with a murmur is not an indicator for starting treatment for CHF. Old small-breed dogs are commonly affected by tracheobronchial disease and by MMVD. In these patients, the cough is often the result of their primary respiratory disease and not heart disease. A recent study has shown that cough was not associated with the presence of active

CHF in 206 dogs with MMVD at different stages. In this study, cough was associated with left atrial enlargement and the presence of an abnormal radiographic airway pattern. Left atrial enlargement compressing the mainstem bronchus is believed to induce cough in patients with primary bronchomalacia.

Diagnosis

The American College of Veterinary Internal Medicine Specialty of Cardiology consensus panel has published guidelines for the diagnosis and treatment of canine chronic valvular heart disease. The guidelines propose a modification of a staging system for MMVD that is currently used to classify human patients with heart failure (Table 25.1). This classification introduces the concept of patients at risk for developing MMVD but that currently do not have heart disease (stage A). The reason for introducing this stage is to encourage veterinarians to develop appropriate screening programs and inform owners regarding the risk of an animal developing the disease.

Diagnosis of MMVD is generally suspected following a careful auscultation. In early stages of MMVD a midsystolic click may represent the only auscultatory finding. The click is often intermittent and can be better appreciated at higher heart rates. It is believed the midsystolic click is caused by vibration of the prolapsing mitral valve leaflets and by the tensing of redundant chordae tendineae. In dogs with mild MMVD and mild mitral regurgitation, a low-intensity, early systolic murmur localized on the left apex can be heard. The murmur can be intermittent and intensity can vary with heart rate and phase of respiration. When moderate to severe mitral regurgitation is present, the murmur becomes holosystolic or pansystolic, more intense, and harsher. In more severe cases, the murmur radiates to the base of the left thorax and to the right side of the thorax. It should be emphasized that the intensity of the murmur does not always correlate with the severity of MMVD; that is, loud murmurs do not automatically indicate severe disease.

The auscultatory findings can be influenced by several factors such as observer experience, obesity, panting, presence of arrhythmias, and breeds. In a study on preclinical MMVD dogs, 26% of dogs with a confirmed echocardiographic diagnosis of MMVD did not have a murmur and large-breed dogs with MMVD have less intense murmurs compared with small-breed dogs. Thus, diagnosis of MMVD should not rely only on auscultatory findings. Indeed, the ACVIM consensus recommends that although the presence of midsystolic click or left apical murmur in a typical breed is strongly suggestive of MMVD, echocardiographic confirmation of the diagnosis is required. Echocardiography can evaluate the morphology of the valve leaflets and quantify the degree of cardiac enlargement. The echocardiographic characteristics of MMVD include prolapse or thickening of one or both mitral valve leaflets (Figure 25.1).

Mitral valve prolapse is defined as an abnormal systolic displacement or bowing of the mitral valve leaflets from the left ventricle toward the left atrium. In dogs, some studies suggest that the right parasternal four-chamber, long-axis view is the gold standard used to identify the presence of mitral valve prolapse. Because

Table 25.1 Classification system for dogs affected by myxomatous mitral valve disease (MMVD)

Stage	Definition
A	Dogs at risk for developing MMVD that have no identifiable cardiac structural disorder (i.e., Cavalier King Charles spaniel, dachshunds)
B1	Dogs with MMVD that have never developed clinical signs and have no radiographic or echocardiographic evidence of cardiac remodeling
B2	Dogs with MMVD that have never developed clinical signs but have radiographic or echocardiographic evidence of cardiac remodeling (i.e., lef-sided heart enlargement)
C	Dogs with MMVD and past or current clinical signs of heart failure associated with structural heart remodeling. Dogs presenting in heart failure for the first time may show severe clinical signs requiring hospitalization
D	Dogs with end-stage MMVD and heart failure that is refractory to standard therapy (i.e., furosemide, angiotensin converting enzyme inhibitors, pimobendan +/- spironolactone)

Source: Adapted from Atkins *et al.* (2009).

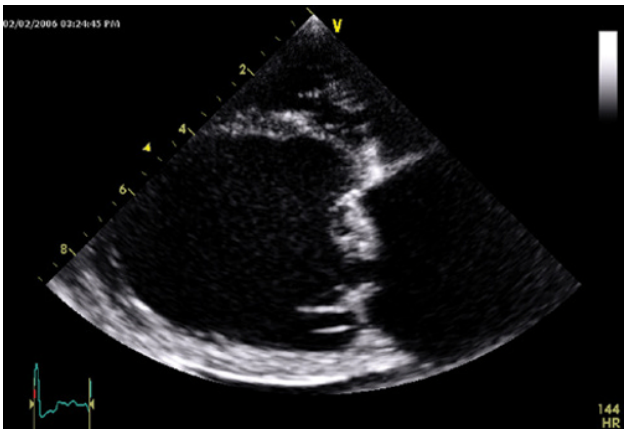


Figure 25.1 Echocardiographic right parasternal long axis view of the left atrium, mitral valve, and left ventricle. The mitral valve leaflets appear thickened and prolapse in the left atrium.

echocardiographic diagnosis of mitral valve prolapse is dependent on the morphology of the valve, and because the normal mitral valve and mitral valve annulus present a wide range of normality, we recommend that the diagnosis of mitral valve prolapse should be confirmed in at least two echocardiographic views. Indeed, we have recently reported that in dogs, mitral valve morphology is saddle shaped, similar to what has been reported in people. Therefore, using the right parasternal long-axis view may lead to an overestimation of the mitral valve prolapse.

The ACVIM consensus statement recommends thoracic radiography for all dogs with MMVD to assess the hemodynamic significance of the murmur through evaluation of heart size and pulmonary vasculature and to obtain a baseline when the patient is asymptomatic. Careful evaluation of thoracic radiographs may help in diagnosing concomitant primary respiratory diseases that may be the cause for clinical signs, such as cough or dyspnea. Thoracic radiographs, together with physical examination, are also essential for monitoring dogs with MMVD. A change in radiographic cardiac dimensions observed between two different time points has been suggested as a powerful predictor of outcome in dogs with MMVD.

Prognosis

Myxomatous mitral valve disease is characterized by a long preclinical period and many affectws dogs die for reasons other than CHF. A study including a population of 558 dogs affected by MMVD at different stages has shown that more than 70% dogs were alive at the end of the follow-up period of 6.6 years (Figure 25.2).

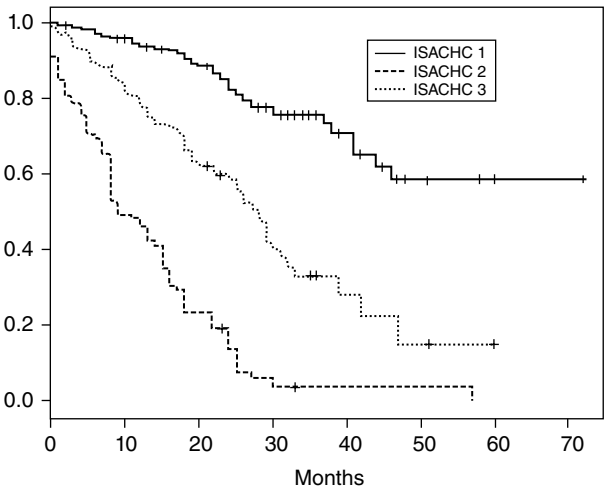


Figure 25.2 Survival curves for dogs with different stages of heart failure according to the International Small Animal Cardiac Health Council. Class 1 ISACHC are dogs with preclinical MMVD, class 2 ISACHC are dogs with moderate congestive heart failure, and class 3 ISACHC are dogs with severe heart failure (showing clinical signs at rest and requiring close monitoring). *Source:* Borgarelli *et al.* (2008). Reproduced with permission of John Wiley.

In another study of 256 dogs affected with preclinical MMVD, the overall mortality was 27%, with cardiac death accounting for 11% during the 833-day observation period. The same study showed that 30/83 dogs that were available for reexamination progressed to a more advanced stage of MMVD. Reported risk factors associated with progression of the disease or death included age, gender, intensity of heart murmur, degree of valve prolapse, severity of valve lesions, the degree of mitral valve regurgitation, degree of left atrial enlargement, severity of eccentric hypertrophy, rupture of chordae tendinae, and increased concentration of natriuretic peptides. Left atrial enlargement, assessed by echocardiography, seems to represent one of the most reliable independent predictors of death. The risk of death from cardiac disease for dogs with a left atrium/aortic root ratio exceeding 1.7 was 2.1 times that of dogs with smaller atria.

Another study reported that plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration and indexed left ventricular end-diastolic diameter were independent risk factors for development of first-onset CHF. The presence of pulmonary hypertension due to MMVD was recently reported to be associated with higher risk of death.

Therapy

The Asymptomatic Dog (Stage B: ACVIM Consensus)

Treatment of dogs with asymptomatic MMVD has been a subject of controversy over the past years. This stage includes dogs with the disease who have never developed CHF. This group represents the majority of dogs diagnosed with MMVD. The ACVIM consensus suggests that asymptomatic dogs could be further subdivided into those with no radiographic or echocardiographic evidence of cardiac enlargement (stage B1) and those with evidence of cardiac remodeling suggested by the presence of left atrial and ventricular enlargement (stage B2). This subclassification emphasizes the fact that asymptomatic dogs are a heterogeneous group, including patients with very mild disease as well as those with more advanced disease that are more likely to develop clinical signs of CHF.

The ACVIM consensus group unanimously recommended not treating dogs with MMVD in stage B1 of the disease. In contrast, no consensus was reached for dogs in stage B2. Two multicenter double-blinded studies evaluating the efficacy of enalapril on delaying the onset of CHF in stage 1B dogs with MMVD have shown no

significant effect of angiotensin converting enzyme inhibitor (ACEI) therapy on the primary outcome variable, which was time from inclusion in the study to the onset of signs of CHF. Based on these results and the observation that only a relatively small percentage of dogs with asymptomatic disease progress to CHF or die as a consequence of the disease, the author does not support treatment with an ACEI.

A recent multicenter clinical trial reported that pimobendan delays onset of congestive heart failure in a subpopulation of dogs with stage B2. It should be highlighted that enrolled dogs had significant cardiomegaly identified by specific echocardiographic criteria. It is possible, although not proven, that dogs in advanced stage B2 may benefit from other medical treatments such as spironolactone. This emphasizes the importance of developing biomarkers able to identify patients at higher risk for developing CHF. A study conducted on 72 asymptomatic dogs with MMVD showed that NT-proBNP at a cut-off of 466 pmol/L had 80% sensitivity and 76% specificity in predicting 12-month progression to cardiac death or CHF. Although these data appear very promising, further studies are needed to confirm the value of NT-proBNP in distinguishing those patients that will progress to CHF. Accordingly, assessment of stage B dogs should include evaluation of multiple parameters including clinical, radiographic, and echocardiographic findings.

The Symptomatic Dog (Stage C: ACVIM Consensus)

According to the ACVIM consensus, stage C includes animals with MMVD and current or previous clinical signs of CHF. Management of these patients is based on administration of a combination of several medications, including diuretics, ACEIs, and pimobendan. Although no study has proven the efficacy of furosemide in dogs with MMVD, there is a general consensus that diuretics are essential for patients with CHF. The majority of dogs enrolled in the multicenter studies evaluating the efficacy of the ACEI and pimobendan in symptomatic dogs with MMVD were on concomitant treatment with furosemide. The diagnosis of CHF should be reevaluated if diuretics do not improve clinical signs in dogs with suspected CHF. The dosage of furosemide should be adjusted in order to keep the patients free from clinical signs. Although the suggested mean dosage for these patients is 2 mg/kg PO q12h, it could range from 0.5 mg/kg PO q12h to 4–6 mg/kg PO q8h.

In human patients with CHF, teaching patients to adjust their furosemide dosage on the basis of monitoring their weight and their clinical signs significantly reduces the number of hospitalizations and may be associated with prolonged survival. A similar approach with dogs in CHF is desirable but difficult. The use of an ACEI together with furosemide in stage C dogs is based on evidence provided by several multicenter double-blind studies which provide evidence that an ACEI added to therapy including furosemide improved the quality of life and survival time.

Two recent studies have shown that pimobendan improved survival and quality of life in stage C dogs compared to standard treatment with an ACEI and furosemide. The first study was conducted as a blinded, randomized, positive-controlled, multicenter study and included 76 dogs. The study had a mandatory 56-day treatment period that was followed by an optional long-term treatment phase. In this study, pimobendan significantly improved a clinical measure of disease severity and survival. The results of this study led to a larger study in 260 dogs with stage C MMVD. This was a prospective multicenter randomized single-blinded study and the primary endpoint was a composite of cardiac death, euthanasia for heart failure, or treatment failure. Dogs were randomized to therapy with either ACEI or pimobendan. Pimobendan was associated with significant improvement in the endpoint variables and this benefit persisted after adjusting for all baseline variables. All dogs enrolled in this study were on concomitant furosemide treatment. It should be stressed that none of these studies answer the question of whether triple therapy involving furosemide, ACEI, and pimobendan would be superior to double therapy with pimobendan plus furosemide. The ACVIM consensus recommended that chronic management of stage C dogs includes a combination of ACEI, pimobendan, and furosemide.

Spironolactone has been recently approved in Europe for treatment of dogs with MMVD. In one study, spironolactone when added to furosemide and ACEI +/− digoxin decreased risk of cardiac-related death or euthanasia for cardiac reasons by 69% in dogs with moderate to severe MMVD. The dosage of spironolactone used in the clinical trial was 2 mg/kg q24h. One criticism of this study is that a relatively low number of cases reached the endpoint compared to other studies evaluating stage C dogs. One possible mechanism of action for spironolactone would be related to its antifibrotic effects. Geriatric dogs affected by MMVD have intramyocardial arterial changes associated with areas of replacement fibrosis. The exact role of vascular or myocardial fibrosis in the pathogenesis of MMVD is still to be clarified. Positive effects of aldosterone blockers such as spironolactone could also be related to the mechanism of aldosterone escape. Aldosterone concentrations can be elevated in dogs with MMVD despite receiving an ACEI. This phenomenon is dependent on the dose of concomitant furosemide and has been attributed to incomplete inhibition of ACE activity.

Digoxin is commonly used to treat dogs with concomitant atrial fibrillation in order to control the heart rate. There are no controlled studies in veterinary medicine evaluating digoxin, but it is believed that its administration could improve clinical signs of heart failure in dogs.

In the author's experience, most dogs can be managed using a combination of furosemide, ACEI, pimobendan, and spironolactone. Treatment should be individualized for each patient and the goal is to keep the animal free of clinical signs of CHF for as long as possible.

The Dog with Refractory Heart Failure (Stage D: ACVIM Consensus)

Stage D includes dogs refractory to treatments for stage C. Many of these dogs also have right-sided heart failure, which leads to congestion of the gastrointestinal tract that can decrease absorption of oral medications. Providing furosemide by subcutaneous injection may help to restabilize the patient. Chronic use of furosemide can also lead to furosemide resistance and it is likely that many stage D patients develop this condition. In these dogs the use of an alternative loop diuretic, such as torsemide, may represent a valid alternative. Adding a diuretic with a different mechanism of action such as a thiazide represents another alternative. The goal in these cases is to induce "sequential nephron blockade" and improve diuresis. Patients on high doses or combinations of diuretics should have their electrolytes and renal function monitored closely.

Amlodipine at the dosage of 0.05–0.1 mg/kg q12h is listed in the ACVIM consensus statement as a possible treatment for dogs with stage D CHF in order to obtain a more effective reduction in afterload and improve cardiac output. Arteriolar vasodilation associated with the use of this drug can lead to severe hypotension. It is, therefore, recommended to uptitrate the dosage of amlodipine and monitor the blood pressure in order to avoid hypotension. In the author's experience, intravenous vasodilators, such as sodium nitroprusside, can also help resolve an acute episode of pulmonary edema.

Valvular Infectious Endocarditis

Etiology and Pathophysiology

Valvular infectious endocarditis (IE) is a severe acquired valvular disease of dogs and cats that is frequently caused by bacterial infections. The most common pathogens associated with IE in the dog and the cat are *Staphylococcus* and *Streptoccoccus* sp. Recently, *Bartonella* sp. has been associated with IE, and has been considered responsible for up to 28% of IE in the dog. Less commonly, IE has been associated with fungi and *Rickettsia* spp. IE starts with damage of the endothelium that triggers the coagulation process. IE requires bacteremia. The most common sources of bacteremia are discospondylitis, prostatis, pneumonia, urinary tract infection, pyoderma, and intravenous catheters. Circulating bacteria can bind to the coagulum and induce inflammation that leads to expression of integrins that further facilitate bacterial adhesion to the damaged tissue. Some bacteria, such as *Staphylococcus* sp., might increase their ability to bind to the coagulum through increased expression of microbial surface adhesive molecules. Vegetative lesions containing bacteria provide a protective barrier and obstacle to antibiotic penetration. Moreover, bacteria can produce enzymes that lead to further tissue damage.

The only cardiovascular disease associated with an increased risk of IE is subaortic stenosis. Historically, periodontal diseases have been thought to increase the risk of bacterial endocarditis, but an association has never been demonstrated.

Epidemiology

Infectious endocarditis is a rare condition in dogs and cats. According to published data, prevalence of the disease varies from 0.005% to 0.09% in the dog. The prevalence in cats has not been reported but IE is less frequently noted in this species. A recent retrospective study has suggested that IE is becoming more common. This might be attributed to the increased recognition of the disease due to the availability of echocardiography. Large-breed dogs are more commonly affected. A review of published data shows that the mitral valve is most commonly affected (60%) followed by the aortic valve (29%). Both the aortic and mitral valves are affected in 5% of the dogs, whereas the pulmonic and tricuspid valves are rarely affected in dogs (4%).

History and Clinical Signs

Clinical signs in patients with IE are various and nonspecific. Many patients show clinical signs related to the underlying systemic disease that produced the bacteremia. Analysis of published case series including 183 dogs with IE showed that the most common clinical sign is lameness (67%), followed by anorexia (55%), lethargy (55%), acute onset of respiratory distress (52%), and syncope/weakness (15%). Fever is reported in 48% of cases. Presence of a murmur is reported in only 55% of cases with a definitive diagnosis of IE. The reason for the relatively low prevalence of murmurs may be similar to what has been previously described for murmurs in patients with MMVD. Moreover, when only the aortic valve is affected, the murmur can be diastolic and difficult to recognize. The recognition of a new systolic

or diastolic murmur in a patient with a predisposing condition should be considered suspicious for IE. Patients with aortic IE and severe aortic insufficiency may present bounding femoral pulses. Thirty-seven percent of dogs with IE present with clinical signs of CHF at the time of the diagnosis.

Diagnosis

Diagnosis of IE is challenging. Antemortem diagnosis involves blood cultures, preferably performed before antibiotic treatment is started. Three to four blood samples should be collected aseptically from different venous sites at least one hour apart and submitted for aerobic and anaerobic culture. Blood samples should also be collected and cultured for *Bartonella* spp. Recently, polymerase chain reaction (PCR) has been proposed as an alternative method for the diagnosis of *Bartonella* infection. A complete blood count (CBC) and serum biochemistry profile should be performed in all patients with suspected IE in order to assess multiorgan involvement. Leukocytosis, thrombocytopenia, anemia, hypoalbuminemia, increased liver enzymes, and azotemia are the most commonly reported laboratory findings in dogs with IE.

Echocardiography allows the identification of vegetative valvular lesions and assessment of the severity of the valvular insufficiency and is complementary to blood cultures in establishing the diagnosis of IE in the dog and cat. Typical lesions are represented by an hyperchoic, mobile, irregular-shaped mass adherent to the valve (Figure 25.3).

Valvular insufficiency is a common finding. Patients with chronic valvular IE and severe valvular regurgitation may present with left ventricular eccentric hypertrophy. Although the presence of typical valvular lesions strongly supports the diagnosis of IE, small lesions on the mitral valve can be difficult to differentiate from lesions due to myxomatous degeneration.

The diagnostic criteria for IE in dogs and cats is modified from the human "Duke criteria". Major criteria for diagnosis are a positive echocardiogram, new valvular insufficiency, and a positive blood culture (≥2 positive cultures or ≥3 positive cultures with common skin contaminants). Minor diagnostic criteria are fever, medium to large dog (>15 kg), subaortic stenosis, thromboembolic disease, immune-mediated disease, positive blood cultures not meeting major criteria, and *Bartonella* serology ≥1:1024. A definitive diagnosis of IE involves the presence of two major criteria or one major and two minor criteria. The presence of one major and one minor criteria or three minor criteria is suspicious for IE.

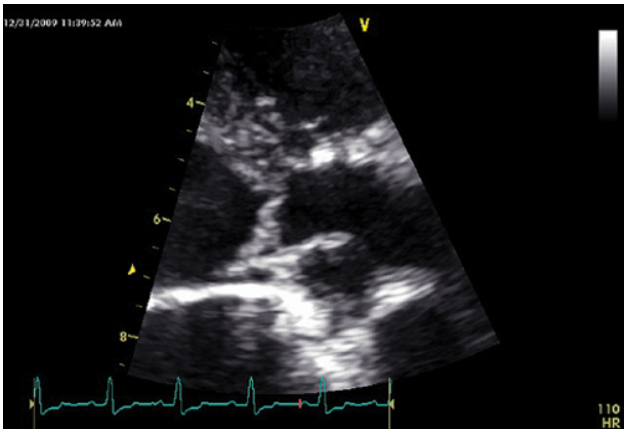


Figure 25.3 Echocardiographic long axis image of the aortic valve. A hyperchoic, mobile, irregular-shaped mass is present adherent to the valve leaflet.

Treatment

Long-term bactericidal antibiotics are the main therapy for patients affected by IE. Broad-spectrum combinations of antibiotics such as enrofloxacin and ampicillin should be administered empirically if blood culture is not available or pending. Treatment of *Bartonella* spp. involves doxycycline, fluoroquinolones, or azithromycin. In dogs requiring hospitalization, intravenous aminoglycosides such as amikacin have been recommended. Ideally, antibiotic therapy is guided by results of culture and sensitivity testing. Oral antibiotics are often continued for 6–8 weeks. Serial echocardiograms or blood cultures are used to monitor response to therapy. Patients with heart failure secondary to IE should be treated with standard CHF treatment.

Prognosis

Generally, patients with IE have a relatively poor prognosis. Outcome is related to the degree of valvular regurgitation and nature of the underlying predisposing cause. Dogs with aortic IE fare worse than dogs with mitral IE (three days versus 476 days median survival time).

Further Reading

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26

Canine Myocardial Disease

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Canine myocardial diseases are those that affect the heart muscle, as opposed to valvular, endocardial, or pericardial diseases. Cardiomyopathies are the most common myocardial diseases in dogs, and are a "heterogenous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction" according to the American Heart Association. They may be classified clinically according to structural and functional phenotype: dilated, hypertrophic, restrictive, and arrhythmogenic right ventricular. Dilated cardiomyopathy (DCM) is by far the most common cardiomyopathy in dogs. Arrhythmogenic right ventricular cardiomyopathy (ARVC) is seen most commonly in the boxer, and hypertrophic cardiomyopathy (HCM) is reported in dogs but is rare. Restrictive cardiomyopathy is not recognized in dogs. Other forms of canine myocardial disease include myocarditis (infectious, inflammatory, toxic, traumatic), infiltrative disease (neoplastic, storage diseases), ischemic disease, myocardial disease secondary to systemic hypertension, and muscular dystrophies affecting the heart. The focus of this chapter is the cardiomyopathies.

Dilated Cardiomyopathy

Etiology/Pathophysiology

Dilated cardiomyopathy is a primary myocardial disease characterized by dilation and systolic dysfunction of the left or both ventricles, in the absence of valvular, pericardial, congenital, coronary artery, or hypertensive heart disease. The DCM phenotype may be the result of various myocardial insults, which are often not identified, rendering many cases idiopathic. In dogs, those "insults" are in many cases genetic mutations leading to altered cardiac protein structure and function, particularly in the pure breeds predisposed to DCM. In humans, 30–50% of cases of DCM are familial or inherited, and mutations involving over 50 cardiac genes have been described to date. Mutations in two genes (PDK4 and titin) have been associated with DCM in Doberman pinschers in North America, but do not account for all cases. The PDK4 mutation was not significantly associated with DCM in a group of European Dobermans in which DCM was linked to a different chromosome (candidate genes yet unidentified). This highlights the complex nature of the role that genetics play in this disease and that multiple genetic factors are involved, even within one breed. Juvenile DCM in the Portuguese water dog has been linked to chromosome 8 and candidate gene identification is ongoing.

Additional well-recognized etiologies in dogs include nutritional deficiencies (taurine, carnitine) and tachycardia induced (secondary to sustained tachyarrhythmia). Infectious and toxic causes of myocarditis, characterized by myocardial inflammation and necrosis, can produce a DCM-like phenotype (ventricular dilation, systolic dysfunction, arrhythmias) in the chronic phase, and may be worth considering as the underlying "insult" in certain clinical presentations or geographic areas. Examples include bacterial (e.g. *Borrelia burgdorferi*, *Bartonella*), viral (e.g., parvovirus, West Nile virus), protozoal (e.g., *Trypanosoma cruzi* [Chagas disease], *Toxoplasma gondii*), fungal (e.g., *Aspergillus*, *Blastomyces*, *Coccidioides*), and toxic (e.g., anthracyclines) agents. The above-mentioned nonfamilial, nonidiopathic causes make up a very small percentage of the total DCM caseload, as idiopathic or familial cases are most common.

On a whole-heart level, the primary abnormality is a reduction in contractility. This results in a reduction in stroke volume (the volume ejected) and an increase in end-systolic volume (the volume remaining in the heart after ejection), in turn resulting in progressive increases in end-diastolic volume. A reduction in

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blood pressure and tissue perfusion activates a number of neuroendocrine and cytokine systems intended to maintain stroke volume and blood pressure, primarily through sodium and water retention and vasoconstriction. Stretch receptors and remodeling pathways are triggered, leading to lengthening of individual myocytes (eccentric hypertrophy) and chamber dilation, maladaptive extracellular matrix remodeling, and cell death. Consequences of these alterations in cardiac structure and function eventually include congestive heart failure (CHF) and arrhythmias (see Chapter 18).

Epidemiology

The prevalence of DCM among canine referral populations has been reported to be 0.3–1% (equivalent to 1–3 cases per 300 patients examined). Underreporting of sudden death (SD) cases might result in underestimation of any figure, thus the true prevalence in the general dog population is unknown. Any prevalence data will be heavily influenced by the distribution of breeds and ages (prevalence increases with age) of the population under study. The prevalence is high in certain breeds based on retrospective studies and prospective screening studies. One European study of Irish wolfhounds (IW) found a prevalence of 24%. In the Great Dane, prevalence has ranged from 12% to 36% in different geographic areas. Prevalence in Dobermans has ranged from 45% to 60% in various studies. Some studies report overrepresentation of males, while in Dobermans there are gender differences in how the disease manifests and at what age, with females having a higher incidence of ventricular arrhythmias as the sole abnormality and males manifesting echocardiographic abnormalities and CHF at an earlier age.

The mode of inheritance is known for specific breed groups. In the Doberman and the Newfoundland, DCM is inherited as an autosomal dominant trait with incomplete penetrance. Both X-linked and autosomal dominant patterns of inheritance have been suggested in the Great Dane, whereas inheritance is autosomal recessive with sex-specific alleles in the IW. The juvenile form described in the Portuguese water dog is autosomal recessive.

The natural history of the disease is such that dogs experience a preclinical or occult phase during which echocardiographic or electrocardiographic evidence of the disease is present (see Diagnosis) but clinical signs are absent (ACVIM stage B). The length of this phase is variable and likely extends over months to years, depending on the breed. In the Doberman, previous retrospective work suggested a median preclinical phase of just over a year whereas new prospective clinical trial data suggest a median of two years with the use of pimobendan. The preclinical phase can be quite prolonged in the IW, averaging 48 months in one trial.

The overt phase follows, characterized by the onset of clinical signs including syncope, SD, or those typical of CHF (ACVIM stage C). In the Doberman, 25–30% experience SD before CHF. Survival time following the onset of CHF or syncope is again breed and etiology dependent, with Dobermans and Great Danes experiencing the shortest survival times among breeds (see Prognosis).

Risk factors for the development of DCM apart from breed may include taurine deficiency (in cocker spaniels, Labrador and golden retrievers, or nontraditional DCM breeds), sustained tachyarrhythmias, myocarditis, or chemotherapy (anthracyclines).

Signalment

Dilated cardiomyopathy occurs predominantly in middle-aged to older, medium- to large-breed dogs. The most commonly reported breeds in North America and Europe include the Doberman pinscher, IW, Great Dane, Newfoundland, boxer, Labrador and golden retrievers, cocker spaniel, Scottish deerhound, Afghan hound, St Bernard, German shepherd, Old English sheepdog, Airedale terrier, standard poodle, Rottweiler, and mastiff. Small-breed dogs are uncommonly affected but sporadic cases can be found.

Age at diagnosis is typically between 4 and 8 years, depending on breed. Much younger and much older dogs may certainly be affected, regardless of breed. Specific juvenile forms of DCM are described in the Portuguese water dog, Doberman, and toy Manchester terrier, resulting in rapidly progressive CHF or SD at weeks to months of age. Sporadic cases in very young dogs of other breeds may occur, and should prompt consideration of viral myocarditis or primary tachyarrhythmia as an underlying cause.

Many studies report a gender bias in males. While this is not corroborated in all studies of individual breeds, it is the case for the majority of studies involving multiple breeds. Male Dobermans and IWs may be affected at an earlier age than females.

History and Clinical Signs

History may be unremarkable and preclinical cases identified by an incidental abnormality on physical exam (such as a heart murmur, gallop, or arrhythmia) or by prospective screening in high-risk breeds. Some of these dogs in the preclinical stage may have surprisingly profound cardiac dysfunction in the absence of clinical signs. More often, dogs are presented because of clinical signs of a fairly acute nature. Respiratory signs are the most common, including coughing and/or increased respiratory rate or effort due to pulmonary edema from left-sided CHF. With severe pulmonary edema, expectoration

of pink-tinged fluid may be noted. Pleural effusion from right-sided CHF can also produce increased respiratory rate and effort. Other signs include exercise intolerance, weakness, syncope, abdominal distension due to ascites, weight loss, and reduced appetite or anorexia (see Chapter 15). Sometimes SD is the first clinical sign noted. The typical clinical signs exhibited may vary by breed. For example, Dobermans tend to have a higher incidence of syncope and SD and their pulmonary edema and resultant respiratory signs are often quite severe, whereas IWs and Newfoundlands frequently present with evidence of right-sided CHF (ascites and pleural effusion).

The most common abnormalities detected on physical examination are a soft systolic murmur over the mitral or tricuspid area (often grade 1–3/6) and weak peripheral pulses. However, various studies have reported murmurs in as few as 33% and as many as 76%, so the absence of a murmur does not rule DCM out, and physical examination may be normal in the early preclinical phase. Additional findings may include a diastolic gallop (low-frequency third heart sound), an arrhythmia (ventricular premature contractions and atrial fibrillation most common), pulse deficits (if an arrhythmia is present), and jugular venous distension or pulsation. For dogs in CHF, additional findings may include pale or cyanotic mucous membranes, increased lung sounds or pulmonary crackles, tachycardia, tachypnea, dyspnea, hypothermia, and hepatomegaly (hepatic congestion) or a fluid wave (ascites) on abdominal palpation.

Diagnosis

The diagnosis of DCM involves a minimum of an echocardiogram and electrocardiogram (ECG). Holter recording (24-hour ambulatory ECG) is the most appropriate form of ECG in breeds where ventricular arrhythmias are common or an early finding such as Dobermans, for longer term heart rate (HR) assessment in atrial fibrillation, or if a cause for syncope is sought. In cases where echocardiography is not immediately available, thoracic radiographs may be useful for detecting cardiomegaly, and plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) level can be useful in Dobermans for assessing likelihood of preclinical disease. For dogs with suspected CHF, thoracic radiographs and serum biochemistry should be performed. The role for blood-based tests including biomarkers, taurine levels, and genetic tests is also discussed below. Screening should be performed yearly in high-risk breeds.

Electrocardiography

While arrhythmias are frequently reported on ECG (89% of cases in one large retrospective study), they can be very intermittent. Ventricular arrhythmias (VA) (ventricular premature contractions [VPCs] or ventricular tachycardia [VT]) and atrial fibrillation (AF) are most common, but are not specific for DCM on their own (Figures 26.1 and 26.2).

There are differences between breeds in arrhythmia manifestation. VA are very common in Dobermans, boxers, and Great Danes, so their presence should always raise suspicion of DCM in these breeds. In one study in Dobermans, one or more VPCs on a 5-min ECG was almost 97% specific for detecting a level of VA on Holter recording that would be suggestive of DCM. However, the presence of VPCs on a 5-min ECG alone is fairly insensitive for detecting DCM. Studies report 44–64% of affected Dobermans and 54% of affected Great Danes



Figure 26.1 Lead II ECG, 12.5 mm/s, 5 mm/mV. VPCs in a Doberman pinscher with DCM. A short run of VT is seen at the beginning of the ECG followed by intermittent single monomorphic VPCs.



Figure 26.2 Lead II ECG, 25 mm/s, 5 mm/mV. Atrial fibrillation in a Golden retriever with DCM. Note the irregular rhythm, absence of P-waves, and presence of baseline undulations or fibrillation waves.

had at least one VPC on a 5-min ECG and during echo exam, respectively, emphasizing that many affected dogs will have a normal in-hospital ECG.

Atrial fibrillation (AF) is more common in IWs and Newfoundlands and is often an early finding in IWs (found in 75% of occult DCM cases, >90% of overt DCM cases). In other breeds it tends to be associated with more advanced or overt disease. Importantly, giant-breed dogs can also have "lone" AF unassociated with gross cardiac pathology, in which case the HR is often normal. However, in the IW, it is hypothesized that AF may be a precursor to DCM in many cases.

Additional ECG findings can include tall and wide QRS complexes (lead II R-wave >3.0 mV, QRS duration >0.06 ms) associated with left ventricular (LV) enlargement, notched R-waves associated with microscopic ischemia, wide P-waves (lead II P duration >0.04 ms) associated with left atrial enlargement, and sinus tachycardia (particularly in CHF cases). Note that these ECG findings are neither sensitive nor specific for DCM.

Holter Recording

Given that arrhythmias apart from AF are typically intermittent and in-house ECGs are relatively insensitive, Holter recordings can be very useful for diagnosing and quantifying arrhythmias, for seeking cause of collapse by coupling clinical signs with rhythm analysis, and for assessing therapeutic response to antiarrhythmics. In Dobermans, the presence of >300 VPCs/24h, or two subsequent recordings within a year with 50–300 VPCs/24h, may be suggestive of DCM. Coupling a Holter recording with a NT-proBNP level can increase sensitivity for initial screening (see Circulating Biomarkers). Whether these Holter criteria are appropriate for breeds other than Dobermans is not known, but in one study, 70% of affected Great Danes had a similar degree of arrhythmia. Holter monitoring is also useful for monitoring HR in cases of AF as it yields a more accurate assessment of rate control. Care should be taken to utilize Holter analyses that have been manually edited and verified by qualified personnel as purely automated analyses are notoriously inaccurate.

Thoracic Radiography

Thoracic radiographs are relatively insensitive to detect the mild cardiac enlargement typical of occult cases. In instances of more severe disease, they can reveal varying degrees of cardiomegaly (left-sided or generalized). Thoracic radiographs are always indicated if CHF is suspected. In addition to LV enlargement, findings in CHF include left atrial and possibly right-sided enlargement, pulmonary venous distension and varying degrees of pulmonary edema (interstitial changes in mild to moderate cases and alveolar opacities with air bronchograms in severe cases). The distribution of pulmonary edema is often greatest in the caudodorsal lung fields, but can be diffuse in severe cases (Figure 26.3).

In Doberman pinschers, the degree of radiographic cardiomegaly is often surprisingly modest, even in the

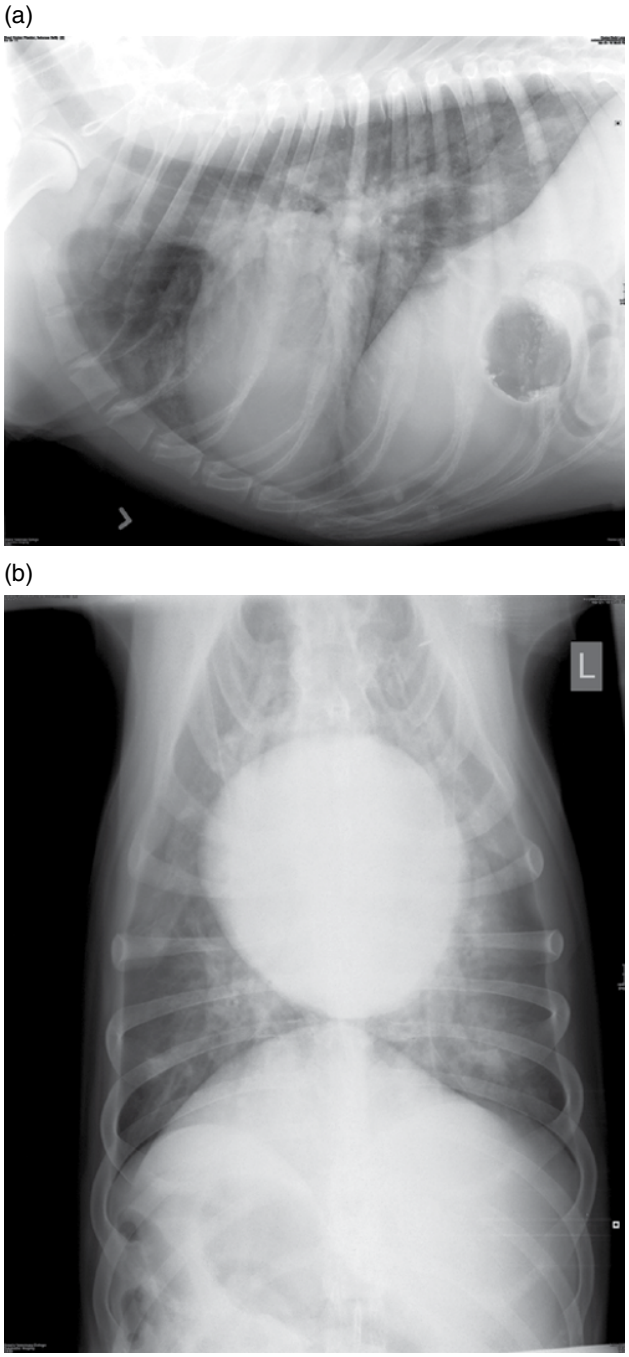


Figure 26.3 Lateral (a) and VD (b) thoracic radiographs in a Doberman with DCM and CHF. Note the cardiomegaly (including left atrium), pulmonary venous distension, and diffuse interstitial pulmonary infiltrates (worse caudodorsally but also present cranioventrally).

face of severe dilation on echocardiography. This phenomenon might be due to the Doberman's relatively deep chest conformation and the relative lack of right heart involvement compared to other breeds. Breeds with frequent right-sided involvement such as IWs and Newfoundlands often also have pleural effusion, as do dogs that develop AF.

Echocardiography

Echocardiography is necessary for identification and quantification of the characteristic structural abnormalities, including LV chamber dilation and systolic dysfunction, and equally important for ruling out other cardiac causes apart from DCM for these findings (e.g., valvular disease, congenital shunt) (Figure 26.4).

Increased LV end-systolic dimension (LVESD) and/or volume (LVESV) is noted, along with increased LV end-diastolic dimension (LVEDD) and/or volume (LVEDV). Linear dimensions (diameters) are generated from an M-mode of the LV in a short- or long-axis view immediately below the mitral valve, and volumes are preferentially generated by tracing the LV endocardium in a right parasternal long-axis or left apical four-chamber view and using automated software for Simpson's method of discs. These parameters are often indexed to body weight (BW) or body surface area (BSA) to normalize for differences in body size and conformation. In Dobermans, volume indices have been shown to be more sensitive in detection of LV dilation than diameters. Normal parameters and breed-specific criteria suggesting the diagnosis of DCM from various studies are presented in Table 26.1. The reader is referred to the Further Reading list for more detailed information on the methods and views used.

Left ventricle wall motion is globally and symmetrically reduced in most cases, but some dogs may have increased septal motion compared to the free wall owing

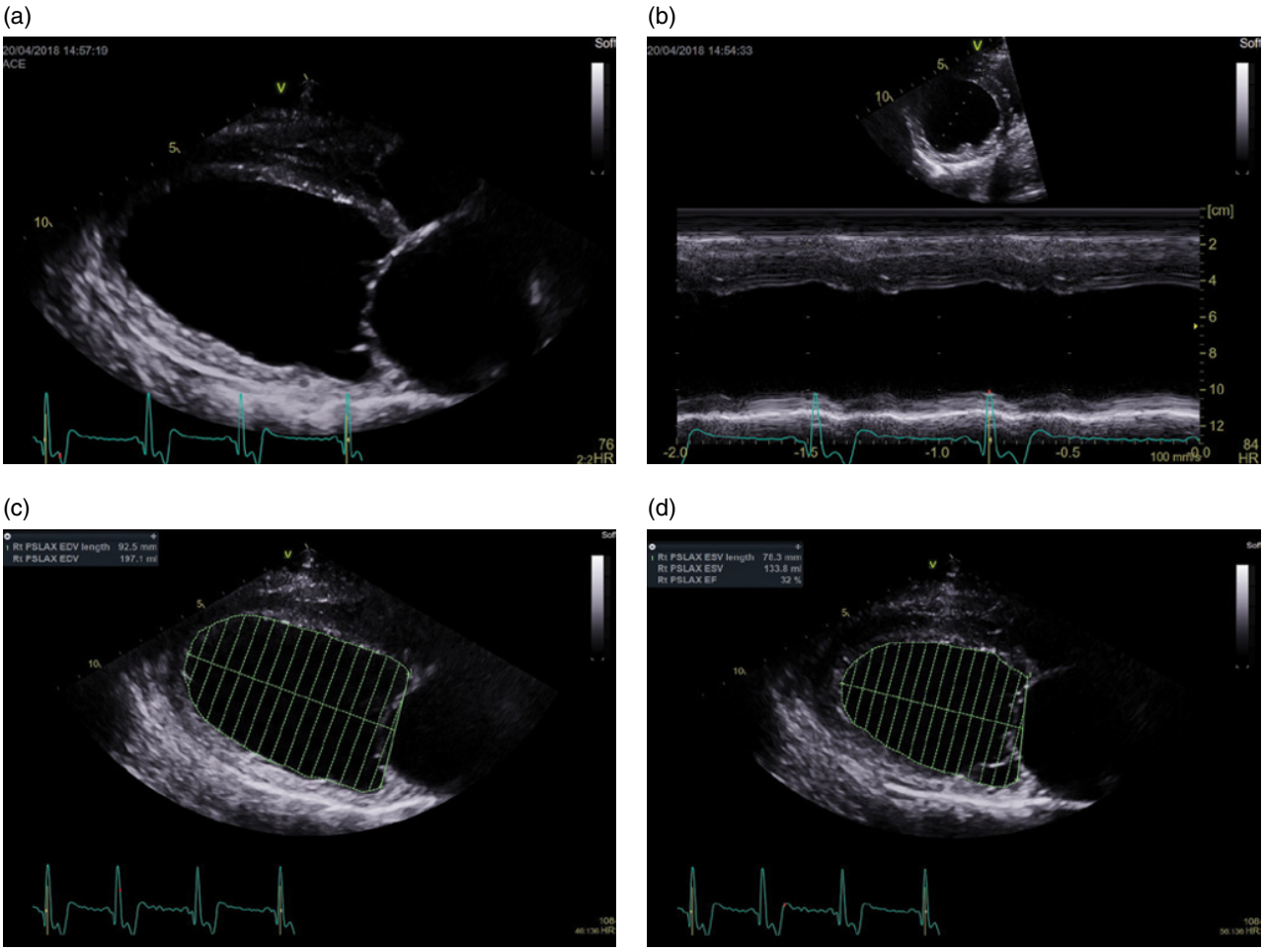


Figure 26.4 Two-dimensional echocardiographic images (right parasternal long-axis view) and M-mode (right parasternal short-axis view) from a Doberman with DCM. The left heart is in the far field and right heart in the near field. (a) Note the dilated LV in this systolic frame. (b) M-mode shows reduced systolic septal and LV free wall motion. (c,d) LV volume measurement in diastole and systole by Simpson's method of discs.

Table 26.1 Echocardiographic parameters in normal dogs and breed-specific criteria suggestive of diagnosis of DCM

Parameter	Normal value
Normal parameters	
LVEDD index = LVEDD ÷ $BW^{0.294}$[a]	1.27–1.85 (95% PI)
LVESD index = LVESD ÷ $BW^{0.315}$[a]	0.71–1.26 (95% PI)
LVESV index (LVESV ÷ BSA)	<30 mL/m^2 (note this value is likely overly conservative)
Parameter	**Abnormal value**
Breed-specific criteria for diagnosis of DCM	
Dobermans[b]	
LVEDD	>48 mm (M) or >46 mm (F)
	Or >0.1749 × BW + 40.3 mm
LVESD	>36 mm (M or F)
	Or > 0.1402 × BW + 35.0 mm
LVEDV index (LVEDV ÷ BSA)	>95 mL/m^2
LVESV index (LVESV ÷ BSA)	>55 mL/m^2
Irish wolfhounds[c]	
LVEDD	>61.2 mm
LVESD	>41 mm
LVESV index (LVESV ÷ BSA)	>41 mL/m^2
Great Danes[d]	
LVEDD	>56.1 mm (M) or >54.0 mm (F)
LVESD	>42.7 mm (M) or >41.7 mm (F)
LVESV index (LVESV ÷ BSA)	>44 mL/m^2

[a] Cornell CC, Kittleson MD, Della Torre P, *et al*. Allometric scaling of M-mode cardiac measurements in normal adult dogs. *J Vet Intern Med* 2004; **18**: 311–21.
[b] Wess G, Domenech O, Dukes-McEwan J, *et al*. European Society of Veterinary Cardiology screening guidelines for dilated cardiomyopathy in Doberman pinschers. *J Vet Cardiol* 2017; **19**(5): 405–15.
[c] Vollmar AC. The prevalence of cardiomyopathy in the Irish wolfhound: a clinical study of 500 dogs. *J Am Anim Hosp Assoc* 2000; **36**: 125–32.
[d] Stephenson HM, Fonfara S, López-Alvarez J, *et al*. Screening for dilated cardiomyopathy in great Danes in the United Kingdom. *J Vet Intern Med* 2012; **26**: 1140–7.
BSA, body surface area; BW, body weight in kg; DCM, dilated cardiomyopathy; F, female; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVESD, left ventricular end-systolic dimension; LVESV, left ventricular end-systolic volume; M, male; PI, prediction interval.

to mitral regurgitation. Indices of ejection such as fractional shortening (FS) and ejection fraction (EF) are reduced (EF <40%). FS, while easy to calculate and often reported, is not a reliable measure of systolic function. As a result, there is not a definitive cut-off below which is diagnostic of DCM and little emphasis should be placed on this number alone. Having said that, in DCM dogs with CHF, FS is often <15%.

Additional two-dimensional findings can include left atrial dilation with more advanced disease, reduced mitral valve excursion, increased mitral valve E-point to septal separation, decreased LV sphericity index, and right ventricular and atrial dilation with biventricular disease.

Doppler findings can include secondary mitral regurgitation due to annulus dilation and papillary muscle dysfunction, evidence of diastolic dysfunction (abnormal transmitral flow patterns including impaired relaxation, pseudonormal, and restrictive), reduced aortic velocities, and reduced myocardial tissue velocities.

Circulating Biomarkers

Cardiac biomarkers include hormones released by cardiac myocytes in response to stretch and other stimuli

(NT-proBNP), or substances released from myocardial tissue in response to injury (cardiac troponin-I [cTnI]). Note that biomarker testing is never intended to be used in isolation and should not replace gold standard testing (e.g., echocardiography, thoracic radiography for CHF); rather, it may be a tool to complement, and in some instances justify, other indicated diagnostics. Diagnoses and therapeutic recommendations cannot be made on biomarker results alone.

The utility of NT-proBNP in identifying likelihood of occult disease has been examined in the Doberman. NT-proBNP >550 pmol/L had a sensitivity of 78.6% and specificity of 90.4% for detecting echocardiographic abnormalities in one study. It is more sensitive in the detection of structural disease than arrhythmic disease. Another study in Dobermans suggests that the combined use of Holter monitoring and NT-proBNP >457 pmol/L (either being abnormal) yields increased sensitivity (94.5%) and specificity (87.8%). A cTnI >0.22 ng/mL (Immulite®, Troponin I, Diagnostics Products Corporation, Los Angeles) yielded 79.5% sensitivity and 84.4% specificity for detection of DCM in another study. Dobermans with NT-proBNP or cTnI greater than these values should be evaluated with echocardiography.

For the differentiation of CHF from primary respiratory disease in dogs presenting with respiratory signs, plasma NT-proBNP >2447 pmol/L (using second-generation assay) was 81.1% sensitive and 73.1% specific in a study including 8% DCM cases in a variety of breeds. This may have utility when physical exam and thoracic radiography are ambiguous and echocardiography is not available, but otherwise may not provide added value.

Plasma Taurine

Whole-blood or plasma taurine should be measured (using heparinized samples) in cocker spaniels, retrievers, Dalmatians, any atypical DCM breed, or any case with a history of lamb-based diet, vegetarian diet, low-protein diet, grain-free diet (currently being investigated), or any unbalanced home-made diet. Whole-blood concentration <150 nmol/mL or plasma concentration <40 nmol/mL indicates significant taurine deficiency. Note that taurine deficiency is not necessarily related to amounts of taurine consumed, but may be due to abnormal absorption or excretion of taurine or its precursor amino acids (methionine and cysteine), abnormal taurine synthesis, or reduced protein digestibility limiting availability of precursors.

Genetic Tests

Tests are available for two genetic markers associated with DCM in Dobermans in North America (PDK4 and titin mutations) through the Veterinary Genetics laboratory at North Carolina State University (https://cvm.ncsu.edu/nc-state-vet-hospital/small-animal/genetics/). Note that these two mutations do not account for all DCM cases in Dobermans, a negative test does not assure a dog will not develop DCM, nor does a positive test assure the dog will develop clinical disease. With this in mind, genetic testing cannot replace standard clinical screening. Appropriate sample types include EDTA whole-blood or buccal swabs. Results may be:

- negative – individual does not carry that particular mutation (but there may be other mutations so not guaranteed to never develop DCM)
- positive heterozygote – individual carries one copy of the mutated gene and may or may not develop clinical disease
- positive homozygote – individual carries two copies of the mutated gene and may or may not develop clinical disease but if so, may be more severe.

The greatest utility of genetic testing is determining suitability for breeding. It is recommended that homozygous dogs not be bred, and heterozygous dogs should be bred only to negative dogs and only so long as they do not express the phenotype.

Therapy

Preclinical DCM (ACVIM Stage B)

Goals of therapy in preclinical cases include slowing systolic dysfunction, preventing ventricular remodeling and disease progression, and delaying CHF or SD. Two drugs for which there is evidence of these benefits are pimobendan and angiotensin converting enzyme inhibitors (ACEI). See Table 26.2 for all drug doses.

Pimobendan, a calcium sensitizer with positive inotropic and vasodilatory effects, delayed the progression of preclinical disease in Dobermans in a multicenter, placebo-controlled, double-blinded clinical trial. The PROTECT trial enrolled 76 Dobermans with preclinical DCM. The pimobendan group had a significantly longer time to the composite endpoint of onset of CHF or SD compared with the placebo group (63% increase in time to endpoint, nine months longer). Additionally, the pimobendan group had significantly longer overall survival time compared with the placebo group. There was no increase in VA noted on one-month recheck Holter monitoring and no increase in SD in the pimobendan group. It is important to note that all dogs in this study had presence of echocardiographic systolic dysfunction, so these results are not necessarily applicable to Dobermans presenting with VA alone. Pimobendan was also shown to prolong the time to CHF or SD in IWs with preclinical DCM, AF, or both. The similarity in pathology and pathophysiology among different breeds would suggest potential benefit in breeds other than Dobermans and IWs, but specific studies are required.

Table 26.2 Doses of commonly used cardiac medications in dogs (see text for indications)

Drug	Dose
ACEI	
Benazepril	0.25–0.5 mg/kg q12–24h PO
Enalapril	0.25–0.5 mg/kg q12h PO
Positive inotrope	
Pimobendan	0.25–0.3 mg/kg q12h PO
Dobutamine	5–15 µg/kg/min IV CRI
Dopamine	1–5 µg/kg/min IV CRI
Diuretic	
Furosemide	2–5 mg/kg q8–12h PO or IV
	0.5–1 mg/kg/h IV CRI
Spironolactone	2 mg/kg q24h PO
Hydrochlorothiazide	0.5–2 mg/kg q12h PO
Antiarrhythmic	
Sotalol	1–3 mg/kg q12h PO
Mexiletine	5–8 mg/kg q8h PO
Diltiazem	0.5–3 mg/kg q8h PO (for immediate release formulation)
	0.05–0.1 mg/kg IV slow bolus
	followed by 1–5 µg/kg/min IV CRI
Digoxin	0.003–0.005 mg/kg q12h PO (to max 0.25 mg/dog q12hr)
Lidocaine	2 mg/kg IV bolus (max. 4 boluses)
	followed by 30–70 µg/kg/min IV CRI
Beta-blocker	
Atenolol	0.25–1.0 mg/kg q12h PO
Carvedilol	0.1–0.5 mg/kg q12h PO
Vasodilator	
Sodium nitroprusside	1–5 µg/kg/min IV CRI
Supplements	
Taurine	500–1000 mg q12h PO (<25 kg)
	1000–2000 mg q12h PO (>25 kg)
L-Carnitine	50–100 mg/kg q8h PO
Omega-3 fatty acids	78 mg eicosapentaenoic acid and 497 mg docosahexaenoic acid per dog per day

ACEI, angiotensin converting enzyme inhibitor; CRI, constant rate infusion; IV, intravenous; PO, by mouth (*per os*).

The role of the renin-angiotensin-aldosterone system (RAAS) in maladaptive cardiac remodeling and progression of systolic dysfunction is well known. In addition to their mixed vasodilatory and natriuretic properties, ACEI exert benefit by antimyocardial remodeling effects. A retrospective study in Dobermans found that time to CHF or SD was significantly prolonged with benazepril treatment, with a 55–64% reduction of risk of those outcomes compared to no treatment. While the strength of evidence is not as strong as that for pimobendan, the author advocates the use of ACEI in preclinical DCM based on the collective evidence in the human and veterinary literature, unless there is a specific contraindication to this class of drug. Evaluation of renal function one week after initiation and periodically thereafter is recommended.

While there is good evidence in the human literature that beta-blocker therapy reverses LV remodeling, improves LV systolic function and patient symptoms, and prolongs life in chronic heart failure, clinical data are lacking on the use and efficacy of beta-blockers in canine DCM. Concerns with beta-blocker use typically include hypotension or CHF due to bradycardia and negative inotropy when first administering; therefore, they must be used with caution and uptitrated slowly.

Taurine supplementation should be initiated in any case suspected or documented to be due to taurine deficiency. L-carnitine can be simultaneously added or initiated after three months if there is inadequate response with taurine alone.

The patient with clinically significant VA is worthy of separate consideration. In humans, the risk of SD increases with declining systolic function or a history of syncope, yet there is no clear evidence that any antiarrhythmic (AA) drug is effective in preventing SD. In Dobermans, increasing LVEDV, presence of VT, and VPCs yielding instantaneous HR ≥260 bpm are associated with increased risk of SD. There are no studies addressing the efficacy of AA therapy in canine DCM. AA therapy may be considered in any DCM patient with frequent VPCs (>1 per minute) or VA with higher complexity or rate (couplets, triplets, or VT with instantaneous HR >180 bpm). Typical choices for AA therapy include sotalol, a AA with both beta-blockade and K+ channel blockade properties (initiating low doses and titrating upwards is often advised due to the beta-blockade), mexiletine, a Na^+ channel blocker, or a combination of the two.

Monitoring the preclinical patient should include physical examination, echocardiography, and ECG or ideally Holter recording every 4–6 months. If AA therapy is initiated, it is best to monitor therapeutic efficacy with Holter monitoring within 1–2 weeks of initiating therapy. Due to a high degree of daily variability, an in-house ECG is an inadequate alternative.

Overt DCM (ACVIM Stage C, CHF): Outpatient Therapy

Therapeutic goals in the CHF patient include resolution of clinical signs and improvement in quality of life

in addition to delay in disease progression and prolongation of survival. Strategies include intravascular volume reduction to resolve pulmonary edema or decrease cavitary effusions, improvement in hemodynamic performance through decreased systemic vascular resistance and improved contractility, neurohumoral modulation, arrhythmia management, and nutritional management.

The mainstay of treatment of edema and effusions remains diuretics, with furosemide the most commonly used agent. It may be administered orally or intravenously depending on the severity of CHF and whether the patient is being treated as an inpatient or outpatient. Following edema resolution, the dose may be lowered to the effective dose that maintains the patient free of respiratory signs and edema. Given its relatively short duration of action, dosing more than twice daily may be more effective. Substantive pleural effusion or ascites should be relieved with thoraco- and abdominocentesis, respectively.

Angiotensin converting enzyme inhibitor is indicated for RAAS blockade and vasodilatory effects, particularly in the setting of furosemide use which heightens RAAS stimulation. The results of veterinary clinical trials using enalapril and benazepril report improved quality of life, and although the improvements in survival did not reach statistical significance for DCM dogs, there is clear evidence of mortality reduction in human patients and ACEI use is considered standard therapy in dogs with DCM and CHF.

Three placebo-controlled trials have found significantly longer time to treatment failure or longer survival time in DCM dogs treated with pimobendan in addition to diuretics and ACEI, so pimobendan is considered part of standard therapy for CHF due to DCM.

The aldosterone antagonist spironolactone significantly reduces morbidity and mortality in humans with CHF and LV systolic dysfunction. While similar evidence is lacking in dogs with DCM, a study in Dobermans with CHF suggested a reduced risk of AF with spironolactone therapy. Spironolactone is often used in the patient that is still symptomatic despite use of triple therapy with furosemide, ACEI, and pimobendan, whereas some, including the author, advocate using it initially as part of standard therapy. Spironolactone is licensed for use in dogs with CHF in Europe.

Management of the overt DCM patient with VA includes optimal management of congestion and hemodynamics to reduce sympathetic nervous system stimulation and improve perfusion. Specific AA therapy may also be indicated. Patients with VA may be managed as outlined above for the preclinical stage. DCM patients with AF and in-hospital HR >150 bpm are candidates for rate control with AA therapy. While cardioversion to sinus rhythm may be physiologically ideal, rate control is much more feasible. Evidence suggests that the combination of diltiazem with digoxin is more efficacious for rate control than either drug alone. A target mean HR <125 bpm on Holter recording is ideal, and given higher HR in hospital, target mean HR on in-hospital ECG should be <140–150 bpm. Alternative therapy choices include a beta-blocker or sotalol, though beta-blockers should not be initiated in the setting of acute or poorly managed heart failure.

Cardiac cachexia is identified commonly in DCM CHF patients and nutritional support is an important part of therapy. Due to anorexia, increased energy requirements, and production of inflammatory cytokines, lean muscle mass is lost in the chronic heart failure patient. Management involves providing adequate calories and protein, and there is evidence that supplementation with omega-3 fatty acids is beneficial. While diets restricted in sodium are commonly advocated, the effects on quality of life or survival have not been assessed in dogs.

Overt DCM – Severe Life-Threatening CHF

Parenteral means of decreasing intravascular volume, increasing contractility, decreasing vascular resistance, and treating arrhythmias may be necessary in cases of severe CHF. Administration of oxygen by nasal prongs, cannula or cage is indicated in the case of hypoxia. Administration of intravenous (IV) furosemide by bolus or constant rate infusion (CRI) is the single most important and effective strategy to initiate promptly. Multiple boluses may be administered 30–60 minutes apart until the respiratory rate drops 50% from initial presentation or effort improves. If there is inadequate response after three doses, CRI should be initiated. Alternatively, one bolus followed immediately by CRI is preferred if the patient has preexisting azotemia or is particularly severe. Careful monitoring of volume status, renal function, and electrolytes is required. Thoracocentesis is indicated if substantive pleural effusion is contributing to dyspnea.

If rapid AF is present, initiation of IV diltiazem is indicated to reduce HR below 140–150 bpm. In cases of VA in the setting of CHF, treatment may be warranted if VT is present, signs of weakness or collapse are present, or the patient is a breed with a high incidence of SD such as Dobermans and boxers. IV lidocaine is typically the first treatment of choice.

In the absence of arrhythmias, IV furosemide may be enough to stabilize some patients whereas others will require the addition of a parenteral positive inotrope +/– vasodilator. Dobutamine CRI is the IV positive inotrope of choice for treatment of severe edema and hypotension. Side-effects include nausea/vomiting and exacerbation of VA, in which case the dose should be decreased. It is important to note that if AF is present, IV diltiazem

should be initiated for rate control before dobutamine to avoid life-threatening tachycardia. Dobutamine is typically administered for <72 hours due to the development of receptor refractoriness. If dobutamine is not available or feasible, then oral pimobendan should be started as soon as possible.

Sodium nitroprusside is a potent mixed vasodilator that may be added as a CRI for the treatment of severe life-threatening edema. Blood pressure must be monitored very frequently, preferably invasively and continuously. Side-effects include hypotension (which can be quickly resolved by stopping or decreasing the dose due to its very short duration of action), and rarely cyanide toxicity with high dose and prolonged use (>72 hours). With the initiation of all of these infusions, careful attention must be paid to the volumes of fluids being administered, and solutions should be concentrated as much as possible to reduce the total volume being administered.

Following stabilization, weaning of IV medications and transition to the oral medications discussed above (as for outpatient) is carried out.

For the refractory CHF patient (those with advanced CHF that continue to have clinical signs despite standard therapy – ACVIM stage D), management strategies include confirming owner compliance with current medications, identifying complicating concurrent conditions (poorly controlled or new arrhythmias, systemic diseases such as hyperadrenocorticism, neoplasia, infectious or inflammatory conditions), and changing medication strategies. The latter can include an increase in the frequency or change in route of furosemide administration (IV bolus or CRI for short periods), addition of diuretics such as spironolactone or hydrochlorothiazide (the latter should be accompanied by a reduction in furosemide dose), stricter sodium restriction, increase in inodilator and/or ACEI dose, or short-term parenteral positive inotrope (dobutamine) or vasodilator (nitroprusside) administration as described above.

Follow-up/Monitoring of Overt DCM

The focus of follow-up is respiratory status (respiratory rate and effort, degree of pulmonary edema or pleural effusion on thoracic radiography), renal status and electrolyte balance (renal chemistry and electrolytes), body condition and hydration (body weight, body condition score [BCS]), HR and rhythm (auscultation, ECG or Holter), and perfusion (body temperature, blood pressure, renal chemistry, electrolytes). These assessments may be made as frequently as weekly at the initiation of therapy to every 1–2 months once patients are stable. While ACEI and pimobendan doses are often optimized at the onset, diuretic doses are adjusted to balance pulmonary and renal/hydration needs. Following initiation of or change in dose of AAs, recheck ECG or ideally Holter is advised within 1–2 weeks to assess VA control or rate control in the case of AF, and medications adjusted accordingly. One cannot expect to eliminate VA but rather a reduction of the frequency, complexity, and HR is a reasonable goal (preferably reduction of >80%). In the case of AF, HR targets must be individualized to what appears to be optimal for the patient based on the assessments above, but a general guideline is a target mean HR <125 bpm on Holter or <140–150 bpm in hospital.

Prognosis

Dogs with preclinical disease may go several years without clinical signs, so the diagnosis does not imply immediate risk of morbidity or mortality. Data on the length of this phase are lacking for most breeds except the Doberman and IW. Based on the PROTECT trial, the median time to CHF or SD following diagnosis of occult disease in Dobermans was 718 days in the pimobendan-treated group and 441 in the placebo group. IW may have a very prolonged preclinical phase, with an average of 48 months in a recent clinical trial.

Unless a reversible underlying cause is identified (e.g., taurine deficiency, primary tachyarrhythmia), the prognosis for DCM is often poor once overt clinical disease (CHF) develops, with most survival times being in months. The median survival time in a large retrospective study with mostly overt dogs was 19 weeks, with one-year and two-year survival rates of 28% and 14%, respectively. Fifty percent of dogs were euthanized for their heart disease in this study, while 40% died from their heart disease, and 3% died for other reasons, emphasizing the almost inevitably terminal nature of this disease. In the Doberman, one-year survival rates of 10% or less have been reported, and treatment with triple therapy (ACEI, furosemide, pimobendan) yielded a median survival time of 130 days. IW may have a better prognosis once in CHF, with median survival time of five months in those dying of their disease but 14 months in those still alive at the time of writing of one study.

Factors associated with shorter time to CHF or SD in the PROTECT trial included an increase in LVESD index, increased baseline HR, and ≥4 VPCs on a 3-min ECG. Factors associated with negative prognosis in overt DCM have included increased LVESV index, decreased EF, presence of pulmonary edema on radiographs, presence of ascites, presence of VPCs on ECG, increased serum creatinine, decreased plasma protein, Great Dane breed, and restrictive transmitral flow pattern on Doppler echocardiography. Factors associated with increased risk of SD in Dobermans include larger LVEDV, presence of VT, VPCs with instanteous HR ≥260 bpm, and higher cTnI.

Arrhythmogenic Right Ventricular Cardiomyopathy

Etiology/Pathophysiology

Arrhythmogenic right ventricular cardiomyopathy is a progressive myocardial disorder characterized by partial to complete replacement of the right ventricular (RV) myocardium with fatty or fibro-fatty tissue, presence of ventricular arrhythmias, and risk of SD. The distribution of pathologic changes is greater in the subepicardium, and the left ventricle is not spared despite being a predominantly RV disorder. In humans, a majority of cases are familial or inherited and genetic mutations in at least 20 genes encoding mostly proteins of the desmosome (region of intercalated discs between myocardial cells involved in mechanical and electrical coupling) have been implicated. A few nondesmosomal genes, including the cardiac ryanodine receptor (RyR2, calcium release channel of the sarcoplasmic reticulum), have also been involved.

Arrhythmogenic right ventricular cardiomyopathy is likewise a familial (inherited) disorder in the boxer. The disease, once referred to as "boxer cardiomyopathy," has been reclassified as ARVC due to its similarities with the human disease. To date, none of the mutations described in people have been found in the boxer. Rather, an 8-base pair deletion in the striatin gene has been linked to ARVC in some American boxers, though its causal role has been challenged. Striatin is an intercalated disc protein that co-localizes with three of the desmosomal proteins implicated in ARVC in people. There is also some suggestion that the RyR2 is involved as affected boxers have a deficiency of calstabin2, a RyR2 protein.

Arrhythmogenic right ventricular cardiomyopathy in dogs manifests as ventricular tachyarrhythmias predominantly of RV origin (left bundle branch block [LBBB] configuration) and patients are at risk of SD from ventricular fibrillation (Figure 26.5).

Supraventricular tachyarrhythmias may also occasionally be noted. In boxers, the hearts are most often structurally normal on gross examination, unlike in humans where RV dilation, systolic dysfunction, and aneurysms are common. A small percent of boxers experience systolic dysfunction and heart failure, whereas this may be more common in English bulldogs, another affected breed.

Epidemiology

The true prevalence of ARVC in the boxer is unknown, but anecdotally it would appear to be quite common. The prevalence in other breeds is very low.

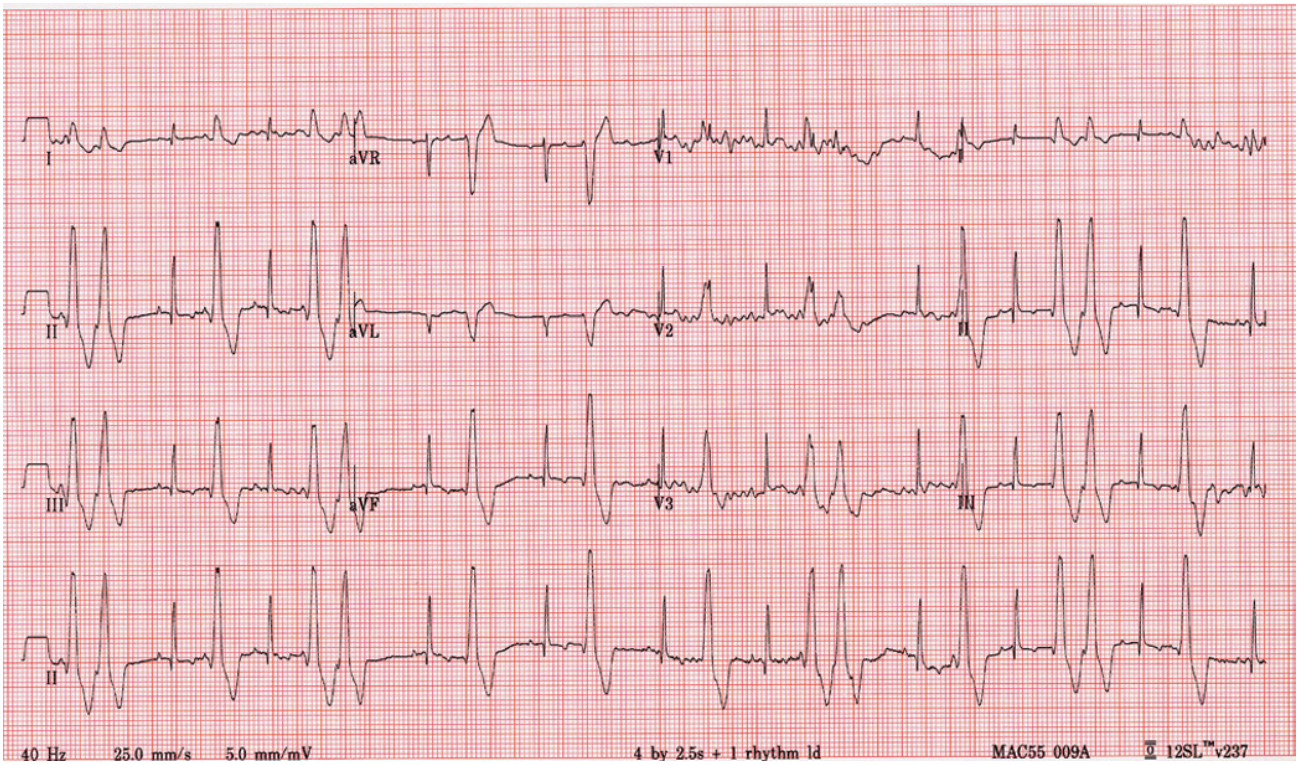


Figure 26.5 Nine-lead ECG, 25 mm/s, 5 mm/mV. Right ventricular VPCs (left bundle branch block configuration) in a boxer with ARVC. There are periods of ventricular bigeminy (alternating VPCs and sinus beats) and several VPC couplets.

The mode of inheritance in the boxer is autosomal dominant with incomplete and age-related penetrance and variable expression. Dogs homozygous for the striatin mutation exhibit a more severe form of disease and there may be association with myocardial failure.

The natural history of the disease in the boxer can be quite variable. Frequently, dogs may present with incidental VA and remain asymptomatic for years. The percentage of boxers that develop syncope has varied from 33% to 68% in different studies. The percentage that experienced SD in one prospective longitudinal study was 31%. Less than 10% of boxers develop myocardial failure and CHF. In contrast, in a case series of 31 English bulldogs with ARVC, 52% had CHF (38% left-sided, 33% right-sided, and 19% biventricular failure).

Risk factors for the development of ARVC apart from breed are unknown. Risk of SD in boxers appears to be higher with a previous history of syncope, more frequent VPCs, more complex VA (couplets, triplets, runs of VT), and more runs of VT. In humans, being a competitive athlete has been linked with increased risk of SD, suggesting the cardiac strain associated with intense exercise can exacerbate VA.

Signalment

Arrhythmogenic right ventricular cardiomyopathy is most common in the boxer breed. Males tend to be overrepresented. The average age at diagnosis is 5–7 years but younger and older dogs may be affected. Multiple cases are now also reported in the English bulldog. Isolated cases of a similar RV cardiomyopathy have been reported in a dachshund, bullmastiff, Labrador retriever, Siberian husky, Shetland sheepdog, Dalmatian, and Weimaraner.

History and Clinical Signs

Many boxers present without any clinical signs and are detected incidentally through identification of an arrhythmia on physical exam or through active screening programs. Roughly one-third to two-thirds may have a history of syncope, and roughly one-quarter experience exercise intolerance. Few present with respiratory signs typical of CHF, whereas this appears to be more common in English bulldogs. It is important to note that there are other causes of syncope in the boxer apart from ARVC.

Physical examination may be normal since the VA are intermittent. Alternatively, intermittent premature beats may be heard on auscultation, or rather the "pause" after a premature beat may be more apparent than the premature beat itself. Bursts of tachycardia may also be noted in more severely affected dogs. Dogs with arrhythmias may have pulse deficits. Soft left base murmurs are common in boxers and not specifically indicative of myocardial disease.

Diagnosis

There is no gold standard for antemortem diagnosis of ARVC in dogs. However, Holter recording is the most valuable diagnostic tool, and should be performed in any boxer with an auscultable arrhythmia, with a history of exercise intolerance or syncope, for active screening in any asymptomatic adult boxer especially with a family history of ARVC or positive genotype (starting at >3 years of age), or for those in breeding programs. Diagnostic criteria have yet to be clearly defined. Greater than 100 VPCs per 24 hours of RV origin (LBBB configuration, "upright" orientation in lead II) is suspicious for ARVC in the absence of another identifiable cause, particularly if there is increased complexity like couplets, triplets, or VT, and >300 VPCs/24h is a more suggestive threshold.

One study proposed three diagnostic criteria (>100 VPCs/24h, presence of couplets, and presence of R-on-T phenomenon) with the presence of two out of three possibly being a more robust way to identify the disease. However, these or any other cut-offs have yet to be validated prospectively, and to rely solely on the total VPC count may be erroneous. The complexity of the arrhythmia and the complete clinical presentation should be considered when making the diagnosis. Holter recordings can have a high degree of day-to-day variability (as much as 80%) and therefore may need to be repeated in dogs with high suspicion yet equivocal results.

Myocardial biopsy is not typically used for diagnosis owing to anesthetic requirements and invasiveness, as lesions may be missed given the epicardial and patchy distribution of pathology, and the risk of adverse effects including provocation of arrhythmias or cardiac puncture.

Unlike in humans, imaging modalities including echocardiography have low diagnostic yield as they are often normal. In few boxers will RV or LV dilation and systolic dysfunction be appreciable whereas in a case series of English bulldogs, 59% had subjective RV dilation. Cardiac MRI may have utility in detecting the fatty infiltration that characterizes the disease, but this remains to be investigated thoroughly in dogs.

Circulating biomarkers including cTnI and NT-proBNP are not useful for detection of ARVC, based on studies in boxers. While cTnI levels did correlate with degree of arrhythmia, the degree of overlap with presumably normal boxers renders it an unsatisfactory screening tool.

A genetic test for the striatin mutation in boxers is available through the Veterinary Genetics laboratory at North Carolina State University (https://cvm.ncsu.edu/nc-state-vet-hospital/small-animal/genetics/). Interpretation and breeding recommendations are as for the DCM genetic tests outlined above, and genetic screening cannot replace clinical screening.

Therapy

While AAs have been shown to reduce VA frequency and syncope, it is uncertain whether they decrease risk of SD because studies are lacking. Nevertheless, AA therapy remains the mainstay of ARVC treatment. A consensus on arrhythmia threshold necessitating treatment is lacking, and each patient must be approached on a case-by-case basis. Even asymptomatic dogs may be at risk of SD, but this must be balanced with proarrhythmic risk of AA drugs and owner factors including commitment to long-term therapy. Suggested candidates for AA therapy include dogs with a history of syncope, those with VT regardless of total VPC number, those with >300 VPC/24h and increased complexity including couplets, triplets, or R-on-T (rapid VPCs), or those with >1000 VPC/24h.

For immediate treatment of VT or VA causing weakness or collapse, intravenous lidocaine is recommended. The most common and effective oral AAs are sotalol, mexiletine, or a combination of the two in more refractory cases (see Table 26.2). Note that therapy may be indicated prior to Holter recording, as in instances where there is a history of syncope and VT is identified on ECG. Therapy should be monitored by Holter examination within 1–2 weeks of AA initiation, and periodically thereafter (every six months). Therapeutic efficacy is supported by a >80% reduction in arrhythmia number and complexity. An increase in syncope post treatment may suggest a proarrhythmic effect and should be evaluated with Holter promptly.

There is some evidence that oral supplementation with omega-3 fatty acids may also be beneficial (see Table 26.2).

For the minority that experience CHF (left, right, or biventricular), therapy with ACEI, pimobendan, and diuretics is indicated as described above for DCM, in addition to AA therapy. L-carnitine may also be added given positive response in a small family of boxers.

Prognosis

While all dogs with ARVC are at risk of SD, many remain symptom free for years. In one prospective study of boxers, the median survival time after identification of >300 VPC/24h was just over four years, and in fact overall survival of the affected group was not significantly different from the control boxer group (survival to 10–11 years of age), whereas a retrospective study of boxers with more advanced disease suggested a median survival time of 365 days (range 7–1971 days). The probability of death within a year was almost five times greater with a history of syncope, just over five times greater with >10 000 VPCs/24h, and 20 times greater with >200 runs VT/24h. In a case series of English bulldogs, a median survival time of 8.3 months was reported, but whether the prognosis is truly worse in that breed is not known, as it is likely that these dogs had more advanced disease at the time of diagnosis than other boxer studies.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is a primary myocardial disease characterized by symmetric or asymmetric concentric hypertrophy (thickening) of the LV in the absence of a stimulus for hypertrophy (e.g., stenosis or hypertension), leading to diastolic dysfunction and arrhythmias that may result in CHF or SD. In humans, 50% or more of cases are related to familial genetic mutations. While common in the cat, HCM is very rare in dogs. Like in the cat, dynamic LV outflow tract obstruction (LVOTO) caused by systolic anterior motion of the mitral valve (SAM) is described in some cases.

Many cases of canine HCM appear to be in young dogs, with males overrepresented. This has raised the question as to whether the disease may be congenital and furthermore, whether LVOTO may represent a form of mitral valve dysplasia predisposing to SAM and secondary hypertrophy. Many affected breeds have been reported and include the pointer, golden retriever, Rottweiler, German shepherd, and shih tzu, amongst others. Cases are frequently evaluated for the presence of an incidental murmur which may be dynamic. Echocardiography is necessary for diagnosis. Treatment is targeted at reducing dynamic LVOTO with beta-blockade (atenolol), and treating CHF or arrhythmias in severe cases. A number of cases in young dogs have been noted to resolve with maturity, while others have persisted and resulted in CHF or SD. It is difficult to estimate prognosis based on the sparse reports of this disease in dogs.

Further Reading

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27

Feline Myocardial Disease

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Myocardial disease is extremely common in cats and will be encountered regularly by any feline clinician, but can be hard to recognize. Feline myocardial disease is very heterogeneous in presentation, clinical findings, and prognosis. Without skilled echocardiography, identifying the different subclassifications of cardiomyopathy is usually difficult. Fortunately, this is not usually necessary, as the main priorities for the clinician are to identify those cats with a specific treatable cause of myocardial disease, and to identify cats at high risk of congestive heart failure (CHF) or aortic thromboembolism (ATE).

Etiology

The term "myocardial disease" includes a range of conditions with varied etiologies. Cardiomyopathies are usually classified according to a phenotype based on cardiac structure and function (Figure 27.1).

The myocardium can be affected by systemic conditions such as hyperthyroidism, systemic hypertension, and anemia, where disturbances in hemodynamic loading conditions may alter cardiac structure and function. The myocardium has a limited range of responses to injury or insult, so that different underlying causes can result in the same phenotype. For example, dietary taurine deficiency, an uncontrolled tachyarrhythmia or doxorubicin toxicity can all result in an identical "dilated cardiomyopathy phenotype" characterized by systolic dysfunction and ventricular dilation. In other cats, no obvious underlying cause is identified, although a genetic predisposition is suspected in some.

Traditionally, feline cardiomyopathies have been classified according to contemporary human classifications, but controversy currently exists over whether human myocardial disease should be classified according to etiology or phenotype. The most commonly recognized phenotype is hypertrophic cardiomyopathy (HCM), characterized by thickened left ventricular (LV) walls. Other phenotypes include restrictive cardiomyopathy (RCM), defined as relatively normal LV walls but with atrial enlargement and increased atrial pressures; dilated cardiomyopathy (DCM), recognized by atrial and ventricular dilation with global LV hypocontractility; and arrhythmogenic right ventricular cardiomyopathy (ARVC), which is typically manifested by fibrofatty replacement of predominantly the right heart. There is considerable overlap between phenotypes, so an additional category of "unclassified cardiomyopathy" or "non-specific phenotype" is sometimes used to describe patients with a phenotype that does not correspond with any of the above criteria.

Unless a causative systemic disease or myocardial insult can be identified, the etiology is unknown for most cats with myocardial disease, although familial HCM is recognized. A genetic cause has been established for HCM in Maine Coon and ragdoll cats, where two different genetic mutations have been identified in the myosin-binding protein C gene. In contrast, an HCM phenotype has been associated with over 1400 different mutations in humans, although a genetic cause is not identified in all human HCM patients.

Pathophysiology

The functional disturbance and consequent pathophysiology vary according to type of cardiomyopathy and severity of disease. With mild myocardial abnormalities, affected cats may not experience any obvious adverse consequences. With severe or advanced myocardial disease, congestive heart failure is the most commonly recognized sign. Sudden death is also a potential sequela, but the prevalence is unknown and probably underestimated. Systemic or arterial thromboembolism is recognized in many advanced cases of cardiomyopathy with left heart involvement.

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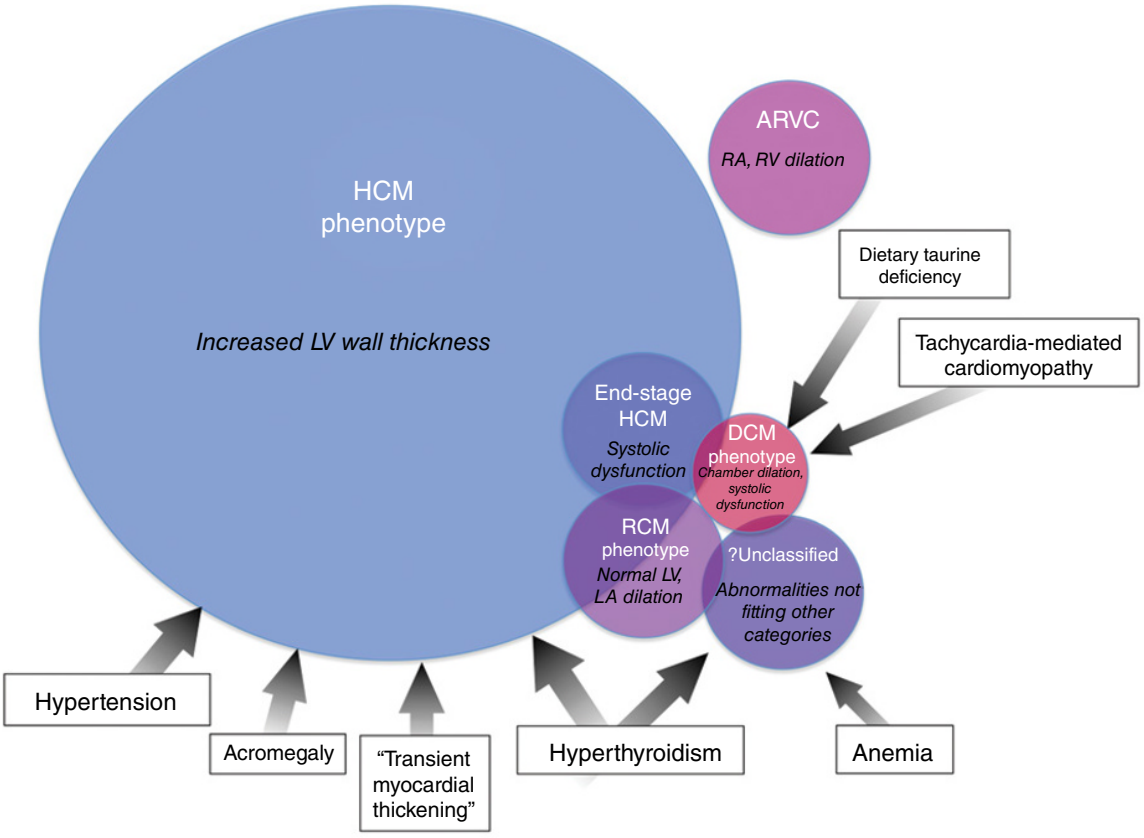


Figure 27.1 Myocardial disease phenotypes. There is overlap in the cardiac characteristics between the different "classic" forms of cardiomyopathy, and it can be difficult to differentiate cardiomyopathies with a genetic or unknown etiology from cardiomyopathies caused by systemic disease on the basis of cardiac characteristics alone. Hypertrophic cardiomyopathy (HCM) is defined as left ventricular (LV) hypertrophy in the absence of an obvious cause, but hypertension, acromegaly, "transient myocardial thickening," and hyperthyroidism can all result in a phenotype that is identical to classic HCM. A minority of cats with severe (primary) HCM develop systolic dysfunction, and are described as "end-stage HCM," overlapping with dilated cardiomyopathy (DCM). A DCM phenotype can be produced by taurine deficiency or a tachycardia-mediated cardiomyopathy though no underlying cause is found in most cats with dilation of all four cardiac chambers and global systolic dysfunction. The classic form of restrictive cardiomyopathy (RCM) is defined as normal LV dimensions with biatrial enlargement, but there is overlap with the above phenotypes. Not all cats fit into one of the categories listed above. Those with predominantly right heart enlargement without an obvious cause are usually presumed to be arrhythmogenic right ventricular cardiomyopathy (ARVC), but others do not fit any category and are sometimes called "unclassified cardiomyopathy" or "non-specific phenotype".

HCM

Key pathologic features of HCM include increased LV mass associated with myocyte disarray, interstitial myocardial fibrosis, and narrowing of small coronary arteries. Myocardial hypertrophy may result in delayed LV relaxation, but this is usually well tolerated under normal circumstances and is not likely to result in clinical signs. Many cats with HCM will remain clinically stable provided they are not subjected to a sudden change in hemodynamic load. Examples of such triggers include the stress of a visit to the veterinarian, which increases myocardial oxygen demand; general anesthesia, which can reduce cardiac output; or intravenous fluid therapy, which can result in volume loading. Any of these short-term hemodynamic stressors can cause a sudden increase in left atrial (LA) pressures and acute pulmonary edema. The cats with subclinical HCM that are most vulnerable to these stressors are likely to be those with LA enlargement. Cats with massive LV hypertrophy may also be at increased risk, but the relationship between LV wall thickness and risk is not linear, and LA enlargement is a better global indicator of advanced disease.

Many cats with well-compensated HCM exhibit dynamic LV outflow tract obstruction, which can be either persistent or only induced by excitement/exertion. Outflow tract obstruction is usually caused by systolic anterior motion (SAM) of the mitral valve, where movement of the anterior mitral leaflet towards the interventricular septum during mid to late systole causes obstruction to ejection of blood flow, as well as mitral

regurgitation. Outflow tract obstruction can be severe enough to result in a pressure gradient across the LV outflow tract of over 100 mmHg for much of systole. In human HCM patients, the additional myocardial oxygen consumption associated with outflow tract obstruction can cause myocardial ischemia, which is further exacerbated by the concurrent narrowing of small coronary arteries that is a feature of HCM in both humans and cats. Clinical signs of outflow tract obstruction in human HCM patients include exertional dyspnea and chest pain. The exact clinical effect in cats is difficult to determine, as chest pain could easily pass unnoticed by owners, and the majority of affected cats appear to be subclinical. Some owners report open-mouth breathing during play, despite an absence of documentable pulmonary edema.

With progression of HCM, diastolic filling of the LV may be further impaired as interstitial fibrosis worsens, and the LV myocardium becomes stiffer. Ischemic episodes can result in focal areas of myocardial damage, resulting in replacement fibrosis. Neurohormonal activation adds to the problem by causing plasma volume expansion through sodium and water retention, and signs of chronic congestive heart failure become more likely. Signs include pulmonary edema, pleural effusion or both. Cats at this stage are also at risk of arterial thromboembolism, as LA contractile function deteriorates with chronic LA enlargement. A minority of cats will develop generalized LV systolic dysfunction, or large areas of ventricular "scarring" with regional wall thinning and replacement fibrosis. Cats with increased wall thickness but systolic dysfunction are sometimes described as "end-stage HCM" (ES-HCM). Although these cats may start with a nondilated hypertrophied LV, over time the LV wall thickness may decrease and LV diameter increases, so that ultimately they may bear little resemblance to the classic HCM phenotype.

Occasionally, cats with HCM will present with acute signs of cardiogenic shock, including hypotension, hypothermia, and, often, bradycardia. These low-output signs may or may not be accompanied by congestive signs.

RCM

Two forms of RCM have been reported: an endomyocardial form characterized by LV bridging scar (eRCM); and a myocardial form where the LV appears structurally normal but is poorly compliant (mRCM). Varying degrees and distribution of myocardial fibrosis are common to both forms. Biatrial enlargement and increased atrial pressures are also common to both. Cats diagnosed with RCM usually demonstrate clinical signs, which can include congestive heart failure, arrhythmias, arterial thromboembolism, or low-output signs. It is difficult to differentiate RCM from the more advanced forms of HCM with myocyte loss or ES-HCM, and they may in fact be part of the same wide spectrum of HCM.

DCM

This form of cardiomyopathy is now very uncommon in cats, despite being the most common phenotype in dogs. A DCM phenotype is characterized by systolic dysfunction with normal or reduced LV wall thickness and is associated with an increase in diastolic and systolic ventricular dimensions. An association was identified in the late 1980s between DCM in cats and dietary taurine bioavailability, and since that time, a change in pet food manufacturing processes has resolved this problem. Accordingly, most cats with a DCM phenotype are found to have normal plasma taurine concentrations. Congestive heart failure, arterial thromboembolism, and low-output signs are all common presentations for DCM.

Arterial Thromboembolism

All of the above forms of cardiomyopathy may lead to intracardiac thrombus formation if disease is sufficiently advanced (i.e., with left atrial enlargement and dysfunction). Arterial embolization of thrombus (ATE) into the systemic circulation causes vascular occlusion and acute ischemia of downstream tissues, resulting in severe pain, electrolyte disturbances, acute renal injury, and for those surviving the initial embolic episode, a high long-term risk of ATE recurrence or CHF. Nevertheless, a minority of cats can survive for periods in excess of a year if they recover from the acute crisis.

ARVC

Arrhythmogenic right ventricular cardiomyopathy also occurs in humans and dogs, and is characterized by fibrofatty replacement of myocytes. The extent and distribution of myocyte replacement are variable, and may result in tachyarrhythmias and/or right atrial and right ventricular dilation. Affected cats may be presented with signs of syncope associated with tachyarrhythmias, but can also develop right-sided congestive signs with ascites.

Epidemiology

The prevalence of HCM in cats is high; approximately 15% of apparently healthy cats are affected, with a prevalence increasing to nearly 30% of cats over 9 years of age. The prevalence of RCM, DCM, and ARVC is harder to gauge, but is likely considerably lower. HCM is the most common type of feline cardiomyopathy, regardless of age, breed or presenting signs. In the absence of longitudinal epidemiologic studies, it is impossible to determine

whether RCM is a separate form of cardiomyopathy or an advanced stage variant of HCM.

Signalment

There is a male predominance in cats with HCM. Most cats with HCM are domestic nonpedigree cats, but a number of pedigree breeds are said to be predisposed, including the Maine Coon, ragdoll, Persian, British shorthair, sphynx, Cornish rex, and Norwegian forest cat. Siamese and Oriental cats may be predisposed towards eRCM. Age at diagnosis varies widely, as any age of cat can be affected with HCM, including kittens and geriatric cats, but the prevalence of LV hypertrophy increases with age.

History and Clinical Signs

Cats with advanced myocardial disease are often perceived by their owner to be healthy until shortly before the onset of CHF, ATE, syncope or sudden death. Typical presenting signs for CHF include respiratory distress and tachypnea, whereas acute limb paralysis/paresis is the most common presentation with ATE. Some cats may develop open-mouth breathing only with stress or exertion, and may be found to have dynamic LV outflow tract obstruction.

Physical examination findings are varied. Murmurs are common in cats with HCM but also in healthy cats with normal hearts, so a murmur should not always be assumed to indicate heart disease. Murmurs are less common in the more severe forms of cardiomyopathy than in well-compensated HCM. A minority of cats with cardiomyopathy have an audible gallop or arrhythmia, and these auscultation findings are more likely to indicate advanced disease, though can also be detected in some geriatric cats with only mild abnormalities. A prominent apical impulse may be apparent in cats with cardiomegaly or a hyperdynamic LV.

Physical exam findings in cats with congestive heart failure will include tachypnea with increased respiratory effort, crackles on pulmonary auscultation with severe pulmonary edema, or absent breath sounds ventrally with a pleural effusion. The presence of a gallop sound in a cat with tachypnea and respiratory distress should prompt treatment for congestive heart failure until further confirmatory tests are possible.

Diagnosis

From the above descriptions, it is clear that establishing a diagnosis of a particular type of cardiomyopathy in an individual cat is challenging. To differentiate end-stage HCM, RCM, and UCM requires a high level of echocardiographic skill and experience. A precise diagnosis can be challenging even for experienced cardiologists unless a cat has a classic HCM or ARVC phenotype, due to poor consensus on the definitions of each cardiomyopathy type. Moreover, the labels "end-stage HCM," "RCM," and "UCM" might not actually reflect distinct disease entities but rather different stages of a single condition. Instead, diagnostic tests should be focused on confirming the presence of heart disease; identifying any underlying systemic cause of cardiomyopathy that should be treated; and identifying cats at high risk of CHF and ATE.

Is Heart Disease Present?

In practical terms, the clinician's first priority when presented with a cat with clinical findings suggestive of heart disease is to establish whether or not cardiac disease is present. The approach will be different for cats with respiratory distress versus those that are asymptomatic.

Tachypneic Cats

Heart disease should always be considered in cats with tachypnea, and the presence of a murmur, gallop or arrhythmia should increase this suspicion (Figure 27.2).

Differentiation of congestive heart failure from other causes of respiratory distress may require diagnostic imaging, but the potential value of radiography or echocardiography must be weighed against the possible risk of subjecting the patient to further stress that could prove fatal. Ultrasound is generally better tolerated than radiography, and has the advantage that patient positioning is less critical. Thoracic ultrasound can demonstrate pleural effusion and can even be used to indicate pulmonary parenchymal changes as with pulmonary edema (B-line artifacts). If sufficient expertise is available, the most useful way to increase confidence of a cardiac cause of respiratory distress is to demonstrate LA enlargement with echocardiography. Thoracic radiography can be used to identify pleural effusion, pulmonary infiltrates, and assess cardiac size, but must be obtained with great care to avoid compromising patient safety. A point-of-care test is available to measure plasma NT-proBNP, providing a simple way to help differentiate cats with respiratory distress due to heart failure versus noncardiac causes.

Asymptomatic Cats

Myocardial disease should be considered in an otherwise healthy cat when a murmur is detected, and should be strongly suspected when a gallop or arrhythmia is auscultated (Figure 27.3). A very loud murmur (i.e., with a precordial thrill) is usually associated with congenital heart disease.

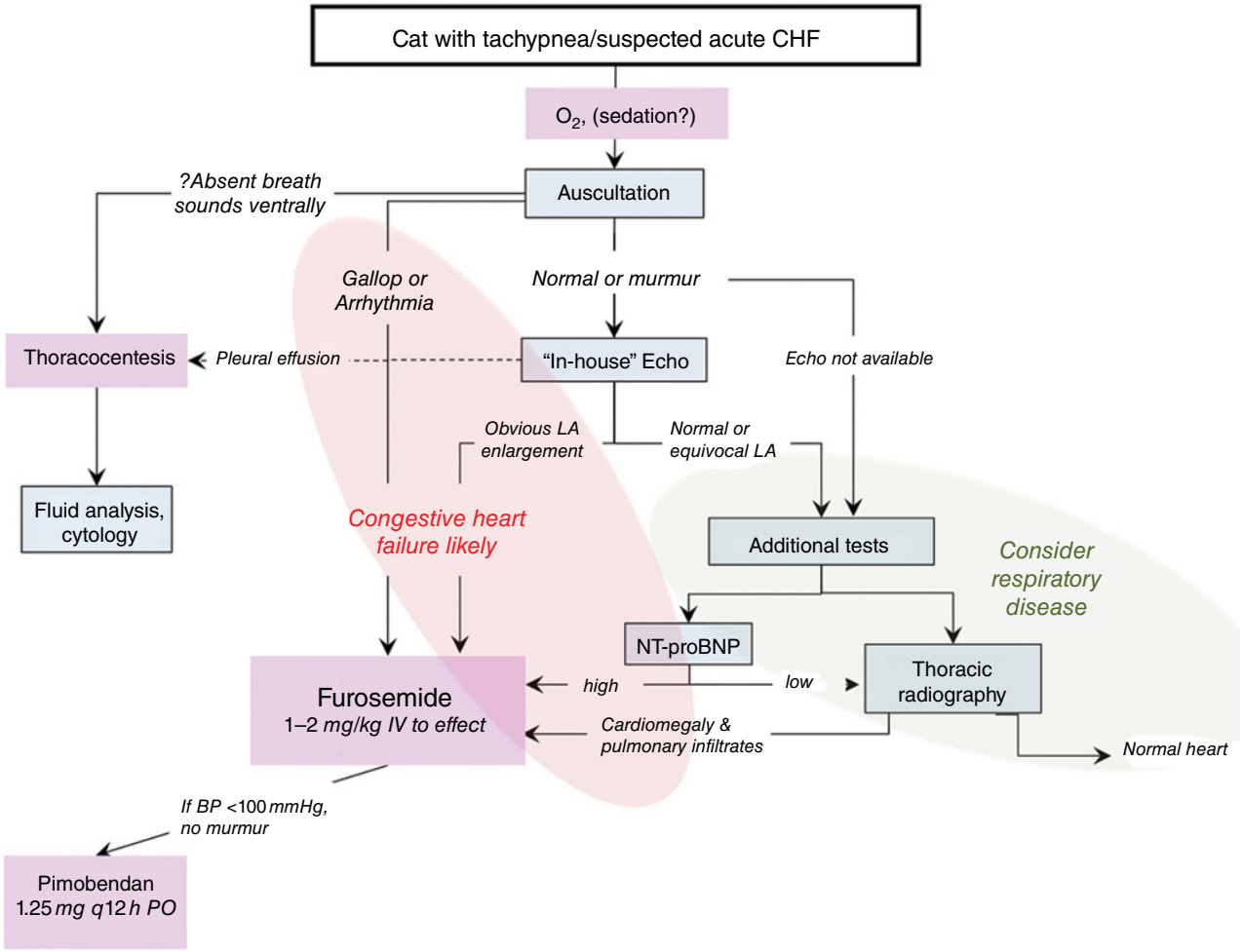


Figure 27.2 Initial approach to the cat with tachypnea and suspected heart disease. Diagnostic tests are shaded in blue, therapy is shaded in pink. A combination of auscultation, rapid and focused "in-house" ultrasound examination, and other diagnostic tests can provide information on probability that the cat's tachypnea is due to congestive heart failure (CHF) or noncardiac disease. BP, blood pressure; Echo, echocardiography; LA, left atrium.

Other common causes of a heart murmur in cats include physiologic (or nonpathologic) murmurs, as well as anemia, hyperthyroidism, and hypertension.

Is There an Underlying Systemic Cause of Myocardial Disease?

It is helpful to view feline myocardial disease in terms of those with and without a specific systemic cause, as treatment of any underlying cause is essential. It is vital to identify hypertension, hyperthyroidism or anemia, as specific treatment requirements will differ for each. Blood pressure should be measured in all cats with suspected heart disease, and T4 concentrations measured in older cats. Hematocrit should be checked if there is any concern that anemia may be responsible for a murmur. For those cats where no cause is identified or can be treated, it is important to evaluate the potential risk of cardiac complications such as CHF or ATE. Classifying cats as either "low risk" or "high risk" facilitates management.

Heart Disease Present; High Risk or Low Risk?

One of the most useful prognostic indicators for cats with cardiomyopathy is LA size. Cats with HCM and normal LA size can be considered to be at low risk of CHF and ATE. Cats with LA enlargement fall into a higher risk category. If echocardiography is not available to assess LA size, thoracic radiographs are reasonably specific but poorly sensitive to detect LA enlargement. ARVC is an exception, as LA size is an indicator of risk for left heart disease and ARVC predominantly affects the right heart. Plasma biomarkers such as NT-proBNP and troponin-I can help provide an indication of the severity of heart disease.

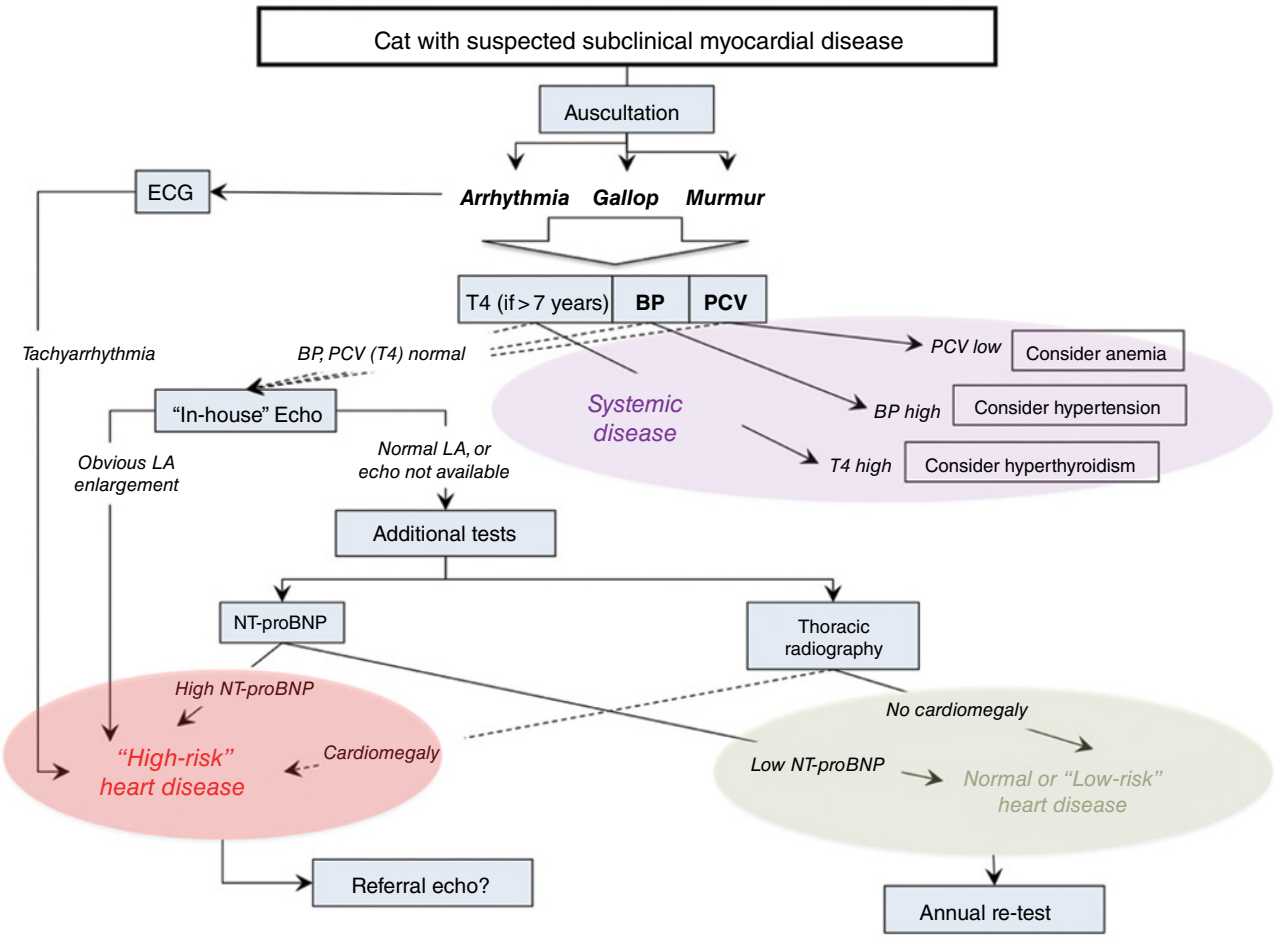


Figure 27.3 Initial approach to the cat with suspected subclinical heart disease. Diagnostic tests are shaded in blue. Secondary systemic causes of myocardial disease should be identified, as further specific testing may be indicated and therapy will be specific for the underlying cause. A combination of auscultation, rapid "in-house" echocardiography, biomarkers, and radiographs can be used to differentiate cats at high risk of congestive heart failure and thromboembolism, versus those at low risk of these complications. More advanced echocardiography can be considered for "high-risk" cats to further characterize the myocardial disease and rule out congenital heart disease. Cats with "high-risk" cardiomyopathy may benefit from antiplatelet treatment, such as clopidogrel. BP, blood pressure; echo, echocardiography; ECG, electrocardiogram; LA, left atrial; PCV, packed cell volume; T4, serum thyroxine concentrations.

Which Cardiomyopathy is This?

Echocardiography is a difficult technique in cats, and it takes an experienced echocardiographer to differentiate many of the more advanced cardiomyopathy phenotypes. Severe forms of ARVC may be easy to differentiate from other cardiomyopathies, but hard to differentiate from tricuspid dysplasia or conditions associated with severe pulmonary hypertension. Milder or atypical forms of any of the cardiomyopathies can be difficult to classify on echocardiography, and can sometimes be challenging even for cardiologists. At the other end of the spectrum, it can be challenging to differentiate cats with mild HCM from those with physiologic murmurs.

There are few clinical consequences in the short term for incorrectly distinguishing normal cats from those with mild HCM (apart from when screening prebreeding pedigree cats for cardiomyopathy), providing these "low-risk" cats continue to be monitored over subsequent years. The rate of progression from normal to mild HCM, or mild HCM to "high-risk" HCM is variable, so such cats should be reevaluated at least annually. Biomarkers can be helpful in this context, as low NT-proBNP concentrations should provide some reassurance that a cat continues to be low risk.

Therapy

Cats with CHF

For cats with life-threatening signs, therapy is focused on relieving critical hypoxemia using a combination of parenteral furosemide, oxygen, and sedation as needed

(butorphanol 0.3 mg/kg, IM or SC) for cats in distress. Initially, furosemide should be given IV at 2 mg/kg, but may be given IM until IV access can be secured. Repeated doses are given every 30–60 minutes, to effect. Response is assessed by monitoring respiratory rate and effort, with the goal of returning respiratory rates to normal (or at least <40 breaths/min). Renal function and electrolytes should also be monitored, as hypokalemia and elevations in BUN are common. Although the effect of therapy on renal function and electrolytes should be considered, the principal goal should be the elimination of congestive signs. Intravenous fluids should be avoided in the presence of congestive heart failure, even in hypotensive cats (systolic blood pressure <100 mmHg). For hypothermic, hypotensive cats without a heart murmur, pimobendan (1.25 mg PO per cat) can be considered.

Hospitalized cats are often stressed, and once respiratory distress is controlled they may benefit from being returned to their home environment.

Cats with "transient myocardial thickening" (TMT) warrant a specific mention, as they have a better than expected prognosis. The cause of TMT is unknown, but affected cats are often young and have a history of a recent stressful event. They usually present with CHF associated with thickened LV walls, but if treated appropriately for their heart failure can make a full recovery, with return to a normal cardiac phenotype.

For outpatient management, parenteral furosemide can be replaced with oral furosemide. The goal of long-term management is to maintain control of congestive signs and to prevent ATE. Evidence-based selection of therapeutic agents for CHF management in cats suffers from the absence of clinical trial data. Angiotensin converting enzyme inhibitors (ACEI), spironolactone, and pimobendan are all currently used off-label in the treatment of CHF in cats. ACEIs have not been associated with any adverse effects in cats with cardiac disease and in theory should counteract furosemide-mediated activation of the renin-angiotensin-aldosterone system (RAAS). Spironolactone should also act on the RAAS and has been reported to have favorable effects in experimental models of HCM, but its use was reported to result in skin lesions in a small minority of cats. Pimobendan is considered contraindicated in cats with HCM and outflow tract obstruction, but is a logical choice for treatment of cats with systolic dysfunction. Diltiazem is rarely used, and beta-adrenergic antagonists such as atenolol are generally considered contraindicated in the presence of congestive heart failure.

Cats with recurrent or persistent CHF despite appropriate doses of diuretics are generally managed by increasing diuretic doses and adding medications such as an ACEI and spironolactone. Cats that have experienced an episode of CHF are likely to be at risk of ATE, so should also receive antiplatelet treatment. Clopidogrel is the first-choice treatment for prevention of ATE (18.75 mg per cat q24h PO), as aspirin (at either 5 mg/kg or 75 mg q72h) does not appear to be as effective, though is well tolerated.

Administering multiple medications is a problem with many cats, so combining tablets in a single gelatine capsule can be helpful.

Asymptomatic Cats

Low-Risk Cats

Many asymptomatic cats will have normal survival times whether or not they receive treatment. It is debatable whether extending survival is possible in low-risk cats, although improving quality of life might be a worthwhile aim. In human HCM patients, LV outflow tract obstruction can be associated with chest pain and exertional dyspnea, which can be relieved with atenolol in some patients. Although atenolol does not seem to confer an obvious survival benefit in cats with HCM and LV outflow tract obstruction, there are anecdotal reports that atenolol might improve activity levels in some cats.

High-Risk Cats

There are currently no therapies that are known to reduce the risk of developing CHF in cats with myocardial disease, apart from treating hyperthyroidism, hypertension, and anemia when present. As high-risk cats are at risk of ATE, they should receive antiplatelet treatment.

Prognosis

Feline myocardial disease has a very varied prognosis, ranging from a benign condition with minimal influence on morbidity and mortality in many cats, to a disabling and potentially fatal condition associated with respiratory distress, sudden death, and pain and paralysis. Factors such as gallop sounds, arrhythmias, LA enlargement, and systolic dysfunction are indicators of a poor prognosis and high risk of cardiac complications, and absence of these factors is likely to indicate a more benign outcome. Of these factors, LA enlargement is the most important predictor and the ability to assess LA size with echocardiography is extremely useful. By focusing on potential risk, the complex issues of cardiomyopathy classification are avoided and therapy can be directed at cats that are in most need.

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28

Pericardial Disease

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The pericardium is a multilayered structure surrounding the heart that isolates the heart from the remainder of the thorax. It creates a potential space that can be filled by fluid, tissue, or air/gas. While pericardial disease is relatively uncommon, it can lead to life-threatening conditions when intrapericardial pressure rises and cardiac output is compromised. A combination of restricted filling, reduced diastolic function, partial obstruction to inflow into the atria, and reduced cardiac output can manifest clinically as weakness, collapse, tachycardia, jugular venous distension, and ascites. Pericardiocentesis is recommended to alleviate clinical signs of pericardial effusion and cardiac tamponade. Congenital and acquired pericardial diseases in cats and dogs will be discussed in detail.

Congenital

Etiology/Pathophysiology

Peritoneopericardial diaphragmatic hernia (PPDH) occurs during development in dogs and cats when the septum transversum does not form or fuse normally, resulting in a communication that allows abdominal contents to displace into the pericardial space. The tissues and organs herniated most often are omentum, liver, gallbladder, and small intestine. Concurrent congenital abnormalities including portosystemic shunt are often present in animals with PPDH.

Intrapericardial cysts have been rarely reported in dogs and cats and in some cases were associated with PPDH.

Epidemiology

The overall prevalence of PPDH at two veterinary institutions was 0.025%, with a greater prevalence in cats than dogs.

Signalment

Although these are congenital abnormalities, they can be detected incidentally in adults so the age at presentation can vary greatly.

History and Clinical Signs

PPDH

Clinical signs with PPDH depend on which abdominal organs herniate. Up to 69% of animals have clinical signs including tachypnea/dyspnea, cough, vomiting, anorexia, and exercise intolerance. Common physical examination abnormalities include muffled heart and lung sounds, borborygmus auscultated in the thorax, and heart murmur.

Intrapericardial Cysts

Symptomatic animals have presenting signs similar to those with pericardial effusion and cardiac tamponade (see Pericardial Effusion section).

Diagnosis

Thoracic radiograph findings include enlarged or globoid cardiac silhouette and, in the case of PPDH, a loss of distinction between the cardiac silhouette and diaphragm or abnormal densities (gas or fat) within the cardiac silhouette (Figure 28.1a,b). Ultrasound confirms the presence of effusion and which organs have herniated. The diagnosis of PPDH can be an incidental finding during diagnostic imaging for another reason.

Therapy

Surgical repair of PPDH is recommended more often for young animals (median age 1.1 years) and those with clinical signs. Successful surgical management of

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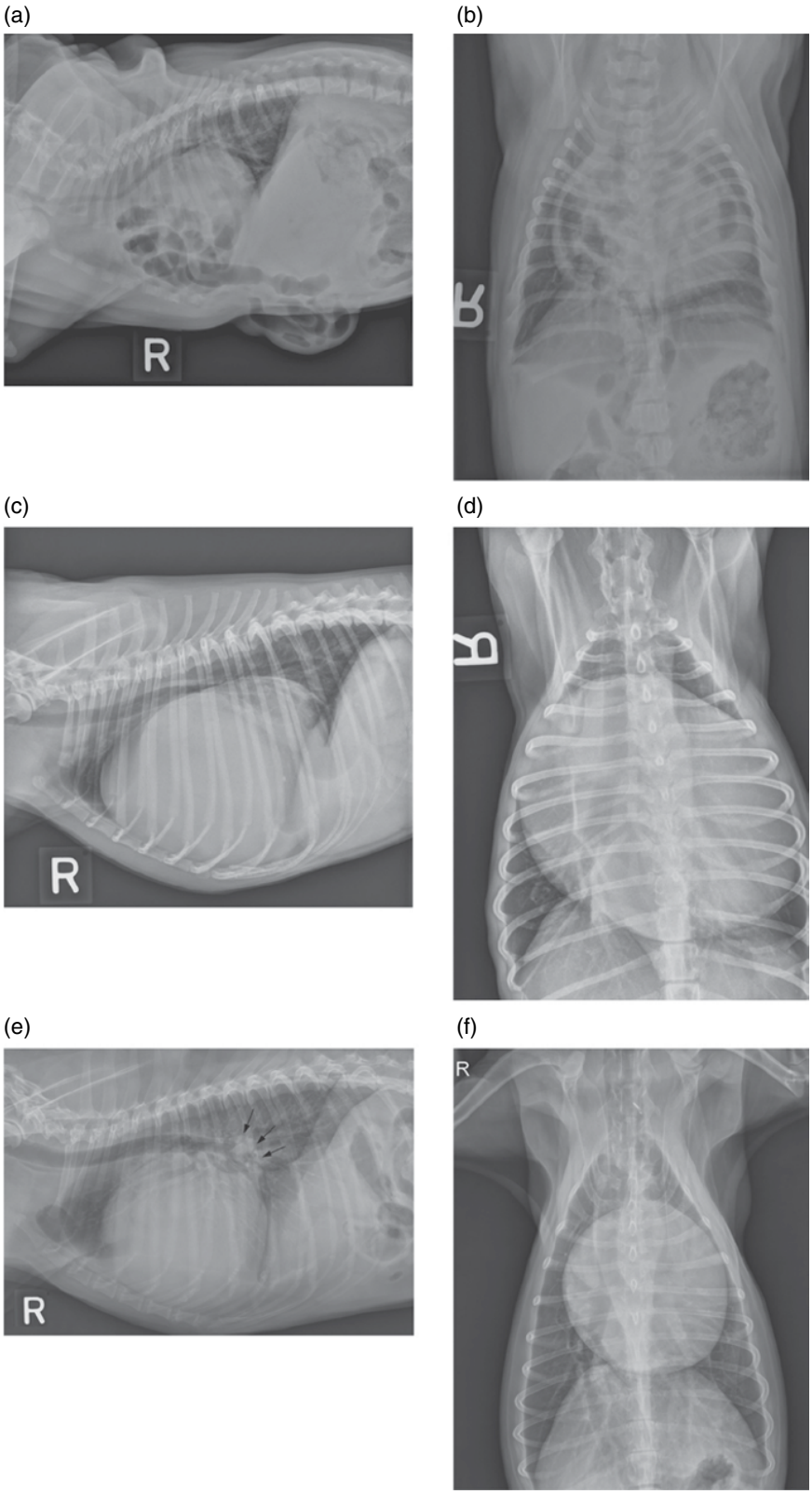


Figure 28.1 Lateral and dorsoventral thoracic radiographs in three dogs with pericardial disease. (a,b) A 4-month-old English bulldog with a peritoneopericardial diaphragmatic hernia seen as an abnormal gas pattern consistent with bowel loops within the cardiac silhouette. (c,d) Severe enlargement of the cardiac silhouette with a large-volume pericardial effusion in a dog that presented for cough. The trachea is dorsally deviated. (e,f) The cardiac silhouette is enlarged with rounded borders in a dog with degenerative mitral valve disease. Left atrial enlargement can be noted as straightening of the caudal aspect of the cardiac silhouette (*arrows*). The left atrium was severely enlarged on echocardiography and a small-volume pericardial effusion was documented that resolved with heart failure management.

pericardial cysts, with repair of a PPDH when present, has been reported.

Prognosis

The majority of animals with clinical signs will improve following surgical correction. The mortality rate following surgery for PPDH varies between 5.1% and 14%. The mortality rate following surgical repair of PPDH is higher if reexpansion pulmonary edema or hemorrhage occurs, although improvements in anesthesia and postoperative management have most likely improved the prognosis.

Pericardial Effusion

Etiology/Pathophysiology

Accumulation of fluid within the pericardial space can cause hemodynamic abnormalities depending on the volume and rate of fluid accumulation as well as intracardiac filling pressures and compliance. The resulting hemodynamic changes and decrease in cardiac output create a clinical syndrome called cardiac tamponade, where increased intrapericardial pressure equals or exceeds intracardiac pressure, with the right side of the heart most susceptible to compromise.

The most common causes of pericardial effusion in dogs are neoplastic and idiopathic with rare cases of infectious pericarditis (bacterial, fungal), coagulopathy, left atrial tear, heart failure, foreign body, and uremia.

The most common causes of pericardial effusion in cats are heart failure, neoplastic and infectious (viral) with rare cases of coagulopathy, foreign body, and uremia.

Dogs

Neoplastic

Primary or metastatic neoplasia is the most commonly reported cause of pericardial effusion in dogs. The incidence of hemangiosarcoma and aortic body tumors (chemodectoma) is higher than mesothelioma with infrequent reports of thyroid carcinoma, myxoma, and others.

Hemangiosarcoma has a 10-fold greater incidence than aortic body tumors in dogs. They are typically located in the right atrium/auricle and are highly malignant. The mean age at presentation is 9.8 years and mean weight is 32 kg. Golden retrievers are overrepresented. Survival times with combinations of pericardiocentesis, pericardiectomy, tumor resection, and/or chemotherapy are short.

Heart base tumors, most often chemodectoma or thyroid carcinoma, are located near the aorta and main pulmonary artery. Chemoreceptor cells are found in groups at the ventrolateral surface of the aorta and the bifurcation of the carotid artery near the base of the heart. The chemoreceptor system responds to changes in pH and the partial pressure of arterial oxygen and carbon dioxide in the blood. These tumors tend to be slow growing and locally invasive, causing compression or infiltration of adjacent structures. Chemodectomas can occur in any breed but brachycephalic breeds appear predisposed (boxer, bulldog, Boston terrier). Mean age at presentation is 10 years. Heart base tumors are intimately associated with vascular structures, making complete surgical excision and radiation therapy problematic. In dogs with heart base tumors assumed to be chemodectomas and clinically significant pericardial effusion, palliation with pericardiectomy significantly extends survival. In the absence of significant pericardial effusion, these tumors can be an incidental finding in dogs undergoing an echocardiogram for another indication.

Mesothelioma is a neoplasm of the pericardium and serosal surfaces. It is relatively uncommon and is not characterized by an easily identifiable discrete mass, making it difficult to diagnose. Diagnosis of mesothelioma requires histopathology of the pericardium and is therefore difficult to distinguish from idiopathic disease. Mesothelioma can develop secondary to chronic effusions. The mean age at diagnosis is 9.5 years.

Idiopathic

A cause for pericardial effusion cannot be identified in up to 23% of cases. Therefore, idiopathic is a diagnosis of exclusion. Affected dogs are typically medium to large breed and middle aged. The reported mean age is slightly less than that reported for dogs with a neoplastic etiology. Of note, reports have identified small tumors on necropsy and confirmed mesothelioma on histopathology of pericardial tissue in dogs initially diagnosed with idiopathic effusions.

Infectious

Rare reports of systemic fungal disease (*Coccidioides immitis*, *Aspergillus niger*), bacterial pericarditis (various bacteria including botryomycosis) and protozoal infection with *Leishmania chagasi* have been associated with pericardial effusion. In some cases, long-term survival can be achieved with a combination of surgical management and long-term antibiotic or fungal therapy.

Other

A left atrial tear can occur in dogs with degenerative mitral valve disease, most often resulting in acute clinical decompensation. An echocardiogram performed at the time may document evidence of a thrombus in the pericardial space. Pericardial effusion secondary to heart failure is uncommon in dogs with heart disease and if it does occur, the effusion is typically scant and does not

result in tamponade. Additional rarely reported causes of pericardial effusion in dogs include renal failure/uremia, coagulopathy, and migrating foreign bodies including grass awns, porcupine quills, and gun pellets.

Cats

Heart Failure

The most common cause of pericardial effusion in cats, it can develop with any significant underlying heart disease including hypertrophic cardiomyopathy. The volume of effusion is typically small with heart failure and resolves with heart failure management. Cats with heart failure-associated pericardial effusion have a shorter survival time than cats with pericardial effusion not caused by heart disease.

Neoplastic

This is a rare cause of pericardial effusion in the cat. The most common tumors reported in cats with pericardial effusion are lymphoma, thymoma, mesothelioma, and adenocarcinoma. The clinical effects of cardiac tumors are related principally to compression or obstruction of adjacent cardiac structures, infiltration of the myocardium, and development of pericardial effusion.

Infectious

In the past, infection was considered the most common cause of pericardial effusion in the cat related to the historical prevalence of feline infectious peritonitis (coronavirus). The prevalence of pericardial effusion in cats with feline infectious peritonitis (coronavirus) is 9.6–12.8%.

Other

Additional rarely reported causes of pericardial effusion in cats include renal failure/uremia, trauma, and coagulopathy.

Signalment

Dogs

In general, dogs are middle aged to older and large breed (golden retriever, German shepherd). Golden retrievers are the most overrepresented breed presenting with pericardial effusion. They are also the most commonly reported breed with hemangiosarcoma. Brachycephalic breeds are predisposed to heart base tumors (chemodectoma). A young adult dog of any breed would be more likely to have an infectious or idiopathic cause.

Cats

Irrespective of cause, the most reported breed is domestic shorthair although pure breeds can be affected. Median age at presentation is 6.0 years.

History and Clinical Signs

Patients can be affected to various degrees, ranging from no overt clinical signs to severe compromise. Clinical signs, when present, are often nonspecific and can include lethargy, anorexia, collapse, cough, and vomiting. Respiratory signs (tachypnea, dyspnea, cough) are common complaints in cats. Abnormal physical examination findings that are suggestive of pericardial effusion can include muffled or distant heart sounds, weak pulses or variation in pulse quality with respiration, and tachycardia. Signs of overt right heart failure (abdominal distension from ascites) and evidence of increased right heart pressures, including jugular venous distension, can also be present.

Diagnosis

A complete diagnostic work-up is recommended to assess clinical status and create a treatment plan. Evaluation includes but may not be limited to a complete blood count, biochemistries, coagulation testing, urinalysis, blood pressure, thoracic radiographs, electrocardiography, and echocardiography. In addition, point-of-care ultrasound in the emergency setting is helpful for rapidly detecting pericardial effusion. Infectious disease testing may be indicated in endemic areas or if one is suspected. Additional tests may be indicated depending on clinical status or presenting signs.

Thoracic Radiographs

An enlarged, globoid cardiac silhouette suggests the presence of pericardial effusion (Figure 28.1c,d). Small-volume pericardial effusions may not cause a rounded appearance. Additional findings include dorsal deviation of the trachea, caudal vena cava distension, and hepatomegaly. Some specific abnormalities indicative of the underlying diagnosis include abnormal bulges at the heart base suggestive of a mass, left atrial enlargement in degenerative mitral valve disease (Figure 28.1e,f), and pulmonary metastasis. When present, pleural effusion often impedes assessment of the cardiac silhouette. Pulmonary edema is uncommon in dogs with pericardial effusion but can be present in cats with heart failure.

Echocardiography

Echocardiography (cardiac ultrasound) provides a non-invasive means of imaging the heart and surrounding structures, and is superior to conventional radiography for identifying pericardial effusion, which appears as a hypoechoic space surrounding the heart (Figure 28.2). Additionally, echocardiography can identify the etiology of pericardial effusion, such as neoplastic or underlying heart disease. Pericardial effusion provides a source of ultrasonic contrast that is helpful when attempting to

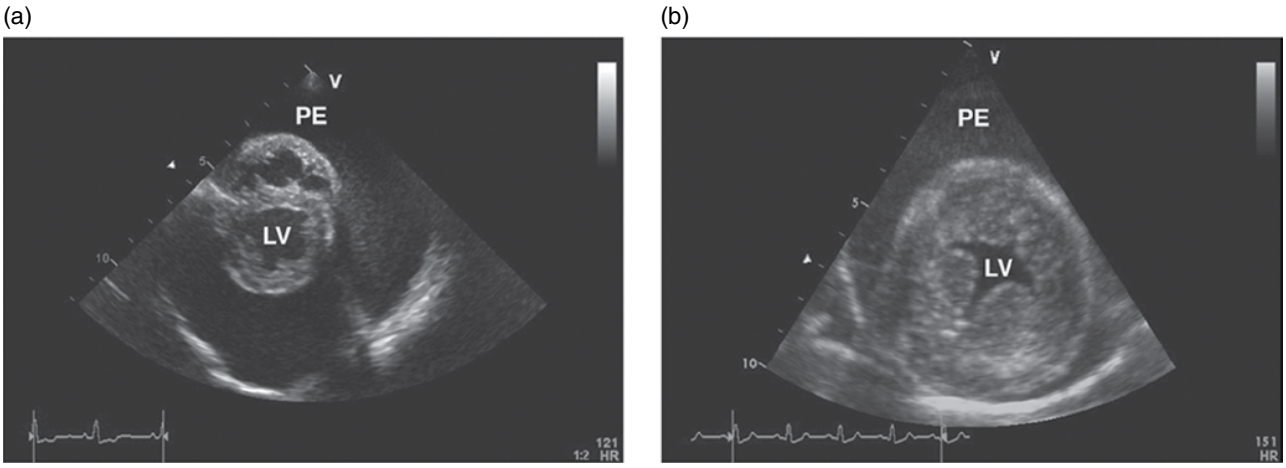


Figure 28.2 Transthoracic echocardiographic images of the left ventricle (LV) from a right parasternal short-axis view. (a) A large-volume pericardial effusion in a dog. (b) A small-volume pericardial effusion in a cat with hypertrophic cardiomyopathy and congestive heart failure. PE, pericardial effusion.

visualize cardiac tumors, but therapeutic pericardiocentesis should not be delayed for an echocardiographic examination in an unstable patient. Tumors are most often located in the right atrial or auricular wall in the case of hemangiosarcoma or at the heart base associated with the aorta or main pulmonary artery (Figure 28.3). They can also be found, more rarely, within the right ventricular myocardium and right ventricular outflow tract. Hemangiosarcomas frequently appear cavitary. Both the right and left imaging windows are recommended for identification and localization. In addition to identifying pericardial effusion, echocardiography can provide evidence of cardiac tamponade by documenting diastolic collapse of the right atrium and ventricle when intrapericardial pressures exceed right atrial or ventricular end-diastolic pressures (Figure 28.4). Left ventricular internal dimensions will measure small when pericardial effusion inhibits preload of the heart.

Pericardial Fluid Analysis

Pericardial fluid is typically hemorrhagic in appearance, although opaque fluid can be seen with chylous effusions and exudates. Most cardiac tumors do not exfoliate well, and for this reason pericardial fluid analysis and cytology often are unrewarding for the identification of cardiac tumors. Careful cytologic evaluation is required so that reactive mesothelial cells are not mistaken for neoplastic cells. Occasionally, lymphoma or an infectious cause can be documented. Culture and sensitivity are indicated for the identification of effusions secondary to infectious etiologies.

Electrocardiography

The most common finding is sinus tachycardia (Figure 28.5a), which is a physiologic compensatory mechanism to improve cardiac output. Low-voltage QRS complexes can be indicative of pericardial effusion in dogs (Figure 28.5b). It is important to recognize that QRS complexes are typically small in cats, making this an insensitive indicator of effusion. Electrical alternans, identified as a beat-to-beat variation in the QRS complexes, is highly suggestive of pericardial effusion, although it is only identified in a small number of dogs (Figure 28.5c). Lastly, a change (depression or elevation) in the ST segment associated with myocardial hypoxia (Figure 28.5d) may be documented. Ventricular arrhythmias are not uncommon and supraventricular arrhythmias can also occur. Most ECG abnormalities will resolve shortly after the removal of pericardial effusion.

Laboratory Work

Comprehensive laboratory evaluation including complete blood count, biochemical analysis, coagulation panel, and urinalysis can provide information regarding underlying etiology and the patient's clinical status. Abnormalities are not uncommon but are often nonspecific. Cardiac troponin I concentrations can be increased in dogs with hemangiosarcoma (>0.25 ng/mL) when compared to other causes of pericardial effusion.

Neoplastic Evaluation

Cardiac tumors are located adjacent to important vascular structures, making the diagnosis challenging. Definitive diagnosis is often made during surgery or at necropsy. Surgical excisional biopsy has been described for the diagnosis of hemangiosarcoma of the right auricle and for chemodectoma but is often not performed as a consequence of the overall risk to benefit ratio.

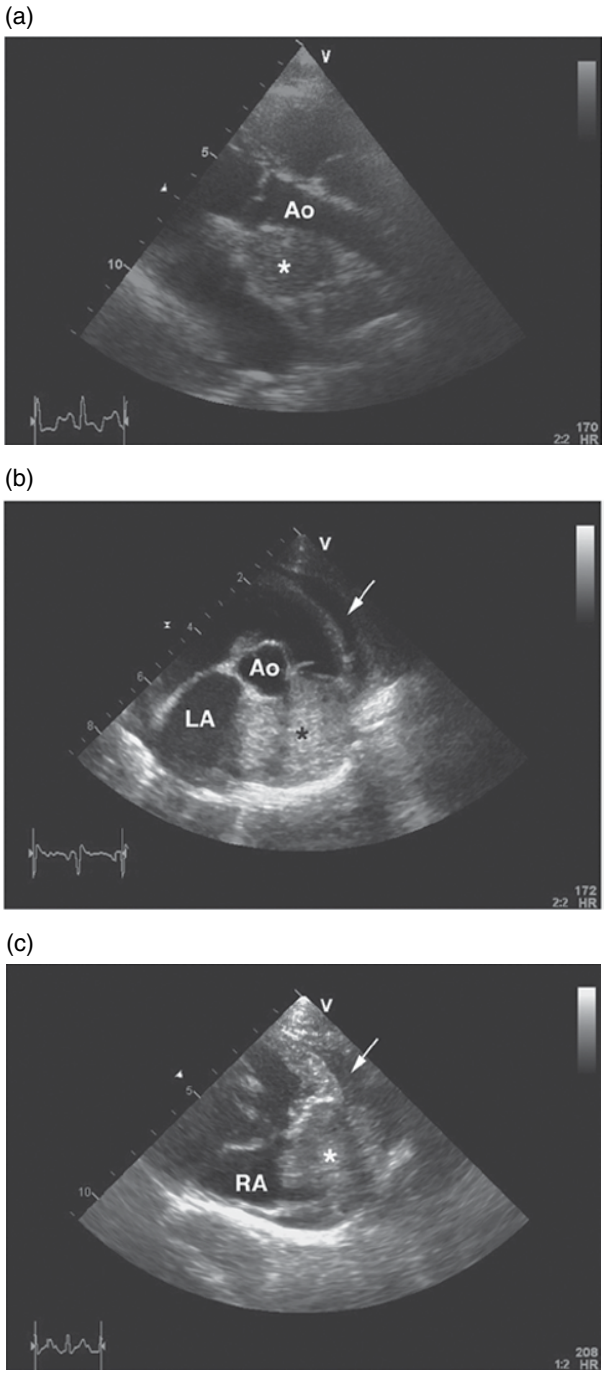


Figure 28.3 Transthoracic echocardiographic images from dogs with cardiac tumors and pericardial effusion. (a) Images obtained from the left cranial window document a mass (*) in direct apposition with the aorta typical of heart base tumors. (b) Right parasternal short-axis view of the heart base documenting a mass (*) near the aorta consistent with a heart base mass. (c) Images obtained from the left cranial window document a mass (*) within the right auricle, most likely a hemangiosarcoma based on location. Ao, aorta; LA, left atrium; RA, right atrium.

Advanced Imaging

Computed tomography and magnetic resonance imaging can provide additional information including tumor location and the presence of metastatic disease.

Therapy

The urgency of pericardiocentesis depends on the clinical status of the patient at the time of evaluation.

Acute Therapy

Critically ill animals require immediate stabilization with intravenous fluid therapy to help restore cardiac output, and pericardiocentesis to resolve tamponade. Dyspneic patients may benefit from a combination of oxygen supplementation and removal of pleural effusion and/or ascites if the volume(s) are significant enough to contribute to respiratory difficulty. Diuretic therapy with furosemide is generally contraindicated because diuretics do not consistently remove free fluid from the pericardium and can contribute to further hemodynamic compromise. One exception is the judicious use of furosemide in cats and dogs with pericardial effusion secondary to congestive heart failure.

Pericardiocentesis

Pericardiocentesis is performed primarily in dogs and is recommended when pericardial effusion is large volume and/or contributing to hemodynamic compromise (tamponade). The majority of cats have small volume effusions secondary to heart failure that resolve with heart failure management.

Several techniques for pericardiocentesis have been described and the technique selected depends on the clinical status of the patient, veterinarian comfort level with the procedure, equipment availability, and technical support. The objective of the procedure is to remove as much pericardial fluid as possible. Complications can occur during pericardiocentesis if the catheter contacts the heart, resulting in arrhythmias, or lacerates lung or other cardiac structures. Pericardial fluid removal typically provides an immediate clinical benefit noted by a reduction in heart rate to a more normal range and an improvement in pulse quality and blood pressure.

Equipment and Supplies

- Over-the-needle catheter with a length appropriate for the patient size (for example: 14 g × 5.25 inch, 16 g × 3.25 inch).
- Extension IV set.
- Three-way stopcock.
- Syringe (20–60 mL).

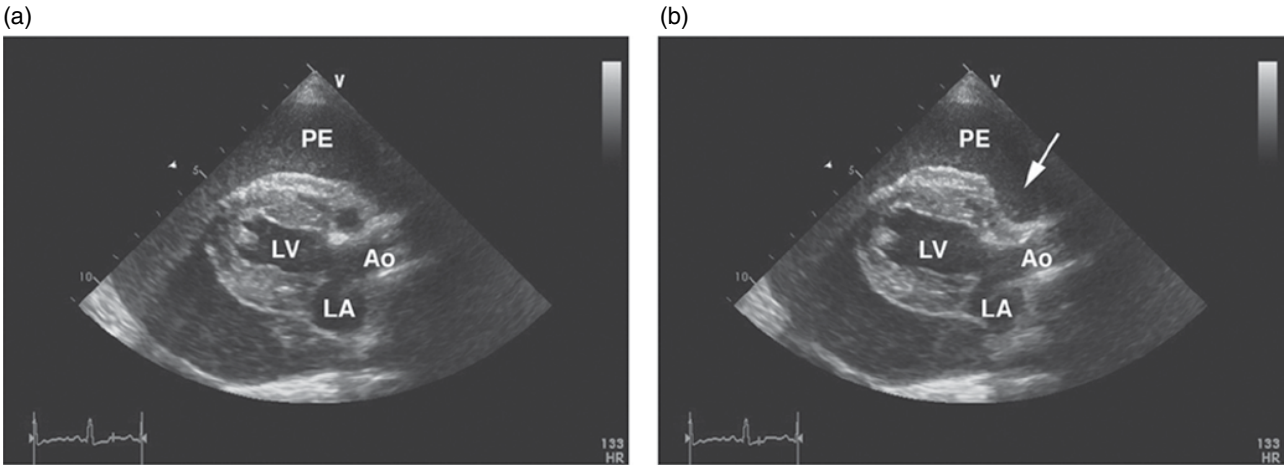


Figure 28.4 Echocardiographic images obtained from a right parasternal long-axis view in a dog with pericardial effusion and collapse of the right atrium (*arrow*) caused by elevated intrapericardial pressure. Ao, aorta; LA, left atrium; LV, left ventricle; PE, pericardial effusion.

- Scalpel blade.
- Collection bowl and graduated cylinder or other volume measuring tool.
- Red-top tube containing no anticoagulants or preservatives.
- Purple- or lavender-top tube containing EDTA as an anticoagulant.
- Sterile gloves.
- Local anesthetic block.
- Continuous ECG – recommended for detecting arrhythmias generated by contacting the heart when advancing the catheter into the pericardial space.
- Echocardiogram/ultrasound machine – useful for identifying a location on the right side of the thorax for obtaining the most direct access to pericardial fluid.
- Sedation – may be required to facilitate the procedure in some cases.

Preparation

Prior to performing the procedure, gather the supplies appropriate for the patient's size, demeanor, and clinical status. Putting together a prestocked kit that contains the necessary supplies for pericardiocentesis is very useful, especially for immediate access in an emergency situation. Light sedation may be required to facilitate the procedure in some cases. The local anesthetic block can be drawn into a syringe, and the right side of the thorax can be shaved in preparation for the procedure.

Procedure (Figure 28.6)

Pericardiocentesis is routinely performed on the right side of the thorax to utilize an approach through the cardiac notch between lung lobes and to avoid damage to the lung and coronary arteries.

1) For the procedure, the patient is positioned in sternal or lateral recumbency with continuous ECG attached.
2) Identify the ideal position for introducing the catheter into the thorax, which is often around the fifth or sixth intercostal space, mid-thorax at the costochondral junction. It can be found by flexing the right front limb and swinging the leg across the thorax and using the intercostal space where the point of the elbow crosses the costochondral junction (Figure 28.6a) or with ultrasound guidance (Figure 28.6b). A permanent marker can be used to identify the spot for catheter entry or to mark multiple spots on the perimeter of the shaved area to triangulate the position.
3) Following sterile preparation of the pericardiocentesis site, inject a local anesthetic block to the skin, intercostal muscles, and pleura (Figure 28.6c). The discomfort associated with the local block can limit its value in some dogs that would otherwise benefit from sedation. After approximately five minutes, use a scalpel blade to make a small stab incision in the skin to facilitate catheter insertion and advancement.
4) Attach the catheter to the extension set tubing with a three-way stopcock placed between the extension set tubing and a syringe. At the predetermined ideal pericardiocentesis site, advance the catheter through the skin, followed by the intercostal muscles, avoiding the caudal aspect of the rib where the intercostal vessels are located, and into the pleural space (Figure 28.6d). An assistant applying gentle negative pressure on the syringe may encounter pleural effusion that is typically straw colored in patients with right heart failure. Continue advancing the catheter until a scratching sensation is detected when the needle comes into contact with the pericardium. Continue to advance

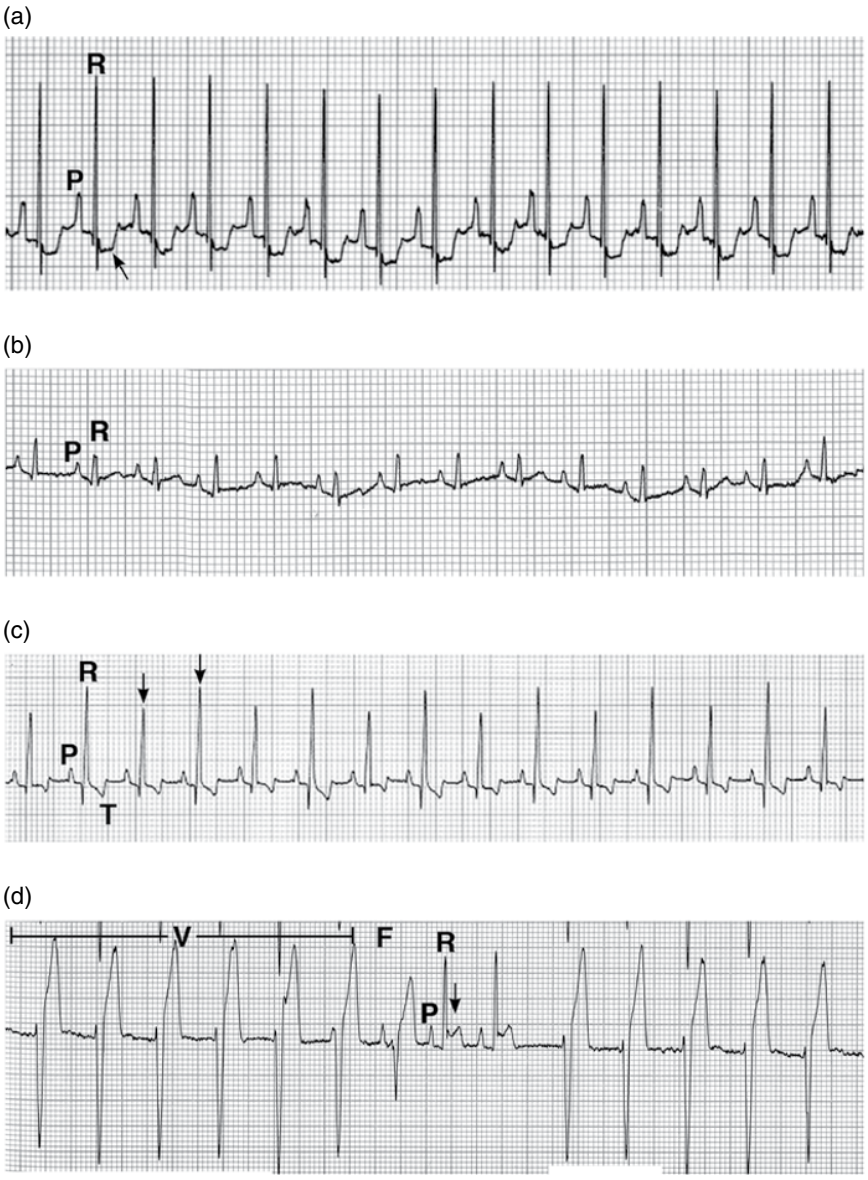


Figure 28.5 Electrocardiogram recordings from dogs with pericardial effusion. (a) Sinus tachycardia. (b) Sinus rhythm with small QRS complexes. (c) Sinus rhythm with electrical alternans, a beat-to-beat variation in R-wave amplitude (*arrows*). (d) Predominantly ventricular rhythm (V) with a single fusion beat (F). Sinus complexes have ST segment elevation (*arrow*). All traces are lead II recorded at 25 mm/s and 10 mm/mV.

the catheter into the pericardial space until fluid, typically hemorrhagic appearing (Figure 28.6e,f), is withdrawn into the extension set tubing. Contact with the heart will make the catheter move with the heartbeat and induce arrhythmias (typically ventricular) as noted on a simultaneous electrocardiogram. If either is encountered, the catheter should be withdrawn quickly. Alternatively, the catheter can be advanced without being attached to the extension set tubing and flash of hemorrhagic fluid will be detected when the catheter is introduced into the pericardial fluid, at which point the needle is removed and the extension set tubing connected.

5) Once pericardial effusion is encountered, detach the extension set tubing from the needle, remove the needle from the catheter, and reattach the extension set tubing directly to the catheter. Removing the needle prevents contact with the heart as the pericardial fluid is removed.
6) Place the initial sample of pericardial fluid in serum (red-top) and EDTA (purple-top) tubes for laboratory analysis. Fluid can be reserved for culture and sensitivity,

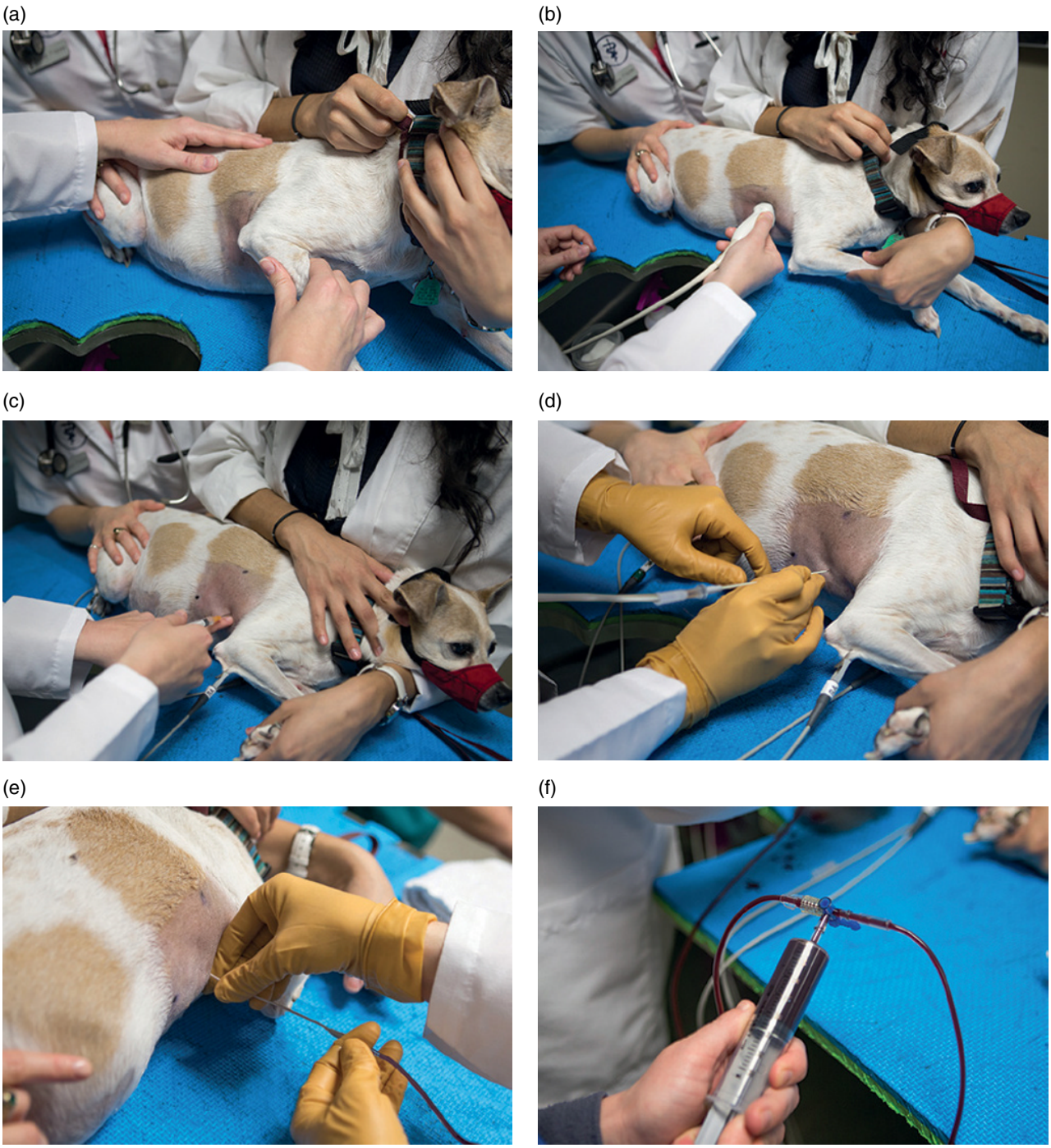


Figure 28.6 Pericardiocentesis in a dog. This dog had a history of biting and no clinical signs of dyspnea. A muzzle was placed as a precautionary measure along with gentle restraint for the procedure. (a) Identify the ideal position for introducing the catheter into the thorax, which is often around the fifth or sixth intercostal space near the costochondral junction. It can be found by flexing the right front limb and swinging the leg across the thorax and using the intercostal space where the point of the elbow crosses the costochondral junction. (b) Locating the ideal site for catheter entry using ultrasound guidance. (c) Following sterile preparation of the pericardiocentesis site, inject a local anesthetic block into the skin, intercostal muscles, and pleura. After approximately five minutes, use a scalpel blade to make a small stab incision in the skin to facilitate catheter insertion and advancement. Note multiple spots were marked on the perimeter of the shaved area to triangulate the position for the anesthetic block and subsequent catheter entry site. (d) At the predetermined ideal pericardiocentesis site, advance the catheter through the skin, followed by the intercostal muscles, avoiding the caudal aspect of the rib where the intercostal vessels are located, and into the pleural space. Note the leads have been attached for monitoring the electrocardiogram during the procedure. (e) The catheter was advanced until a scratching sensation was detected when the needle contacted the pericardium. Once pericardial effusion was encountered, the extension set tubing was detached from the needle, the needle removed from the catheter, and the extension set tubing reattached directly to the catheter. Removing the needle prevents contact with the heart as the pericardial fluid is removed. (f) Two extension sets are connected with a three-way stopcock. One extension set tubing is connected to the end of the catheter and the second is emptying into a collection bowl. Note the fluid is hemorrhagic in appearance, characteristic of pericardial effusion.

when indicated. The fluid in the red-top tube should be monitored for clotting, which could indicate inappropriate intracardiac placement of the catheter. Pericardial fluid does not routinely clot. A packed cell volume (PCV) on the effusion can be obtained to confirm that the fluid is not blood.

7) Once pericardial effusion is no longer withdrawn, ultrasound can be used to confirm the pericardial effusion has been removed or has drained into the thoracic cavity. Pleural effusion can be removed prior to withdrawing the catheter from the thorax.

Monitoring and Follow-Up

Pericardiocentesis often results in immediate clinical improvement. Careful monitoring of the patient for further hemodynamic collapse or clinical improvement is recommended following the procedure. Ideally, dogs should not be sent home immediately after pericardiocentesis and are monitored in the hospital for 12–24 hours. Rapid (minutes to hours) reaccumulation of pericardial fluid and significant arrhythmias are possible following pericardiocentesis. If pericardiectomy is not scheduled (see Surgical Management for recommendations), recheck within 2–4 weeks and consider pericardiectomy if the pericardial effusion has reaccumulated.

Cancer Therapy

Palliative or definitive cancer therapy rarely is successful with cardiac neoplasia. Complete surgical excision can rarely be achieved because of tumor proximity to vital structures. There are reports of a positive response to chemotherapy for lymphoma and hemangiosarcoma. Consultation with an oncologist is recommended for the most current therapeutic strategies.

Surgical Management

Despite fluid removal and immediate clinical improvement, pericardial effusion is likely to recur in most instances. Surgical pericardiectomy (partial or subtotal) allows improved visualization for the surgeon to identify the underlying etiology and/or biopsy a tumor. Echocardiography is very specific for identifying a tumor but not 100% sensitive, particularly for small tumors that may be readily identified by a surgeon. A small pericardial window provides palliation but can potentially lead to constrictive pericarditis of the remaining pericardium or allow herniation of a portion of the heart through the pericardial opening. Pericardiectomy can be curative for idiopathic and infectious etiologies and extend survival for dogs with chemodectomas. Thoracoscopic pericardiectomy has the benefit of offering lower patient morbidity but requires a skilled operator to achieve optimum results. Balloon pericardiotomy has been described as a palliative procedure for neoplastic effusions.

Prognosis

Prognosis depends on the underlying cause of the effusion. Pericardiectomy can result in clinical improvement or cure in idiopathic cases and in infectious cases when combined with appropriate antibiotic or antifungal therapy. Pericardiectomy extends survival time in dogs with heart base tumors and is associated with minimal improvement with hemangiosarcoma and mesothelioma. In cats, prognosis with effusion secondary to heart disease and heart failure is guarded to poor due to the presence of severe underlying heart disease.

Constrictive Pericarditis

Etiology/Pathophysiology

Constrictive pericarditis is characterized by a stiff, fibrous pericardium that impairs ventricular diastolic filling even if no fluid is present. Although considered uncommon, the diagnosis is difficult to make and can be overlooked. It is characterized by an absence of pericardial effusion though combined constrictive-effusive disease does occur. Chronic pericardial and pleural effusion including chylous effusion and infectious pericarditis secondary to fungal organisms can result in constrictive pericarditis.

Signalment

Similar to pericardial effusion.

History and Clinical Signs

Similar to pericardial effusion with a high incidence of signs of elevated right heart pressures.

Diagnosis

Echocardiography

Pericardial effusion is often absent or small volume. Tamponade may be documented with only a small volume of effusion. The pericardium can appear thickened. Advanced Doppler studies show respiratory changes in the peak velocities of mitral and tricuspid valve inflow profiles highly suggestive of constrictive physiology.

Cardiac Catheterization

Characteristic patterns in atrial and ventricular pressure profiles are indicative of constrictive physiology although administering a fluid bolus may be required to generate

the pattern. Right atrial pressure traces are characterized by a prominent Y descent. Right ventricular pressure traces have a characteristic dip and plateau (square root sign) with elevated end-diastolic pressure.

Therapy

Surgical management with subtotal pericardiectomy to remove the fibrotic pericardium is generally required to resolve clinical signs. If the epicardium is involved, epicardial stripping is more difficult and associated with important complications.

Prognosis

Prognosis is poor without surgical management and associated with an increased rate of complications with epicardial involvement.

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Section 4

Respiratory Disease

29

A Respiratory Pattern-Based Approach to Dyspnea

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The initial approach to a patient with respiratory distress is of the utmost importance as it can determine whether these critical patients live or die. Classic clinical signs of respiratory distress include tachypnea, head and neck extension, open-mouth breathing, anxiety, cyanosis, nares flaring, abducted elbows, orthopnea, and paradoxical movement of the chest and/or abdomen. Overt signs of respiratory distress are more commonly seen in dogs than cats. Unfortunately, cats readily mask disease severity, and commonly the only evidence of respiratory dysfunction may be tachypnea and prominent respiratory motions in sternal recumbency.

The first step in examining a patient with a respiratory emergency is to perform a primary survey, efficiently evaluating airway, breathing, and circulation (ABCs). If the airway is not patent, it must be cleared of obstruction and immediate orotracheal intubation performed. If an upper airway obstruction prevents orotracheal intubation, an emergency tracheostomy must be performed. If there are no airway patency issues, a clinician should evaluate the patient's breathing pattern and work of breathing. Particular attention should be given to the phase of breathing affected, and effort should be made to determine if the breathing pattern is obstructive or restrictive.

Anatomical localization of the cause of respiratory distress is assessed through a "look, listen and feel" approach, and may be a very powerful tool for assessing underlying structural changes. Increased inspiratory effort is commonly associated with extrathoracic disorders while increased expiratory effort is most often due to intrathoracic diseases. An obstructive breathing pattern indicates inappropriate movement of air into and/or out of the lungs and is frequently associated with a slower respiratory rate and deeper breaths than normal. A restrictive breathing pattern is characterized by inadequate expansion of the chest wall and/or lungs, resulting in shallow tachypnea. The initial evaluation of a patient should ideally begin from afar, as the breathing pattern may change with manipulation. Making an accurate assessment after handling can be far more challenging.

Upper Airway

The upper respiratory tract, that includes the nares, nasal cavity, pharynx, and larynx, is simply a conduit from the nares to the glottis. Diseases of the upper respiratory tract are relatively common in both dogs and cats (Table 29.1). Upon presentation, the owner may report that a patient snores and/or has exercise intolerance, dysphagia, regurgitation, and/or posttussive retching. They may also report that these clinical signs are associated with and/or exacerbated by excitement, humidity, and/or elevated ambient temperatures. Physical examination may identify referred upper airway sounds, orthopnea, bilateral elbow abduction, restlessness, dysynchronous breathing, and cyanosis. Affected patients commonly have abnormal respiratory sounds and pattern of breathing; the classic upper airway breathing pattern is characterized by increased inspiratory time and effort compared to expiration. Increased nasal noise (stertor) and/or laryngeal noise (stridor) may also be present, depending on the site of airflow turbulence. Occasionally, pulmonary crackles that form due to noncardiogenic pulmonary edema may be auscultated.

Diseases of the upper airway commonly cause at least partial airway obstruction that markedly reduces proper airflow. The resultant turbulent airflow promotes the formation of edema and inflammation that subsequently increases the work of breathing and further narrows the affected airway, creating a vicious cycle. Combined with a reduced ability to effectively eliminate heat from the body via evaporation, affected patients may readily

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Table 29.1 Common diseases affecting the upper airway

Site	Examples
Nares	Stenotic nares
Nasal cavity	Inflammation, neoplasia, infection (bacterial, fungal, parasitic), granuloma, foreign body
Pharynx	Neoplasia, polyp, abscess, granuloma, elongated soft palate, foreign body, stenosis/stricture
Larynx	Paralysis, collapse, neoplasia, abscess, granuloma, everted saccules, foreign body

develop severe secondary hyperthermia. Patients affected by upper airway disorders should always be handled with minimal restraint, as they may experience respiratory arrest with minimal manipulation.

Patients with upper airway diseases with partial obstruction should be given appropriate sedation and supplemental oxygenation as soon as possible in an effort to reduce the work of breathing and anxiety. The least stressful method of supplemental oxygen provision should be employed, and viable options include flow-by, facemask, oxygen cage, nasal cannulation, modified Elizabethan collar (i.e., Crowe collar), and transtracheal catheterization. A commonly used sedative protocol for cardiovascularly unstable patients is the combination of a pure mu opioid (i.e., fentanyl 2–4 µg/kg IV; oxymorphone 0.05–0.1 mg/kg IV/IM; methadone 0.2–0.5 mg/kg IV; hydromorphone 0.1–0.2 mg/kg IV) with a benzodiazepine (i.e., diazepam 0.1–0.5 mg/kg IV; midazolam 0.2–0.4 mg/kg IV). Acetylpromazine (0.02–0.1 mg/kg IV/IM) and butorphanol (0.1-0.2 mg/kg IV/SQ) may be appropriate for cardiovascularly stable patients.

While provision of sedation and supplemental oxygen is sufficient to relieve clinical signs for many patients with upper airway diseases, some will not meaningfully respond. These patients must have their airways captured via orotracheal intubation immediately, and the astute clinician must be prepared to perform an emergency tracheostomy for those patients with complete oropharyngeal and/or laryngeal obstruction. Passive and active cooling measures should be employed for patients with body temperatures greater than 40.5 °C (105 °F), but should be discontinued with body temperatures reach 39.4 °C (103 °F).

Once stable, a thorough physical examination should be performed in an effort to determine the underlying cause of the upper airways signs (if not obvious). Diagnosis of specific airway abnormalities in an individual patient requires thorough evaluation of the nares, oral and nasal pharynx, and larynx. Diagnostic investigation may include a sedated orolaryngeal examination, aural and otoscopic examination, thoracic and cervical radiography, tracheal fluoroscopy, and nasal computed tomography with rhinoscopy. Arterial blood gas analysis commonly identifies hypoxemia with hypercapnia.

Lower Airway

The lower airway is composed of the intrathoracic trachea, primary and lobar bronchi, and bronchiolar arborization. Dogs may be affected most commonly by intrathoracic tracheomalacia, bronchomalacia, and chronic bronchitis, while feline patients are most commonly diagnosed with asthma. Foreign body obstruction must be considered. While neoplasia may affect the lower airway, they rarely induce acute dyspnea due to their chronic, insidious nature. Owners may report a chronic and/or progressive history of coughing that is frequently productive although the sputum is most often swallowed. Affected patients commonly have a respiratory pattern characterized by prolonged expiration despite normal inspiratory time and effort; additionally, a clinician may observe abdominal effort during expiration (abdominal push) and/or auscultate expiratory wheezes. Patients may display orthopnea, and feline patients may breathe with an opened mouth. A murmur is not expected unless lower airway disease has contributed to the development of cor pulmonale. Tracheal sensitivity may be noted in dogs with tracheobronchomalacia and chronic bronchitis.

Feline bronchial asthma is a common respiratory condition caused by altered immunosensitivity of the respiratory tract to inhaled allergens. This hyperresponsiveness causes various structural and chemical changes in the tracheobronchial tree, including adrenergic–cholinergic imbalance and abnormal mucus production. No pathognomonic clinical signs and/or laboratory assays have been identified, and definitive diagnosis is based on history, physical examination findings, and exclusion of other disease entities from the list of differential diagnoses.

The cause of canine chronic bronchitis is not definitively known, and is typically considered idiopathic in nature. Establishment of a clear link between this disease and environmental pollutants, hypersensitivity reactions, and/or poor dental health has been challenging. Accordingly, a definitive diagnosis is currently made with documentation of lower airway inflammation and elimination of other potential causes. Tracheobronchomalacia is characterized by progressive flaccidity of the tracheal cartilages that results in collapse of the tracheal and/or bronchial lumina. The definitive cause of this disease has not yet been identified, and possible contributing factors include airway allergies inducing chronic inflammation, genetic predisposition, and cartilage matrix degeneration. During exhalation, the intrathoracic trachea and/or

bronchi collapse, contributing to common clinical signs, most notably coughing. Definitive diagnosis is made via imaging that may include thoracic and cervical radiography, fluoroscopy, and/or tracheobronchoscopy.

Clinicians should follow a standard and consistent protocol for assessing and hopefully stabilizing a patient suspected of having lower airway disease, focusing initially on performing an efficient primary survey. Patients should be given appropriate sedation and supplemental oxygenation as soon as possible in an effort to reduce the work of breathing and anxiety. Minimal handling is advocated, as the stress of manipulation may be lethal. The least stressful method of supplemental oxygen provision should be employed, and viable options include flow-by, facemask, oxygen cage, nasal cannulation, modified Elizabethan collar (i.e., Crowe collar), and transtracheal catheterization.

A commonly used sedative protocol for cardiovascularly unstable patients is the combination of a pure mu opioid (i.e., fentanyl 2–4 µg/kg IV; oxymorphone 0.05–0.1 mg/kg IV/IM; methadone 0.2–0.5 mg/kg IV; hydromorphone 0.1–0.2 mg/kg IV) with a benzodiazepine (i.e., diazepam 0.1–0.5 mg/kg IV; midazolam 0.2–0.4 mg/kg IV). Acetylpromazine (0.02–0.1 mg/kg IV/IM) and butorphanol (0.1-0.2 mg/kg IV/SQ) may be appropriate for cardiovascularly stable patients. Inhaled albuterol (90–180 µg), a rapidly acting beta-2 agonist, should be administered; terbutaline (0.01 mg/kg SC) is a reasonable alternative if a metered-dose inhaler is not available. Corticosteroids are commonly used for chronic management of feline asthma and canine chronic bronchitis, but their use is not necessarily warranted in the initial management of these diseases; a brief (i.e., 7–10 days) tapering regime of antiinflammatory corticosteroid may be beneficial in the acute management of tracheobronchomalacia to help break the cycle of coughing commonly present in affected patients.

Once stable, a thorough physical examination should be performed in an effort to determine the underlying cause of the lower airways signs. High-quality, three-view thoracic radiographs are an essential part of the diagnostic investigative process. Indirect visualization via fluoroscopy and/or direct visualization of the lower airways via tracheobronchoscopy may be invaluable, and lower airway cytology and culture should be pursued to rule out infectious diseases.

Pleural Space

The pleural cavity is the potential space between the parietal pleura associated with the body wall and visceral pleura associated with lungs. When this potential space is occupied by air, fluid, masses and/or viscera, the lungs are unable to expand normally. As a result, intrapleural pressure increases and ultimately exceeds the intrapulmonary pressure, effectively reducing tidal volume. Accordingly, a patient must breathe rapidly to maintain adequate minute ventilation. Classically, affected patients manifest a restrictive breathing pattern characterized by shallow tachypnea. With reduced tidal volume, alveoli progressively collapse to cause hypoventilation and hypoxemia due to ventilation–perfusion mismatch.

Thoracic auscultation varies depending on the nature of the pleural disease. Pneumothorax may develop secondary to blunt or penetrating thoracic trauma, but may also occur spontaneously due to primary pulmonary parenchymal disease. A patient with pneumothorax has lung sounds that are most audible ventrally. Pleural effusion may occur secondary to accumulation of blood (hemothorax), infectious exudate (pyothorax), neoplasia, chyle (chylothorax), and heart failure; hypervolemia and hypovolemia are rare causes of pleural effusion. A patient with pleural effusion commonly has dull ventral lung sounds with audible and possible increased lungs sounds dorsally. Borborygmi may be heard in those patients with a congenital or traumatic pleuroperitoneal diaphragmatic hernia. A cardiac murmur and/or dysrhythmia may be auscultated in those living with heart disease.

Patients with pleural disease should be provided supplemental oxygenation as soon as possible via the least stressful method. Sedation should also be administered, ideally prior to thoracocentesis; this is not always feasible if imminent respiratory arrest is anticipated. A commonly used sedative protocol for cardiovascularly unstable patients is the combination of a pure mu opioid (i.e., fentanyl 2–4 µg/kg IV; oxymorphone 0.05–0.1 mg/kg IV/IM; methadone 0.2–0.5 mg/kg IV; hydromorphone 0.1–0.2 mg/kg IV) with a benzodiazepine (i.e., diazepam 0.1–0.5 mg/kg IV; midazolam 0.2–0.4 mg/kg IV). Diuretic therapy is not indicated for the emergency management of pleural space disease.

Thoracocentesis should generally be performed prior to thoracic radiography if pleural space disease is suspected. A thoracocentesis is typically performed at the seventh to ninth intercostal space. If a pneumothorax is suspected, the site of pleural puncture is perpendicular to the body wall just ventral to the thoracic hypaxial musculature; the level of the costochondral junction is the site of pleural puncture for those patients with suspected or confirmed pleural effusion. If available, thoracic focused assessment with sonography for trauma, triage and tracking (tFAST[3]) may be used to confirm pneumothorax and pleural effusion, help determine site of pleural puncture, and may be performed in lateral or sternal recumbency. Thoracocentesis has been uncommonly associated with hemorrhage, pulmonary parenchymal injury, and iatrogenic infectious disease

transmission. Rapid and fatal reexpansion pulmonary edema may rarely occur in patients with chronic pleural effusion. Ideally, pleural fluid and/or air should be removed until negative pressure is achieved, but this is not always possible. If negative pressure cannot be achieved, if more than two thoracocenteses are required in a one-hour period, or more than three thoracocenteses are required in a 24-hour period, a thoracostomy tube should be placed.

Once stable, a thorough physical examination should be performed in an effort to determine the underlying cause. Traumatic pneumothorax commonly resolves without surgical intervention, but injuries may require several days to heal. The presence of pneumothorax without a history of trauma should always prompt a search for pulmonary parenchymal disease. Pleural effusion should be immediately evaluated in-house for obvious sepsis and/or neoplastic cells, and one should submit samples (i.e., pleural fluid sample in EDTA-containing tube, unstained slide, fluid sample on appropriate culture media) to a veterinary reference laboratory for evaluation by a board-certified veterinary clinical pathologist. Echocardiography and cardiac biomarker (i.e., NT-proBNP) measurement may be helpful in those patients suspected of living with cardiac disease, and diaphragmatic hernias should be surgically repaired as soon as the patient is cardiovascularly and metabolically stable.

Pulmonary Parenchyma

The pulmonary parenchyma may be affected by a number of diseases, and a thorough history will help the astute clinician develop an appropriate diagnostic investigation and therapeutic interventions. Dogs frequently have a history of a cough that may or may not be productive, but cats rarely manifest this clinical sign. A history of laryngeal paralysis or recent vomiting should raise concern for aspiration pneumonitis, and patients with trauma may develop pulmonary contusions and/or noncardiogenic pulmonary edema. Recent generalized seizure activity, electrocution, traumatic brain injury, and/or strangulation should also raise concern for noncardiogenic pulmonary edema that develops secondary to endothelial injury and vascular leakage into alveoli. Conversely, patients with primary cardiac disease are at risk for developing cardiogenic pulmonary edema.

Performing a complete physical examination is invaluable for patients with suspected pulmonary parenchymal disease. Affected patients do not have a specific respiratory pattern, and frequently manifest respirations that are rapid and deep. They may be presented with cyanosis and dyspnea, and increased abdominal effort is relatively common. Auscultation commonly reveals end-inspiratory crackles, adventitious lung sounds that represent the sudden opening of fluid-filled alveoli. Alveolar fluid may be blood, purulent exudate or transudate. Alveolar hemorrhage may occur secondary to trauma and/or coagulopathy. A patient with cardiogenic pulmonary edema secondary to left-sided heart disease may have a systolic murmur and hypothermia while a patient with pneumonia or aspiration pneumonitis may have pyrexia. Patients should be efficiently examined for evidence of ecchymoses, obvious soft tissue and/or orthopedic injury and thermal injury (i.e., lingual or oral commissure).

Patients should be given appropriate sedation and supplemental oxygenation as soon as possible in an effort to reduce the work of breathing and anxiety. The least stressful method of supplemental oxygen provision should be employed. A commonly used sedative protocol for cardiovascularly unstable patients is the combination of a pure mu opioid (i.e., fentanyl 2–4 µg/kg IV; oxymorphone 0.05–0.1 mg/kg IV/IM; methadone 0.2–0.5 mg/kg IV; hydromorphone 0.1–0.2 mg/kg IV) with a benzodiazepine (i.e., diazepam 0.1–0.5 mg/kg IV; midazolam 0.2–0.4 mg/kg IV). A single dose of furosemide (dogs: 2 mg/kg IV/IM; cats: 1 mg/kg IV/IM) may be provided to those in which primary heart disease is suspected to be contributing to clinical signs until a definitive diagnosis is made. While provision of sedation and oxygen is sufficient to relieve clinical signs, some will not meaningfully respond; these patients must have their airways captured via orotracheal intubation immediately and mechanical ventilation should be initiated. Provision of positive end-expiratory pressure (PEEP) at a level of 3–5 cm H_2O may promote recruitment of collapsed alveoli.

Diagnostic imaging should be performed once the patient has been appropriately stabilized. Commonly employed thoracic imaging modalities include tFAST[3], veterinary bedside lung ultrasound examination (VetBLUE), and thoracic radiography. A tFAST[3] evaluation may be used to detect chest wall, lung, pleural and/or pericardial pathology, and may be performed in lateral or sternal recumbency. Five points are evaluated, and fur is not shaved but rather is simply parted with alcohol or sonographic gel (Table 29.2). Patients with pulmonary parenchymal disease may have B-lines (aka: comet tail artifacts, lung rockets) that suggest interstitial disease or interlobar edema is present; thus a clinician should be suspicious of pulmonary edema (cardiogenic and noncardiogenic) and pneumonia/pneumonitis. A VetBLUE scan is similar to a tFAST[3], as it is performed rapidly in sternal recumbency, measures the presence of B-lines and does not require hair coat shaving; in contrast, eight locations (four per hemithorax) are evaluated during the scan (see Table 29.2). The absence of B-lines in all evaluated lung fields rules out pulmonary edema and suggests a nonrespiratory cause of distress.

Table 29.2 Areas evaluated during tFAST[3] and VetBLUE examination

tFAST[3]		VetBLUE	
Right hemithorax	Left hemithorax	Right hemithorax	Left hemithorax
Chest tube site (CTS)	Chest tube site	Caudodorsal lung lobe (CdLL)	Caudodorsal lung lobe
Pericardial site (PCS)	Pericardial site	Perihilar lung lobe (PHLL)	Perihilar lung lobe
Diaphragmatic-hepatic (DH)		Middle lung lobe (MDLL)	Middle lung lobe
		Cranial lung lobe (CrLL)	Cranial lung lobe

Table 29.3 Common etiologies based on thoracic radiographic patterns of distribution

Pattern of distribution	Common underlying etiology
Cranioventral	Pneumonia, aspiration pneumonitis
Perihilar	Cardiogenic pulmonary edema (dogs)
Caudodorsal	Noncardiogenic pulmonary edema, hematogenous pneumonia
Nodular	Pulmonary mycoses, neoplasia

One must understand that VetBLUE and tFAST[3] scans do not replace the diagnostic utility of thoracic radiography when evaluating patients with pulmonary parenchymal disease. Indeed, evaluation of soft tissue parenchymal patterns may be uniquely helpful in determining the underlying disease process (Table 29.3). Interstitial, interstitial-to-alveolar, and alveolar patterns are most commonly reported in patients with pulmonary parenchymal diseases.

Animals with primary left-sided cardiac disease may have cardiomegaly, left atrial enlargement, and pulmonary venous dilation. While a perihilar radiographic distribution is highly suggestive of cardiogenic pulmonary edema in dogs, cats do not have classic radiographic patterns for most parenchymal diseases. The choice of additional diagnostic investigation should be based on patient history and physical examination. Tracheal washing or bronchoalveolar lavage for airway cytology and culture (bacterial & fungal) may be appropriate for patients with suspected infectious pneumonia or aspiration pneumonia/pneumonitis. Metastatic screening via abdominal radiography and/or ultrasonography may be indicated for those patients suspected of living with neoplasia, and fungal urine antigen and serology should be performed in those with suspected pulmonary mycoses. Definitive treatment is based on a patient's ultimate diagnosis.

Pulmonary Thromboembolism

Pulmonary thromboembolism (PTE) occurs when venous thrombi formed in large, deep veins travel through the right side of the heart and lodge in the pulmonary arterial bed. The caudal lung lobes are more likely to be involved as they receive most of the right ventricular output. Consequences of PTE include hypoxemia, bronchoconstriction, ventilation–perfusion (V–Q) mismatch, and hyperventilation. With time, further complications arise, including atelectasis, pulmonary edema, and pleural effusion. Hemodynamic complications from PTE depend on the extent to which the pulmonary vasculature is occluded and the amount of preexisting cardiac and pulmonary compromise. If pulmonary vasculature reserve capacity is exceeded, pulmonary vascular resistance increases to augment right ventricular afterload and ventricular oxygen demand. If the oxygen supply is exceeded, ischemia, dysrhythmias, and/or right ventricular failure may occur. Decreased cardiac output is caused by reduced pulmonary venous return induced by pulmonary blood flow obstruction.

Diagnosing PTE is difficult. Clinical signs commonly include tachypnea, dyspnea, and hypoxemia, none of which is pathognomonic for PTE. Initial assessment should include thoracic radiography, abdominal ultrasonography, arterial blood gas analysis, a complete blood count, biochemical profile, urinalysis and heartworm testing. Reported radiographic abnormalities associated with PTE are pleural effusion, regional oligemia, alveolar infiltrates, cardiomegaly, hyperlucent lung regions, and enlargement of the main pulmonary artery. While the majority of patients with PTE will have radiographic abnormalities, radiographs may also be normal in 9–27% of dogs and 7% of cats with PTE. Arterial blood gas (ABG) analysis is frequently a very useful diagnostic tool. In one canine PTE study, hypoxemia was documented in 80% of affected patients and increased alveolar-arterial (A-a) gradients on room air in all dogs. Basic blood and urine testing is performed in an effort to identify predisposing conditions, including hyperadrenocorticism, protein-losing nephropathy, protein-losing enteropathy, hypothyroidism, and/or diabetes mellitus.

If these tests fail to identify an underlying disease process, echocardiography and measurement of prothrombin and partial thromboblastin times may be helpful.

Echocardiography may show a right-sided thrombus or a thrombus in the main pulmonary artery, or may also demonstrate changes suggestive of pulmonary hypertension. A normal echocardiogram does not rule out PTE. Measurement of D-dimers may have diagnostic utility in patients with PTE. A 2003 study determined that D-dimer concentrations >500 ng/mL were 100% sensitive for predicting thromboembolic disease but specificity was 70%; conversely, D-dimer concentrations greater than 1000 ng/mL had 80% sensitivity and 94% specificity. The sensitivity of D-dimer in the diagnosis of PTE is more important than specificity, as false negatives may have fatal consequences. Tests for hypercoagulability, such as antithrombin, fibrinogen, and thromboelastography, should also be considered. Advanced imaging such as V–Q scans, spiral computed tomography, and/or pulmonary angiography might ultimately be required for definitive diagnosis of PTE.

Pulmonary thromboemboli dissolution may begin without treatment within hours of formation and completely dissolve within days. Nevertheless, a prothrombotic tendency persists to promote continued formation of pulmonary thromboemboli. Goals of treatment are reversal of the prothrombotic state and correction of hemodynamic and pulmonary changes responsible for morbidity and mortality. Treatment usually consists of supportive care, oxygen supplementation, and anticoagulant therapy; systemic or locally delivered thrombolytic agents may be used, but the benefits must be weighed against potential serious risks. Oxygen administration aims to correct hypoxemia caused by V–Q mismatch, alveolar hypoventilation, and/or diffusion impairment. However, the response to oxygen depends on the degree of vascular obstruction; pulmonary shunt occurs when more than 50% of the circulatory bed surface area is occluded, yielding venous admixture and decreased oxygen responsiveness. Resolution of the underlying disease process should always be the primary goal.

Chest Wall

The chest wall is composed of bone and soft tissue structures, including skeletal muscles, external fascia, costal parietal pleural nerves and vasculature; all play structural and functional roles in respiration. The craniodorsal external intercostals and parasternal intercostals promote inspiration by pulling ribs in a cranial direction. The interosseous portion of the internal intercostals and the caudalmost external intercostals contribute to expiration by pulling the ribs caudally. Given the normal negative pressure within the pleural space, it is potential in nature with the parietal pleura held in constant contact with the visceral pleura in the absence of disease. As thoracic cavity dimensions are increased in response to respiratory muscle action, the lungs expand because of the constant negative intrapleural pressure.

Common thoracic wall injuries include blunt trauma, penetrating trauma, and flail chest. Blunt trauma may cause crush and shear injuries to both soft tissues and skeletal structures; advantageously, the skeletal structures of the chest wall are relatively resistant to blunt force trauma. However, muscle is uniquely sensitive to crushing injury, and when damaged in low-velocity accidents may become edematous and inelastic, and may lose the ability to efficiently and effectively contract. Accordingly, thoracic wall compliance decreases and work of breathing subsequently increases. This may manifest as tachypnea but breaths may be shallow or deep; subsequent hypoxemia and/or hypoventilation are relatively common. High-velocity accidents are also associated with shearing injury. While soft tissue damage to the thoracic wall rarely contributes to patient morbidity, energy may be readily transmitted to intrathoracic organs to induce both crush and shearing injuries at these sites. Additionally, a blunt force applied laterally to the thoracic wall may cause rib fractures. However, pressure applied dorsoventrally to the thoracic cage infrequently results in rib and/or sternebrae fractures but such injuries may contribute to reduced thoracic compliance.

Penetrating injuries to the thoracic wall are relatively common in domestic dogs and cats, and common examples include bite injuries and missile (i.e., bullet, arrow) trauma. These wounds readily induce stretching and crushing of tissues in the direct path of penetration. While the actual chest wall penetration is frequently a minor issue in affected patients, one must be acutely aware of the potential underlying pleural and intrathoracic injuries caused by the penetrating trauma. The type and severity of injury directly influence how a patient is presented, and the medical team must be prepared to triage a patient in profound respiratory distress that is in need of immediate orotracheal intubation and intrathoracic stabilization.

Flail chest results from the segmental fracture and/or dislocation of two or more adjacent ribs. This type of injury is uncommon in dogs and cats because of the inherent compliance and anatomic shape of the thoracic cage. Blunt trauma and bite injuries are the most common causes of flail chest, and concurrent pulmonary damage, most notably pulmonary contusions and direct injury from costal fractures, is a major contributor to morbidity associated with this condition; these contusions may lead to decreased pulmonary compliance, hypoventilation, and shunting, all of which cause hypoxemia. The pathognomonic respiratory pattern is paradoxical movement of the unstable ribs (flail

segment) during respiration. Splinting due to pain associated with respiration leads to a decreased cough reflex, hypoventilation, hypoxemia, and atelectasis. Several techniques for stabilization of flail chest have been reported, but the primary focus should be on oxygen supplementation, underlying intrathoracic injuries, and multimodal analgesia.

Diaphragm

As a major respiratory muscle responsible for the creation of subatmospheric intrathoracic pressure, the diaphragm is essential for adequate oxygen and ventilation. Many conditions may induce partial or complete diaphragmatic paralysis, including pleuroperitoneal hernias, botulism, and phrenic nerve damage or degeneration. The classic respiratory pattern of a patient with a dysfunctional or ruptured diaphragm is tachypnea with marked inspiratory excursion of the cranial half of the thorax. Paradoxical abdominal movement is also common, and may be due to either thoracic displacement of abdominal viscera during vigorous inspiration or an inability to maintain abdominal girth during inspiration.

Nonrespiratory Causes

There are multiple causes of tachypnea and dyspnea that do not directly arise from the respiratory tract. Perhaps the most common example is nonpyogenic hyperthermia which may be the sole cause of respiratory signs or be secondary to a concurrent medical condition. Accordingly, measurement of body temperature is essential in patients presented with respiratory signs, and appropriate cooling measures should be implemented when hyperthermia is documented.

Intracranial diseases may directly stimulate the respiratory center located in the medulla. Patients with traumatic brain injury, intracranial neoplasia, and/or inflammatory/infectious central nervous system diseases may have abnormal respiratory patterns. Neurological examination typically identifies other deficits that may aid in determining a definitive diagnosis. Pain and acid–base disorders may also induce tachypnea without hypoxia in patients. Distension of the abdominal cavity is another common cause of tachypnea and dyspnea in dogs and cats, chiefly through elevation of intraabdominal hypertension and development of abdominal compartment syndrome; specifically, intraabdominal hypertension impairs diaphragmatic contraction, thereby impeding the ability to generate subatmospheric intrathoracic pressure. Additionally, pulmonary parenchyma may be compressed, leading to decreased oxygen transport across the pulmonary capillary membrane, increased alveolar dead space, and alveolar atelectasis.

Common examples of intraabdominal pathology that may cause and/or contribute to respiratory compromise include severe paralytic ileus, marked abdominal discomfort inducing splinting of abdominal musculature, large-volume peritoneal effusion, intraabdominal neoplasia, and gastric dilation-volvulus. Whenever possible, abdominal decompression should be performed, and possible decompression methods include peritoneocentesis, therapy for ileus and capillary leak, adequate analgesia to allow for abdominal muscle relaxation, and surgical decompression.

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Feline Bronchial Asthma

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Feline bronchial asthma is one of the most commonly recognized diseases of the lower respiratory tract of cats and is estimated to affect up to 5% of the cat population. The broad range of clinical manifestations that characterizes this condition, its similarities to the human form of the disease, the challenges inherent to its diagnosis, and the necessity for life-long treatment warrant significant consideration of feline bronchial asthma in both human and veterinary respiratory medicine.

Etiology and Pathophysiology

Feline bronchial disease is a general term that has been applied to inflammatory disease of the lower airways that does not have an apparent etiology. Feline asthma is considered to be a specific form of bronchial disease that is distinguished from other inflammatory airways diseases by reversible airflow limitation. This airflow obstruction is caused by smooth muscle hyperreactivity and hypertrophy, increased mucus production, inflammation, and permanent airway remodeling. Airflow restriction reverses either spontaneously or in response to pharmacological intervention. Intermittent bronchoconstriction, predominantly eosinophilic lower airway inflammation, and an allergic immunopathogenesis differentiate feline asthma from chronic bronchitis, which is typified by neutrophilic airway inflammation in response to a previous insult. Accordingly, asthma is recognized by its three hallmark features: airway eosinophilic inflammation, hyperresponsiveness, and permanent remodeling.

Although the exact etiopathogenesis has not been determined, type I hypersensitivity response is widely accepted to be the basis for the development of feline bronchial asthma. This response begins with dendritic cells within the airways that process inhaled allergen. These cells migrate to the regional lymph nodes and present the antigen, bound to major histocompatibility complex class II receptors, to naïve CD4+ T helper cells, triggering these cells to differentiate into T helper 2 cells. T helper 2 cells, in turn, produce interleukins (IL) 4, 5, and 13. IL-4 in particular induces B cells to switch from production of immunoglobulin (Ig) G to antigen-specific IgE that then binds to Fc receptors on the surface of mast cells. Allergen particles that are subsequently inhaled cross-link IgE molecules on the surface of mast cells, initiating an intracellular cascade of events that culminates in mast cell degranulation. Histamines and leukotrienes released from degranulating mast cells promote increased vascular permeability, smooth muscle contraction, and mucus production, generating the clinical manifestations associated with asthma. IL-4, IL-5, and IL-13 that are also released by mast cells recruit eosinophils to the airways. Major basic protein, eosinophil peroxidase, and cationic proteins released by degranulating eosinophils induce the tissue damage that characterizes asthma.

Epidemiology

Cats of any age can develop asthma but young to middle-aged cats are most often affected. A predilection for the Siamese breed has been proposed.

History and Clinical Signs

A wide spectrum of clinical signs characterizes feline asthma. Acute manifestations arise from bronchoconstriction and can include severe dyspnea, orthopnea, tachypnea, cyanosis, open-mouth breathing, and wheezing. Episodes of dyspnea may occur on a daily basis or as infrequently as once or twice yearly. Chronic manifestations are typified by paroxysmal episodes of coughing.

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The cough is usually described as harsh and "gagging" and results from activation of bronchial cough receptors by inflammatory debris, mucus, and smooth muscle spasm. Inhalation of mechanical or chemical irritants can trigger cough, leading to the sporadic nature of the clinical signs. Further, acute exacerbations may be observed in patients with chronic signs, which can result in periodic wheezing or dyspnea in patients with a long-standing history of occasional cough. Clinical signs referable to the upper airways, including sneezing, nasal discharge, and stertor, have been anecdotally reported in asthmatic cats. In fact, histopathologic inflammatory changes have been documented in the nasal passages of cats with experimentally induced asthma. Inspiratory stridor and dyspnea associated with dynamic upper airway obstruction have also been described in an asthmatic cat. Signs of systemic illness, including inappetence, lethargy, and depression, are not typically reported.

Physical examination findings in asthmatic cats are likewise variable. Due to the intermittent nature of the clinical signs, physical examination may yield no abnormalities. Alternatively, observation of the respiratory pattern may reveal an end-expiratory "push" as air trapped within the lungs following inspiration is forcefully expelled through narrowed airways during expiration. In severely affected patients, air trapping can lead to lung hyperinflation, resulting in decreased compliance of the thoracic wall and, subsequently, a "barrel-shaped" appearance to the thorax. Tachypnea with prolongation of the expiratory phase may be observed at rest. Resistance to airflow caused by reduced intraluminal airway diameter results in turbulence, which is exhibited clinically as wheezing that may be audible with or without a stethoscope. Inspiratory crackles, increased bronchial sounds, and/or rhonchi may also be identified on thoracic auscultation, or no abnormal sounds may be appreciated. In some patients, palpation of the trachea elicits cough. Stress associated with restraint can greatly exacerbate the clinical signs.

Diagnosis

In human patients, asthma is definitively diagnosed on the basis of pulmonary function testing such as spirometry that requires a voluntary expiratory maneuver. Since such maneuvers are not feasible in feline patients, there remains at present no gold standard diagnostic test by which feline asthma is diagnosed.

Currently, clinical diagnosis relies on compatible clinical signs, pathology noted on thoracic radiography, airway cytology abnormalities, and exclusion of other causes of similar findings. In an acute setting, conditions such as congestive heart failure and pleural space disease can lead to respiratory distress that resembles signs of severe asthma on initial evaluation. Plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) can be used to differentiate between congestive heart failure and primary respiratory disease in cats with acute dyspnea when specific cut-off values are used. Parasitic bronchitis caused by *Aelurostrongylus abstrusus*, *Capillaria aerophila*, *Paragonimus kellicotti*, or pulmonary migration of *Toxocara cati* is characterized by eosinophilic lower airway inflammation and can be associated with clinical signs that mimic chronic manifestations of asthma. Heartworm-associated respiratory disease complex should also be considered a differential diagnosis for feline bronchial asthma. Specific testing (i.e., Baermann fecal examination, fecal flotation, heartworm antibody testing) should be performed to exclude these conditions before a diagnosis of feline asthma is reached.

Laboratory abnormalities seen with feline asthma are nonspecific but can include a peripheral eosinophilia, occurring in 20–57% of patients. A peripheral neutrophilia can also be noted in moderately to severely affected cats. Hyperproteinemia due to hyperglobulinemia may develop consequent to chronic inflammation. Results of serum biochemistry analysis are typically unremarkable.

Thoracic radiography is standardly employed in the diagnostic evaluation of suspected asthmatics. However, thoracic radiography should not be solely relied upon for diagnosis, as findings can be variable and nonspecific. A bronchial pattern is most commonly seen, consistent with airway inflammatory infiltrates. Interstitial, alveolar, and mixed patterns have also been documented in asthmatic patients. Consolidation of the right middle lung lobe may be observed and results from obstruction of the bronchus by mucus plugging that preferentially occurs in this lung segment due to its perpendicular orientation to the mainstem bronchus. Hyperinflation of the lungs, identified by flattening of the diaphragm, is also consistent with asthma. Importantly, no pulmonary abnormalities may be detected in as many as 25% of cases.

Bronchoscopy provides additional information that can be used to support a diagnosis of feline asthma. The most common bronchoscopic finding identified in cats with lower airways disease is airway obstruction by mucus. Nodular irregularities of the epithelium, airway hyperemia, static or dynamic airway collapse, and bronchial stenosis are also frequently seen. As with radiography, these findings are not specific for feline asthma. Complications ranging from hemoglobin desaturation to pneumothorax have been documented in up to 24% of cats undergoing bronchoscopy. Pretreatment with terbutaline has been associated with a lower incidence of these complications. When the necessary precautions are taken, bronchoscopy can be performed safely in

asthmatic cats and can provide evidence that is crucial in reaching a diagnosis.

Airway cytology remains the most definitive means of diagnosing feline bronchial asthma after other conditions are excluded. Bronchoalveolar lavage (BAL) can be accomplished with bronchoscopic guidance to collect samples from specific segments of the lower airways for cytologic analysis. Alternatively, BAL can be performed using an unguided technique in patients with diffuse distribution of disease when bronchoscopy is not available or feasible. The procedure is performed under general anesthesia that is induced and maintained with short-acting injectable anesthetic agents such as propofol. Prior to inducing anesthesia, the patient is preoxygenated for 5–10 minutes with flow-by or mask oxygenation methods. The procedure is performed with the patient in sternal or lateral recumbency with the most diseased side positioned ventrally. While avoiding oropharyngeal contamination as much as possible, the patient is intubated with a sterile endotracheal tube. A sterile red rubber or polypropylene catheter is then inserted through the lumen of the endotracheal tube and advanced until resistance is met, indicating that the catheter is wedged within a distal airway. Using a syringe, a 5 mL/kg bolus of warmed, sterile 0.9% saline or phosphate buffered saline is instilled through the catheter followed by a 5 mL bolus of air. The empty syringe is then used to aspirate the fluid from the airways. This may be repeated twice to obtain an adequate sample. Retrieval of 46–68% of the total infusate has been reported. The caudal half of the patient may be elevated during aspiration to facilitate retrieval of fluid. Supplemental oxygen is administered postprocedurally for 5–10 minutes. Samples reserved for cytologic analysis should be kept on ice and processed within one hour of collection to avoid deterioration of cells. Hypoxemia is a significant complication associated with BAL but can usually be reversed with oxygen supplementation. Bronchospasm may also occur as a consequence of BAL and can be managed with bronchodilators.

Increased numbers of eosinophils are classically noted in cytologic samples collected from the airways of asthmatic cats. However, a significant neutrophilic component has also been reported in cats with both naturally occurring and experimentally induced asthma. Discrepancy exists regarding the percentage of eosinophils considered abnormal within feline airway cytology samples. Eosinophil proportions ranging from 16% to 28% have been documented in airway samples collected from healthy cats. As such, cytologic findings must be interpreted in light of other diagnostic results in order for a diagnosis of asthma to be verified.

Bacterial culture of airway lavage samples collected from cats with lower airways disease produces variable results. Bacterial growth has been found in airway samples collected from healthy cats, though growth of *Mycoplasma* spp. has not been documented. Therefore, a diagnosis of secondary bacterial infection in an asthmatic patient must be based on growth of a large number of colonies of a single organism or intracellular bacteria seen cytologically. Organisms that have been detected on airway samples collected from cats with bronchopulmonary disease include *Pasteurella multocida*, *Streptococcus* spp., *Staphylococcus* spp., *Mycoplasma* spp., *Moraxella* spp., and *Bordetella* spp.

Due to the degree of invasiveness, lung biopsies are not routinely performed in the diagnostic evaluation of cats with lower airways disease. Histopathology of postmortem lung samples from cats with experimentally induced asthma revealed epithelial hypertrophy and hyperplasia, marked smooth muscle hypertrophy of the terminal and respiratory bronchioles, and mucous cell metaplasia.

Pulmonary function testing, though not employed standardly in clinical settings, has been investigated as a means of assessing asthmatic cats. Specifically, barometric whole-body plethysmography (BWBP) has been employed to assess airway responsiveness in cats with experimentally induced asthma. This noninvasive technique measures pressure changes generated by an awake, spontaneously breathing cat in a transparent, ventilated chamber. Pause and enhanced pause are variables used to estimate lung resistance. These values have been shown to increase significantly following bronchoprovocation in healthy cats and cats with artificially induced asthma. Tidal breathing flow-volume loops have also been utilized to assess lung resistance in cats with bronchial disease. These loops are generated in awake cats using a facemask attached to a pneumotachograph to assess airflow. Cats with bronchial disease have reduced expiratory flows and tidal breathing expiratory volumes and prolonged expiratory time compared to healthy cats. Additionally, ventilator-acquired mechanics have been used to measure airway resistance, positive end-expiratory occlusion pressure, and end-expiratory breath hold pressure following bronchoprovocation in anesthetized cats with experimentally induced asthma.

Advances in the diagnostic approach to feline asthma have included the development of minimally invasive methods that may have utility in a future clinical setting. In particular, exhaled breath condensate (EBC) can be collected from nonanesthetized cats briefly housed within an acrylic chamber and analyzed for hydrogen peroxide, a marker of oxidative stress. The concentration of hydrogen peroxide in the EBC of artificially sensitized cats has been shown to correlate with the degree of eosinophilic lower airway inflammation, suggesting that analysis of EBC may prove to be a useful screening tool for suspected asthmatics.

Identifying the allergens responsible for inciting the asthmatic response in individual cats is a critical step in devising targeted therapies. Methods have been developed to detect IgE that is specific for the allergens used in sensitization in the serum of cats with experimentally induced asthma. Moreover, intradermal skin testing, a practice most often used in the diagnosis of atopic dermatitis, has been shown to be a sensitive means of detecting aeroallergen sensitization in experimental models of asthma. Other minimally invasive immunodiagnostic methods that have been investigated in asthmatic patients include the use of flow cytometry to detect proliferation of allergen-specific T lymphocytes in the peripheral blood.

Treatment

Supplemental oxygen, stress reduction, and bronchodilation are the tenets of therapy for the asthmatic cat in acute crisis. For the patient presenting with dyspnea and cyanosis, supplemental oxygen should be provided immediately at a FiO_2 of 40%. This can be effectively accomplished by placing the patient in an oxygen cage, which also minimizes restraint and handling that can exacerbate dyspnea, with fatal outcomes in some instances.

Beta-2-adrenergic agonists such as terbutaline are most commonly used to induce bronchodilation in an acute setting. Bronchodilation results from airway smooth muscle relaxation triggered by stimulation of beta-2-adrenergic receptors. Activation of these receptors triggers adenylyl cyclase to increase production of cAMP, which sequesters intracellular calcium, thereby reducing smooth muscle contraction. Other potentially beneficial effects of these agents include inhibition of mast cell mediator release and airway microvascular leakage, increased mucociliary clearance, decreased neutrophil activation and endothelial adhesion, and induction of neutrophil apoptosis. Adverse effects associated with beta-2-adrenergic agonist therapy include tachycardia, CNS stimulation, hypokalemia, and tremors. For this reason, these agents should be used with caution in patients with co-morbid cardiac disease, hypertension, hyperthyroidism, seizure disorders, and diabetes mellitus. Beta-2-adrenergic agonists can interact with tricyclic antidepressants such as amitriptyline and clomipramine and should be used with caution in patients receiving these medications. Terbutaline sulfate can be administered IM or SC at an initial dose of 0.1 mg/kg to induce bronchodilation in an acute setting. Decreased respiratory rate is expected within 15–30 minutes of dosing, and repeated doses can be administered as needed.

Albuterol sulfate is a beta-2-adrenergic agonist that may be administered in inhalant form to cats presenting with severe, acute dyspnea. A metered dose inhaler is used to deliver the medication into a chamber device attached to a facemask (Aerokat® Feline Aerosol Chamber, Trudell Medical International). This apparatus facilitates inhalation of the aerosolized particles into the lower airways. An initial dose of one 90 µg puff can be administered to dyspneic patients that will tolerate having the facemask held over the nose and mouth for the 7–10 seconds necessary for the complete dose to be inhaled. This dose may be repeated every 30 minutes for up to four hours. Albuterol can also be dispensed for at-home administration as a "rescue inhaler" for management of acute exacerbations in established asthmatics until veterinary care can be provided. However, chronic use of racemic albuterol should be avoided as the S-enantiomer in this mixture has been shown to cause airway inflammation in healthy and experimentally asthmatic cats.

Status asthmaticus is defined in human medicine as severe, acute asthma that is refractory to repeated doses of beta-agonists. Severely dyspneic feline asthmatics that do not respond to bronchodilators and supplemental oxygen may stabilize only after initiating antiinflammatory therapy with a rapidly acting glucocorticoid such as dexamethasone sodium phosphate. An initial dose of 0.25–2 mg/kg can be administered IM or IV to quickly reduce airway inflammation if necessary.

Lifelong glucocorticoid therapy is the key to chronic management of feline asthma. Because the aeroallergen that provokes the asthmatic response usually cannot be identified or completely removed, avoidance of the offending allergen is often impossible in feline patients. Thus, it is postulated that lower airway inflammation is continually present in asthmatic cats, even in the absence of clinical signs. Lower airway inflammation has been shown to persist in feline asthmatics treated with high-dose glucocorticoid therapy despite resolution of clinical signs. To minimize the permanent airway remodeling that ensues from long-standing inflammation, continuous antiinflammatory therapy is necessary.

Glucocorticoids are the most effective antiinflammatory agents used in the management of feline asthma. They exert their antiinflammatory effects by binding to a cytosolic receptor, then translocating to the nucleus where the glucocorticoid–receptor complex binds to a glucocorticoid response element on the genes that regulate production of inflammatory cytokines such as IL-3 and IL-5. Glucocorticoids also increase vasoconstriction to reduce airway edema; decrease airway hyperresponsiveness over time; decrease mucus secretion; inhibit macrophages, T cells, eosinophils, and mast cells; increase the synthesis of secretory leukocyte protease

inhibitor to reduce airway remodeling; and prevent the downregulation of beta-adrenergic receptors.

Orally administered glucocorticoids are used in the initial management of stable asthmatics. Prednisolone is preferred over prednisone in cats because of impaired hepatic bioconversion of prednisone. No standardized dosing regimen and tapering schedule exists for the use of glucocorticoids in the management of feline bronchial asthma. Patients are typically started on therapy at doses near or at the immunosuppressive range (1–2 mg/kg PO q12h). Long-term therapy with systemic glucocorticoids can be associated with numerous undesirable effects such as polyuria, polydipsia, polyphagia, weight gain, alopecia, thinning of the skin, increased susceptibility to infections, and the development of diabetes mellitus. Systemic steroids can also exacerbate underlying cardiac disease. To minimize these complications, the initial prednisolone dose is tapered by 25–50% once clinical signs have resolved and after at least seven days of therapy.

Inhaled glucocorticoids are associated with negligible adverse effects compared to those seen with systemic therapy and are a very effective means of managing feline asthma long term. Inhaled steroids are minimally absorbed into the systemic circulation and undergo extensive first-pass metabolism. Fluticasone propionate is the most commonly prescribed inhaled glucocorticoid in veterinary medicine. It has the longest receptor residency time and greatest lipophilicity of the inhaled glucocorticoids as well as a high therapeutic index. Treatment with inhaled fluticasone has been shown to reduce airway inflammation and hyperresponsiveness in cats with naturally occurring lower airways disease and in cats with experimentally induced asthma. Suppression of the hypothalamic-pituitary-adrenocortical axis has been demonstrated in healthy cats following treatment with inhaled glucocorticoids, but significant suppression of the systemic immune response was not noted. Fluticasone doses of 44 µg, 110 µg, and 220 µg q12h were shown to reduce airway inflammation in experimental models of feline asthma with similar efficacy. Fluticasone is available in a metered dose inhaler formulation and can be administered to cats using a chamber and facemask as with inhaled albuterol. Systemic steroid therapy should be continued during the first 14 days of treatment with fluticasone to allow the inhaled glucocorticoid to reach full effect. The oral glucocorticoid dose can then be gradually tapered and eventually discontinued while inhalant therapy is continued long term. Inhaled budesonide (400 µg q12h) has also been evaluated in asthmatic cats and has been shown to reduce airway responsiveness while causing suppression of the hypothalamic-pituitary-adrenal axis in a subset of treated cats.

Methylxanthine bronchodilators can be used in conjunction with antiinflammatory therapy for chronic management of refractory disease. Theophylline is the methylxanthine derivative that has been studied most extensively in cats. The mechanism by which methylxanthines induce bronchodilation is postulated to be related to inhibition of phosphodiesterase, which leads to increased intracellular cAMP and, subsequently, smooth muscle relaxation. However, theophylline does not inhibit phosphodiesterase at therapeutic concentrations. Inhibition of adenosine or interference with intracellular calcium levels may instead explain the bronchodilatory effects of these agents. Theophylline also prevents mast cell degranulation, reduces microvascular leakage, and increases respiratory muscle strength. When administered in the evening, sustained-release theophylline achieves higher peak plasma concentrations compared to morning administration. The recommended dose of slow-release preparations is 20–50 mg/kg PO q24h. Adverse effects associated with methylxanthine derivatives include central nervous system stimulation, tachyarrhythmias, increased gastric acid secretion, and diuresis. Because of this, methylxanthines should be used cautiously in patients with preexisting cardiac disease, seizure disorders, hyperthyroidism, and gastric ulcers. Long-acting bronchodilators such as theophylline should be used adjunctively with steroid therapy to achieve improved control of clinical signs in patients that do not completely respond to glucocorticoid therapy alone.

Ciclosporin has been promoted for management of feline asthma that is refractory to glucocorticoid and bronchodilator therapy. A calcineurin inhibitor, ciclosporin inhibits T cell activation and proliferation by interfering with the transcription of genes related to cytokine production, particularly IL-2. In an experimental model of feline asthma, treatment with ciclosporin prior to and during chronic antigen challenge decreased the amount of IL-2 secreted from peripheral blood lymphocytes, prevented an increase in airway hyperresponsiveness after chronic antigen stimulation, and resulted in reduced airway smooth muscle thickness and mucosal eosinophil infiltration histologically compared to untreated cats. Following acute antigen challenge in the same model, pretreatment with ciclosporin did not prevent mast cell degranulation or an increase in lung resistance. Despite this, tracheal smooth muscle harvested from these artificially sensitized cats did not contract in response to antigen exposure when incubated with ciclosporin *in vitro*. Given these differential findings, ciclosporin should be reserved for patients with a poor response to standard asthma therapies. An initial dose of 10 mg/kg PO q12h is recommended with the goal of achieving blood trough levels of 500–1000 ng/mL. Adverse effects associated

with ciclosporin use in cats include anorexia and gastrointestinal upset. Nephrotoxicity and hepatotoxicity may develop at high blood levels.

Antiserotonergics, antileukotrienes, and antihistamines have been investigated for use in feline asthma to reduce airway inflammation while circumventing the adverse effects associated with systemic glucocorticoid therapy. Serotonin released during mast cell degranulation mediates airway smooth muscle contraction in cats. Cyproheptadine, a serotonin receptor antagonist, has been shown to attenuate constriction of airway smooth muscle from antigen-sensitized cats *in vitro*. In live cats experimentally sensitized to aeroallergen, cyproheptadine did not uniformly diminish airway responsiveness, degree of airway eosinophilic inflammation, plasma or BAL fluid serotonin concentrations, or serum content of allergen-specific IgE following allergen challenge. Similarly, cysteinyl leukotrienes are produced by mast cells as well as eosinophils and contribute to many of the pathophysiologic processes underlying asthma, including bronchoconstriction, smooth muscle proliferation, mucus production, and inflammatory cell influx. The leukotriene receptor antagonist zafirlukast was evaluated in an experimental model of feline asthma and was demonstrated to have no effect on airway eosinophilia, airway reactivity, or serum levels of allergen-specific IgE compared to placebo. In another study, urine concentrations of cysteinyl leukotrienes in allergen-sensitized cats did not increase after allergen challenge. These results suggest that leukotrienes may not be a critical factor in the generation of the feline asthmatic response. Histamine plays a crucial role in inducing bronchoconstriction in human asthmatics, though its importance in mediating the feline asthmatic response remains questionable. Cetirizine is a second-generation histamine 1 receptor antagonist that has been evaluated in cats with experimentally induced asthma and was shown to have no effect on eosinophilic airway inflammation or plasma histamine concentrations. Until additional studies are conducted, pharmaceutical agents that inhibit serotonin, leukotrienes, and histamine are not recommended as monotherapy in the management of feline asthma.

Allergen-specific immunotherapy holds promise as the only potentially curative therapy for feline asthma. This form of therapy, which is most commonly employed in veterinary medicine in the management of atopic dermatitis, is proposed to alter the immune response so as to reestablish tolerance to a specific allergen. In particular, rush immunotherapy (RIT) is a modified version of allergen-specific immunotherapy that involves subcutaneous administration of gradually increasing doses of a specific antigen over an accelerated period of time, generally a couple of days or less. The immunomodulatory effects of RIT are hypothesized to be related to production of IgE-blocking antibodies, induction of T cell unresponsiveness, shift from a T helper 2 to a T helper 1 cell response, elaboration of immunosuppressive cytokines such as IL-10 from T regulatory cells, and decreased lymphocyte proliferation in response to allergen. In cats experimentally sensitized to Bermuda grass allergen (BGA), RIT significantly decreased eosinophilic airways inflammation, induced lymphocyte hyporesponsiveness to BGA, increased mRNA transcription of IL-10 in BAL fluid, and decreased mRNA transcription of IL-5 in BAL fluid. Adverse effects associated with RIT in this model included localized swelling around the injection site, increased heart and respiratory rate, hyperthermia, vomiting, agitation, and systemic anaphylaxis noted in one cat. These adverse effects were less severe when RIT was adjuvanted with CpG oligodeoxynucleotides, immunostimulatory DNA sequences that induce a polarized Th1 response. Intranasal administration of RIT has also been evaluated in an experimental model of feline asthma and was shown to be equally effective in reducing the degree of eosinophilic airway inflammation as subcutaneously administered RIT, although subcutaneous RIT more consistently abolished the clinical signs induced by aeroallergen challenge. Both antiinflammatory and immunomodulatory therapy may be necessary in severely affected cats. When administered concurrently with RIT, oral glucocorticoid therapy has been shown to dampen the long-term effectiveness of RIT, which may limit the benefits of RIT as monotherapy in patients with severe disease.

The challenge in applying RIT to cats with naturally occurring asthma lies in elucidating which antigen is triggering the asthmatic response. Intradermal skin testing has been employed to identify the inciting antigens in veterinary patients with atopic dermatitis. This method has been shown to be highly sensitive in detecting a known inciting antigen in cats artificially sensitized to a specific allergen. Concurrently, detection of allergen-specific IgE in the serum of experimentally sensitized cats was shown to be highly specific in identifying the antigen used for sensitization. When evaluated in cats with naturally occurring small airway disease, significantly more positive allergen reactions on serum IgE testing and intradermal skin testing were noted compared to cats without airways disease, though the clinical relevance of these allergens could not be determined. Even though isolating the specific inciting antigen is the ideal means of guiding immunotherapy, RIT using antigens that did not completely match those used to induce the asthmatic phenotype in experimental feline models was shown to reduce eosinophilic airways inflammation. Immunotherapy is likely to play a prominent role in the management of feline asthma in the future, but additional studies in patients with naturally occurring disease

are necessary before allergen-specific immunotherapy can be employed standardly in clinical practice.

Several novel therapies have been investigated using cats with experimentally induced asthma and may be applicable to the management of patients with naturally occurring disease. Specifically, the antiinflammatory effects of omega-3 polyunsaturated fatty acids (ω3 PUFAs) extracted from New Zealand green-lipped mussel have been evaluated in artificially sensitized cats. Airway responsiveness but not eosinophilic inflammation decreased following treatment, suggesting that ω3 PUFAs may have some benefit as adjunctive therapy in the management of feline asthma. Masitinib, a tyrosine kinase inhibitor, has been demonstrated to reduce eosinophilic airway inflammation and improve respiratory compliance in cats with experimental asthma and may emerge as an effective treatment strategy for patients with glucocorticoid intolerance or refractory disease. Stem cell therapy has also been investigated as a means of reducing airway remodeling, one of the hallmarks of feline asthma. Administration of allogenic mesenchymal stem cells to cats experimentally sensitized to a common aeroallergen resulted in attenuation of changes consistent with chronic lung remodeling based on computed tomography. Nebulized lidocaine has been evaluated in cats with experimentally induced asthma and was shown to reduce airway hyperresponsiveness without adverse effects, indicating that it may be effective as palliative therapy when used in combination with glucocorticoids.

Monitoring

Response to therapy is most effectively evaluated by assessing clinical signs. Due to the intermittent nature of clinical signs in some patients, overall improvement in clinical condition should be judged after at least a few weeks of therapy. Decreased frequency of episodes of coughing and/or dyspnea is the expected outcome of successful treatment. A more objective assessment of clinical improvement involves "cough counts" performed by owners at home prior to and after starting therapy. Due to permanent airway remodeling, radiographic manifestations of asthma may not change significantly with treatment, limiting the use of repeated thoracic radiography to monitor response to therapy. The exception is radiographic evidence of atelectasis of the right middle lung lobe, which is expected to resolve with antiinflammatory and mucolytic therapy. The limited availability of pulmonary function testing prohibits its practical application as a means of assessing response to treatment, but it may prove useful for this purpose in the future.

Prognosis

Most asthmatic patients that receive appropriate treatment demonstrate a favorable response with a good long-term prognosis. However, continuing antiinflammatory therapy for life is crucial to prevent further permanent airway remodeling unless the inciting allergen can be identified and exposure prevented. Severe, refractory forms of feline asthma do exist and can present management challenges. Moreover, even patients with apparently well-controlled asthma are at risk for potentially life-threatening episodes of severe, acute bronchoconstriction. The adverse effects associated with systemic glucocorticoid therapy can complicate prognosis and lead to the development of life-limiting complications, including congestive heart failure and diabetes mellitus. Long-term treatment can be further impaired by patients that will not tolerate oral administration of medications or placement of the facemask required for administration of inhalant therapy. In addition, the expense associated with inhaled medications may prevent their use in some patients. Despite these challenges, feline asthma is a readily manageable condition, and successful treatment can prevent acute death and significantly improve quality of life in the majority of patients.

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31

Canine Chronic Bronchitis

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Etiology/Pathophysiology

Canine chronic bronchitis (CCB) is the most common cause of a chronic cough. It is characterized by a cough that is present for at least two months, inflammation in the airways, and a lack of an identified underlying disease that may cause a cough. There is some evidence that environmental pollutants, second-hand smoke or other inhaled noxious chemicals may be contributors to the etiology. A specific role of bacteria in CCB has not been established. The diagnosis of CCB is largely through exclusion, and treatment is based on a patient's clinical history, diagnostic results and response to therapy.

Canine chronic bronchitis airway inflammation is neutrophilic, and there is an increase in the production of mucus. The inflammatory response perpetuates the coughing cycle, which in turn stimulates continued inflammation. This positive feedback sets up a vicious cycle that ultimately leads to permanent changes in the airways, including hyperplasia of mucous glands and goblet cells, hypertrophy of smooth muscle, and fibrosis of the lamina propria. These changes are often accompanied by obstruction of small airways and airway collapse. Some cases of chronic bronchitis can progress to permanent dilation of the bronchi and destruction of the structural integrity of the bronchial walls. This condition is known as bronchiectasis. Cocker spaniels have an increased risk of bronchiectasis. Left unidentified and untreated, the aforementioned changes to the airway can contribute to a progressive decline in lung function. Box 31.1 gives a list of many of the common differentials for CCB.

Epidemiology

The most common signalment for CCB is middle-aged to older, small-breed dogs.

History and Clinical Signs

The history and clinical signs of patients with CCB are similar to those presenting for collapsing trachea and mitral valve insufficiency. Patients with collapsing trachea have a chronic cough associated with narrowing of the airway combined with chronic tracheal inflammation, and a perpetual dry honking cough. Mitral valve insufficiency can lead to enlargement of the left atrium and subsequent compression of the mainstem bronchi that stimulates a chronic coughing reflex. CCB is less commonly diagnosed in large-breed dogs. Exhaustive consideration of alternative causes of a chronic cough in these patients should occur. For example, a Doberman with a history of cough should be thoroughly evaluated for dilated cardiomyopathy, and heart failure should be suspected until proven otherwise. A 12-year-old Labrador with a history of cough should be evaluated for laryngeal paralysis with intermittent aspiration pneumonia or pulmonary metastatic disease. It is imperative that the clinician be astute in differentiating between the potential causes of chronic cough as a misdiagnosis could result in inappropriate treatment and a worsening of the patient's condition.

A thorough history can assist in the differentiation of CCB from other causes of chronic cough. Patients that have had exposure to other dogs in any setting for any period of time should be suspect for canine infectious respiratory disease (CIRD). Commonly, exposure occurs at a groomer, boarding facility, doggie day-care, or dog park, or via a visiting family pet or a new puppy in the household; however, any known interaction, even limited, should raise suspicion. These patients can be any age or breed, and can have clinical signs that range from a mild dry-hacking cough to systemic illness. Pets with evidence of systemic disease that have a history of cough are unlikely to have CCB as their primary ailment, and

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Box 31.1 Common differential diagnoses for CCB

- Bacterial pneumonia – *Escherichia coli*, *Klebsiella*, *Pasteurella*, *Pseudomonas* sp., *Streptococcus*, and *Staphylococcus* are commonly associated with pneumonia in dogs.
- Canine infectious respiratory disease complex – *Bordetella bronchiseptica*, canine influenza, *Mycoplasma*, etc.
- Congestive heart failure
- Fungal pneumonia – histoplasmosis, blastomycosis, and coccidiomycosis.
- Interstitial lung disease.
- Parasitic pneumonia – *Aelurostrongylus* sp., *Capillaria aerophila*, *Crenosomavulpis*, *Filaroides hirthi*, and *Paragonimus kellicotti*. *Oslerus osleri* can result in coughing, but is found in the trachea rather than the lower airways. *Dirofilaria immitis* (heartworm disease) also results in cough.
- Pleural effusion.
- Protozoal infections – *Neospora caninum* and *Toxoplasma gondii*.
- Pulmonary neoplasia.
- Tracheal collapse.
- Upper airway dysfunction (laryngeal paralysis).

attention should be focused on investigating their systemic illness. Questions about weight loss, anorexia, lethargy, and other behavior changes could lead to the detection of a systemic illness. A clinical history should also include questions that discuss potential exposure to passive (second-hand) smoke, the presence of excessive environmental odors/perfumes, and prior prescriptions or home remedies and their clinical effect on the cough.

Physical examination of most patients with CCB is relatively unremarkable. Patients tend to be systemically well, with the only major clinical sign being coughing. Patients are often seen due to an acute exacerbation in their coughing secondary to exposure to environmental irritants or allergens, secondary development of a bacterial infection, or the unveiling of an unrelated concurrent disease. Some dogs will present with tachypnea or increased expiratory effort (labored breathing). Physical examination should focus on the cardiopulmonary system and signs of systemic illness (weight loss or gain, anorexia, lethargy, etc.). Careful auscultation of the lungs can provide clues to lower airway disease, and the presence or absence of a murmur should be noted. Although heart disease and CCB can coexist, the presence of a sinus arrhythmia supports the airway/pulmonary system as the primary cause of coughing.

Sometimes a cough can be elicited with palpation of the trachea due to nonspecific inflammation of the airways. This may assist with characterization of the cough by the clinician and exclude other conditions such as reverse sneezing or other upper airway noises that may be mistaken for a cough. Whether a cough can or cannot be produced during physical examination, a descriptive history should be gathered from the owners – is it dry or productive, paroxysmal or intermittent, is there a relation to eating or certain activities, does it occur at specific times during the day/night, has there been any voice change or reluctance to bark? Some dogs may have syncopal events associated with coughing. This is known as the cough-drop syndrome, which is most likely associated with high vagal tone.

Box 31.2 Recommended laboratory tests

- Complete blood cell count (CBC)
- Biochemistry profile
- Urinalysis
- Heartworm antigen test
- Fecal Baermann and flotation
- NT pro-BNP

Diagnosis

Diagnostic evaluation should be tailored to the individual patient, and prioritized with regard to clinical assessment and history.

Recommended laboratory tests can be found in Box 31.2. These diagnostic evaluations are typically normal in patients with CCB but they assist with the general assessment of the patient's health. A CBC may be suggestive of an infectious component to the cough, while appropriate fecal evaluation may lead to the identification of lungworm larva or eggs, and a NT-proBNP has been shown to be useful in the identification of left atrial enlargement/congestive heart failure.

Thoracic radiographs are essential in the evaluation of a coughing dog. In patients where diagnostic testing is limited, thoracic radiographs have been shown to be the most useful test. Patients with CCB may show findings consistent with bronchial thickening, evidenced by increased "donuts and tramlines" (Figure 31.1). Additional findings consistent with CCB include hyperinflation and bronchiectasis. Although radiographs are relatively insensitive for the diagnosis of CCB, they provide the benefit of assisting with the exclusion of other conditions that result in coughing, such as cardiomegaly, lung masses, pleural effusion, and interstitial lung disease. It is important to remember that normal chest radiographs do not exclude a diagnosis of CCB.

Fluoroscopy may be useful in evaluation for tracheal and bronchial collapse, but does not typically provide benefit for evaluation of chronic cough unless concurrent



Figure 31.1 Thoracic radiographs with a diffuse bronchial pattern evidenced by increased "donuts and tramlines."

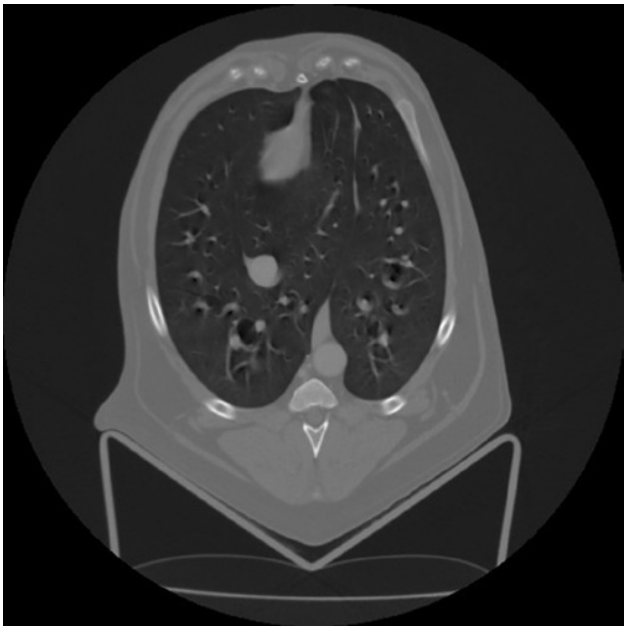


Figure 31.2 Computed tomography slice of the thorax showing a "ground-glass" appearance.

airway collapse is suspected. Ultrasound of the thoracic cavity may assist with diagnostic sampling of isolated lesions that are observed on radiographs (masses or consolidation), or when pockets of pleural effusion are identified; however, it does not assist in the diagnosis of CCB.

Computed tomography (CT) is widely used in people with airway disease, and is becoming more popular in veterinary medicine for the evaluation of canine bronchial disease. The increased resolution of CT compared to radiographs and the ability to perform 3D reconstructions may prove to be more sensitive for the diagnosis of CCB, and allow earlier detection and treatment of the disease (Figure 31.2). Diagnostic CT scanning in veterinary medicine does require brief general anesthesia, and if permissible should be combined with evaluation of laryngeal function, collection of airway cytology samples, and bronchoscopy for a complete airway evaluation.

If available, bronchoscopy is the preferred technique to evaluate and visualize the airway. A recent study showed that patients with CCB often demonstrate an irregular mucosal surface without the glistening seen in healthy airways. Most airways were also noted as having a granular mucosal appearance with a roughened texture, increased amounts of mucus, hyperemia of mucosal vessels, and partial collapse of larger airways during expiration secondary to weakened walls. Bronchial dilation in patients with bronchiectasis can also be noted in CCB patients. Bronchoscopy is also beneficial for the diagnosis or exclusion of some other large airway diseases such as collapsing trachea/bronchi, obstructive intraluminal masses or granulomas caused by some parasites, and foreign bodies.

Transtracheal washes, endotracheal washes, and blind or visualized bronchoalveolar lavages are very useful in characterizing the type of inflammation present in the airways, and for the diagnosis of CCB. Samples should be submitted for bacterial cultures and cytology (fungal cultures should be submitted when appropriate). The airway sampling technique chosen often reflects clinician preference, and availability of supplies and equipment (see Box 31.3 for a detailed description of techniques).

Cytologic samples should be immediately placed into EDTA tubes, and processed promptly to avoid changes in cell counts and appearance. In cases where analysis will be delayed, a small portion of the sample should be centrifuged, decanted, and a direct smear of the supernatant and precipitation should be prepared. Evaluation of respiratory cytology from dogs with CCB typically reveals a predominant neutrophilic infiltrate with excessive mucus (Figure 31.3), small numbers of lymphocytes, eosinophils, goblet cells, ciliated and epithelial cells, and a variable number of alveolar macrophages. Samples that show a marked eosinophilia should be suspected of having an eosinophilic bronchopneumonopathy, rather than CCB. Bacterial cultures should be submitted in all cases; however, the role of bacteria is unclear, as colonization is common, but may not reflect a clinical infection.

Pulmonary function testing is widely used in human medicine to better characterize the severity of and specific

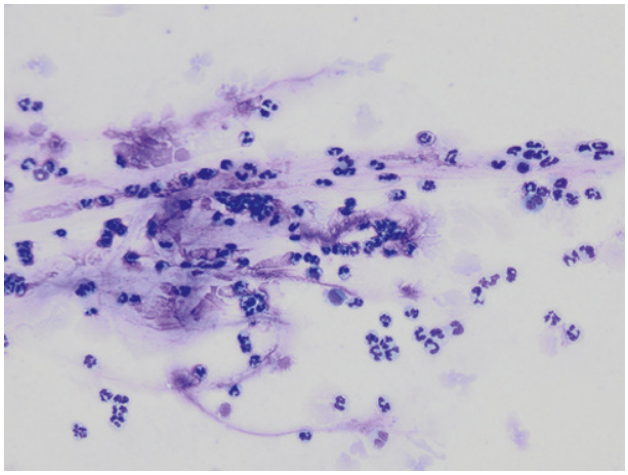


Figure 31.3 Photomicroscopy from a patient diagnosed with chronic bronchitis showing a typical cytologic representation with abundant mucus and neutrophils, and prominent "Curschmann spirals." *Source:* Image courtesy of Eric J. Fish, DVM, DiplACVP.

defects associated with chronic bronchitis. Although tidal breathing flow-volume loops have been described in veterinary medicine, they are not widely used due to lack of patient cooperation. Forms of pulmonary function testing that are more practical and may be used in dogs include the collection of arterial blood gas samples, the measurement of oxygen saturation with pulse oximetry, and use of the six-minute walk test (6MWT). Arterial blood gas analysis may document hypoxemia (PaO_2 <80 mmHg) or an increased alveolar-arterial (A-a) gradient (>15), although due to difficulty with technique and a lack of necessary equipment, this is not commonly performed in the clinical setting. Pulse oximetry is widely available in practice, and may be used to estimate arterial saturation with a value of >97% considered normal. Pulse oximetry may also be assessed after a short walk, as desaturation may be more commonly observed after exercise in patients with more mild compromise to their airway function. The 6MWT formally measures the distance that a dog can walk over six minutes; distances less than 400 meters are supportive of significant lung disease. The 6MWT may also be combined with pre- and post-walk pulse oximetry to evaluate for exercise-induced oxygen desaturation.

Treatment

Due to the lack of a definitive treatable etiology for CCB, the treatment options are limited to therapy to ameliorate known clinical signs and co-morbid conditions. Primary treatment focuses on limiting inflammation, limiting cough, and improving exercise stamina.

Possible environmental causes should be identified and eliminated. Owners should be advised not to smoke indoors, or in closed environments with affected pets. Any air-borne irritants should be eliminated such as perfumes, incense, scented detergents, and aerosolized cleaners. Owners should also be encouraged to remove as much dust from the environment as possible. Cloth furniture should be cleaned or removed, carpets cleaned or removed, and frequent vacuuming/dusting should be encouraged. If extensive remodeling is planned that is likely to produce potentially noxious fumes or a large amount of aerosolized particles then plans should be made for CCB patients to stay with friends or family. Exposure to potentially sick puppies should be avoided as well as trips to dog parks, grooming parlors, and boarding facilities. If a patient is obese, an appropriate weight loss program should be established. Activities that incite excess barking or strenuous exercise should be curtailed. The importance of replacing neck collars with harnesses should be emphasized.

Antiinflammatory medications are typically employed to assist with reducing inflammation in the airway, and glucocorticoids are still the mainstay of treatment. Reducing inflammation can limit cough and assist in reducing the positive feedback cycle that perpetuates CCB. Glucocorticoids may be administered orally or via inhalation. Prednisone is the most commonly used glucocorticoid. Initial dosing of prednisone is 1–2 mg/kg/day though it should be tapered to the lowest effective dose that controls clinical signs. Inhaled glucocorticoids have been widely used in people, and there is growing frequency of their use in veterinary medicine. Inhaled steroids are delivered via a spacer chamber and facemask designed specifically for dogs (e.g., AeroDawg, wwww.trudellmed.com). Inhaled glucocorticoids are more expensive than oral steroids, but the benefits include a directed therapy approach that limits systemic absorption and subsequent steroid side-effects. One study demonstrated benefits of therapy with fluticasone at 125 µg q12h.

Bronchodilators are commonly prescribed for dogs with CCB and evidence supports an improvement in clinical signs in approximately half of treated dogs. Theophylline (extended release, 10 mg/kg PO q12h) has been shown to have nonspecific effects that may benefit patients with CCB. These include decreasing diaphragmatic fatigue, increasing mucociliary clearance, and enhancing the efficacy of glucocorticoid activity. Beta-2-agonists, such as terbutaline, may be less effective due to the lack of reversible bronchoconstriction in some patients. The use of theophylline versus beta-2-agonists is still a clinical preference. It should be noted that beta-2-agonists might cause some anxiety and restlessness when initiated although these signs often resolve within a few day.

Box 31.3 Airway sampling techniques

Cytologic samples can be obtained from the airway via a tracheal wash, blind bronchoalveolar lavage, or with bronchoscopy.

Transtracheal wash (TTW) is best suited for tolerant medium- or large-sized dogs. This technique should be avoided in brachycephalic breeds, and obese patients where easy palpation of the trachea is limited.

- TTW is performed in unsedated or lightly sedated dogs.
- After aseptic preparation of a small area over the cervical trachea or larynx and a local anesthesia block is performed, a through-the-needle catheter is passed through the cricothyroid ligament or between tracheal rings; the catheter is fed down the trachea (beveled edge down).
- Two to three aliquots of 5–10 mL 0.9% sterile saline are flushed into the trachea, and promptly retrieved. Retrieval volume is typically about 50%, and the remaining fluid is rapidly absorbed from the airway.
- Collection of a diagnostic sample is facilitated by a patient's ability to cough resulting in an increased likelihood in retrieving a representative cytology from more areas of the airway.

Endotracheal wash (ETW) is commonly performed in smaller patients, patients that are less amenable to restrain, brachycephalic breeds, and obese patients.

- ETW is performed by briefly anesthetizing the dog with propofol then performing a clean intubation with a sterile endotracheal tube. Lubricating gel should not be used.
- In a sterile fashion, a 5–8 Fr catheter is fed through the endotracheal tube and sterile saline is infused and reaspirated. Alternatively, a modified technique using suction, a Lukens specimen container, a three-way stopcock, and a red rubber or Argyle feeding tube can be used (Figure 31.4a,b).
- 0.9% saline aliquots of 3, 5, and 10 mL are used for dogs <5 kg, 5–15 kg, and >15 kg, respectively.
- A sterile collection cup may be used to collect any additional samples that may be expectorated.

(a)



(b)

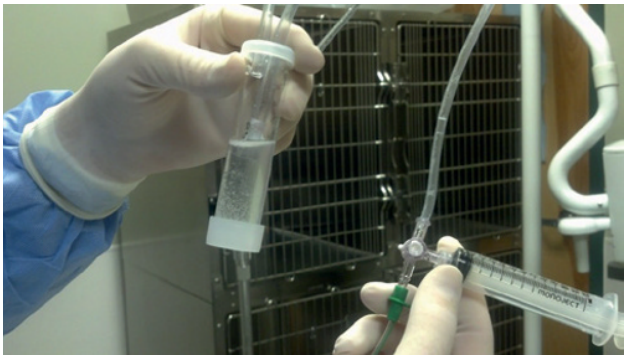


Figure 31.4 Equipment set-up for a modified technique to perform bronchoalveolar lavage or endotracheal tube lavage using suction, a Lukens specimen container, a three-way stopcock, and a red rubber or Argyle feeding tube.

- Supplemental oxygen should be available during this procedure and for recovery.

Blind bronchoalveolar lavage (BAL) is performed similarly to an ETW with the exception of the following.

- The flexible catheter is advanced until it is lodged in the lower airways.
- A larger volume of 0.9% saline is used, dependent on the patient's size.
- A simple technique using a modified stomach tube has been used successfully.

Bronchoscopic bronchoalveolar lavage can be used to collect samples via bronchoscopy by flushing sterile 0.9% saline through the chamber of a sterilized scope and reaspirating it back through the biopsy channel.

Antibiotics are warranted in dogs with an acute exacerbation of their clinical signs of CCB, or in those with evidence of an infection on airway cytology and/or culture. Doxycycline and azithromycin have antiinflammatory and antimicrobial properties, and should be considered in CCB patients with no specific bacterial culture and sensitivity data. Clinician preference is often influenced by cost, formulation, and availability of products. Fluoroquinolones are also a good choice for patients with CCB due to their high airway tissue concentrations although it is important to remember that concurrent administration of fluoroquinolones and theophylline may results in theophylline toxicity. If simultaneous administration of both drugs is necessary then the theophylline dose should be reduced by approximately 30–40%.

Cough suppressants are typically used to reduce the positive feedback cycle of cough begets inflammation and inflammation begets cough, and to improve the quality of life of the patient and owners. Over-the-counter cough suppressants are rarely effective in dogs. Narcotic cough suppressants are the most effective, with hydrocodone (0.22–0.5 mg/kg PO q6–12h) the most widely used. Butorphanol (0.5 mg/kg PO q6–12h) may also be considered as a primary cough suppressant. A human study has recently reported on the efficacy of gabapentin for control of cough in humans though data in dogs are lacking.

Prognosis

The clinical course of CCB is highly variable. In the majority of patients, permanent changes are present in the airways at the time of diagnosis, and as a result treatment is not curative. Appropriate medical management can typically help ameliorate the clinical signs and palliate the disease by stopping or slowing progression of bronchial damage. Periodic relapse of cough is not uncommon, and will frequently respond to temporary or permanent adjustment in the therapeutic regimen, or treatment of a developed concurrent illness such as pneumonia. As techniques are developed to screen for and diagnose CCB at earlier stages and more directed medical therapy is established, the prognosis for and probability of cure of CCB will improve.

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32

Pulmonary Thromboembolism

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Pulmonary thromboembolism (PTE) refers to obstruction of a pulmonary vessel or vessels by a thrombus and encompasses both *in situ* thrombus formation and embolization from elsewhere in the vasculature. In small animals, PTE is the preferred term because these mechanisms are difficult to differentiate clinically and both share a common pathophysiology. PTE is associated with numerous diseases and disorders in small animals (Table 32.1) and many patients with PTE have more than one predisposing condition. These underlying conditions can be categorized by how they affect Virchow's triad, although formation of thrombi *in vivo* typically involves more than one such effect.

The true incidence of PTE in dogs and cats is unknown but it is probably more common than the literature suggests. Difficulties definitively diagnosing PTE antemortem, limited numbers of postmortem examinations being performed, and rapid postmortem fibrinolysis mean some cases are missed. In a retrospective case series of 29 dogs with confirmed PTE, there was antemortem suspicion in less than 40% of dogs in which it was subsequently identified at necropsy. This study suggested a prevalence of PTE in dogs of 0.9% over a 10-year period. In cats, PTE was suspected in ~25% cats with respiratory signs and in only 14% of cats in which it was subsequently diagnosed postmortem. Subsequently, a 24-year prevalence of 0.06% was reported for PTE in cats.

Pathophysiology

Pulmonary thromboembolism frequently results in hypoxemia, hyperventilation, and dyspnea. Arterial hypoxemia in patients with PTE is secondary to abnormal ventilation/perfusion (V/Q) ratios within affected lungs, potentially complicated by diffusion impairment due to interstitial and alveolar edema. The V/Q mismatches occur due to small airway constriction, reduced surfactant production, and development of pulmonary edema and atelectasis. Small airway constriction occurs in both nonperfused and nonembolized areas of lung, which may lead to airway closure and alveolar collapse. Surfactant production is reduced in dogs with experimental PTE, leading to fluid transudation into alveoli (pulmonary edema). Edema may also develop in nonembolized regions due to increased hydrostatic pressure combined with increased microvascular permeability resulting from neutrophil activation. Rarely, pulmonary infarction and pleural effusion may result from complete occlusion of distal pulmonary vascular branches.

The cardiovascular consequences of PTE are dependent upon the extent of vessel occlusion. There is substantial reserve capacity in the pulmonary vasculature, which likely accounts for the subclinical nature of many PTE events. In healthy dogs, >60% of the pulmonary vasculature must be occluded before alterations in pulmonary vascular resistance (PVR) reduce pulmonary arterial flow. Reflex vasoconstriction secondary to alveolar hypoxia, humoral factors such as serotonin released from activated platelets, and neurogenic reflexes may also contribute. Significant pulmonary vascular occlusion leads to pulmonary hypertension and increased right ventricle (RV) afterload. Severe, acute changes in RV afterload result in dilation and dysfunction. As the RV dilates, the interventricular septum shifts leftward, impairing filling and reducing diastolic distensibility, a concept known as ventricular interdependence. Consequent reductions in left ventricular filling decrease cardiac output and may lead to signs of forward failure (hypotension, cardiogenic shock). If the patient survives an acute crisis but has residual pulmonary hypertension, then clinical signs of backward failure (hepatomegaly, ascites, pleural effusion) may develop over the medium to long term.

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Table 32.1 Recognized risk factors for PTE disease processes with a known association with thromboembolic disease in the dog. Those conditions also associated with an increased risk in the cat are marked by an asterisk. Proposed mechanisms for these risk factors are included

Disease process risk factor	Hypercoagulable state	Vascular flow abnormalities/stasis	Endothelial injury/ dysfunction
*Corticosteroid administration	✓		
Diabetes mellitus	✓		
Dirofilariasis	✓		✓
*DIC (secondary to other disease)	✓		
Endocarditis (tricuspid/pulmonic)	✓		✓
*Feline infectious peritonitis	✓		✓
Hyperadrenocorticism	✓		
Hypothyroidism	✓		
*IMHA	✓		?
*Indwelling venous catheters		✓	✓
Myocardial disease	✓	✓	✓
*Neoplasia	✓	✓	
*Pancreatitis	✓		✓
*Protein-losing enteropathy	✓		
*Renal amyloidosis/PLN	✓		
*Sepsis	✓		✓
*Surgery/trauma	✓	✓	✓

Source: Adapted from Goggs *et al.* [1].
DIC, disseminated intravascular coagulation; IMHA, immune-mediated hemolytic anemia; PLN, protein-losing nephropathy.

Clinical Signs

The clinical signs of PTE are variable, inconsistent, and nonspecific. The degree of physiologic impairment and thus the severity of clinical signs reflect both the magnitude of the PTE and the patient's ability to compensate. The most common signs are dyspnea, tachypnea, and depression. Other signs include coughing, hemoptysis, cyanosis, syncope, collapse, and sudden death. In dyspneic patients, physical examination may reveal harsh lung sounds and crackles suggestive of pulmonary edema. Occasionally, lung and heart sounds may be muffled due to pleural effusion or in very rare cases pneumothorax. In eupneic patients, lung field auscultation will likely be normal. On cardiac auscultation, tachycardia with a split second heart sound may be noted or, more commonly, a loud second heart sound associated with pulmonary hypertension. Signs compatible with backward heart failure (jugular distension or pulsation, ascites) or forward heart failure (poor peripheral pulse quality, pallor, prolonged capillary refill time) may be present. Complicating the picture may be clinical signs attributable to the predisposing intercurrent disease.

Clinicians should suspect PTE in patients with no history of cardiopulmonary disease who develop respiratory distress acutely, particularly where known risk factors exist.

Diagnosis

Suggested Diagnostic Approach

Pulmonary thromboembolism is commonly suspected but infrequently conclusively diagnosed, probably because of variability in clinical signs, low test specificity, and limited availability of definitive diagnostics. Establishing a clear diagnosis of PTE remains a challenge in veterinary medicine, even with a logical approach. In human medicine, where definitive diagnostics are widely available, the major challenge is to identify which patients to prioritize for definitive imaging studies. This need has driven the development of clinical prediction rules and diagnostic algorithms.

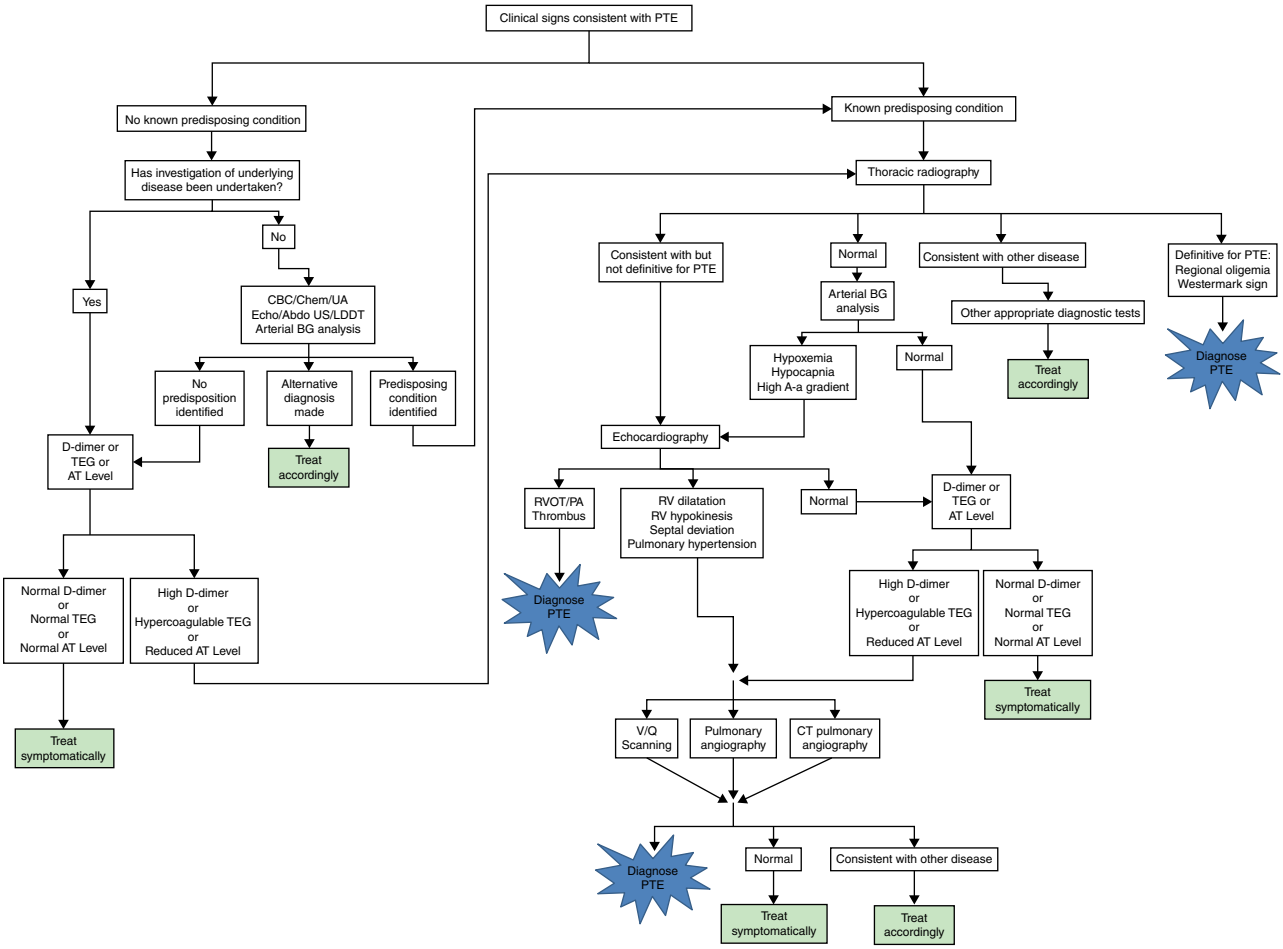


Figure 32.1 A possible diagnostic algorithm for the investigation of small animals with suspected PTE.

Patients at high risk must be identified for expedited diagnostic evaluation. A possible diagnostic schema for small animals is proposed in Figure 32.1. All patients with consistent clinical signs should undergo thoracic radiography, ideally in combination with arterial blood gas analysis. Occasionally, thoracic radiography will be diagnostic but most patients will require additional tests, particularly if arterial blood gas analysis is consistent with PTE. Echocardiography is a reasonable next step. It is noninvasive, can be performed bedside, and eliminates key differentials, clarifying which patients require advanced imaging. Cardiac biomarkers may also contribute to decision making. In patients with clinical signs but without known risk factors, coagulation testing with D-dimers, antithrombin (AT) activity, or thromboelastography (TEG) may help identify patients with evidence of thrombin activation, AT depletion or hypercoagulability, respectively. Recognition of a dyspneic, hypercoagulable patient should prompt reevaluation for predisposing conditions and mandates imaging studies for PTE.

Initial Diagnostics

Survey Thoracic Radiography

Up to 30% dogs with PTE have normal thoracic radiographs, but most small animals in the literature with confirmed PTE had abnormalities visible. This finding might reflect an inability to detect small emboli, as abnormal thoracic radiographs might only occur in severe PTE. It has therefore been suggested that PTE should be suspected in all markedly dyspneic patients with normal thoracic radiographs. Similarly, where risk factors are present, PTE should be considered as the cause of unexplained pulmonary infiltrates on thoracic radiographs.

Various radiographic abnormalities can be seen in PTE. Pulmonary infiltrates are the most common finding and are typically alveolar or alveolar-interstitial in appearance, present focally or multifocally. These infiltrates likely represent edema, atelectasis, hemorrhage or infarction and often have indistinct borders. Hypovascular lung areas are hyperlucent regions

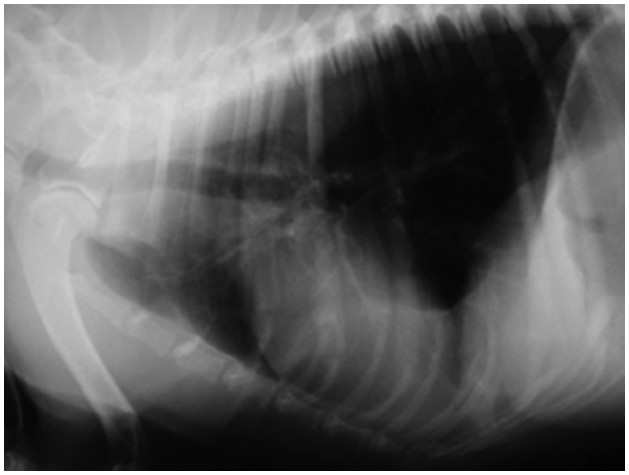


Figure 32.2 A lateral thoracic radiograph from a dog with pulmonary thromboembolism showing an area of regional oligemia (Westermark sign) affecting the right caudal lung field.

representing zones of reduced blood flow distal to sites of vascular occlusion. This finding, known as the Westermark sign (Figure 32.2), is rare but pathognomonic for PTE. Pulmonary infarcts appear as distinct pleural-based, wedge-shaped densities. Other potential abnormalities include uneven vessel diameter, pulmonary arterial enlargement, lobar vein or artery attenuation, pleural effusion, and right-sided cardiomegaly.

Arterial Blood Gas Analysis

Typical blood gas abnormalities associated with PTE in dogs are hypoxemia, hypocapnia, and an increased A-a gradient. In some cases, this hypoxemia may respond poorly to oxygen therapy due to intrapulmonary shunt. These findings are not specific for PTE, however, and should be interpreted in light of other data. Similarly, normal blood gas values do not rule out PTE. Using the A-a gradient may be more sensitive than solely looking for hypoxemia, since the degree of hypoxemia is proportional to the extent of thromboembolic occlusion. Arterial blood gas analysis may be useful in assessing disease severity, monitoring response to therapy, and determining prognosis. The ratio of PaO_2:$PaCO_2$ in PTE patients was highly predictive of outcome in a recent human study. Blood gas values in cats with PTE have not been reported to date but are expected to mirror those in dogs.

Risk Profiling

Antithrombin and D-Dimers

Antithrombin inhibits coagulation factors IIa, IXa, Xa, XIa, and XIIa. In patients with active thrombin production, plasma AT activity is reduced by consumption and urinary AT loss has been linked to the hypercoagulable states associated with protein-losing nephropathy and hypercortisolemia. Measuring patient levels of AT activity may allow thrombosis risk stratification. Based on extrapolations from humans, reductions of AT activity between 50% and 75% moderately increase risk, while activities below 30–50% markedly increase thrombosis risk.

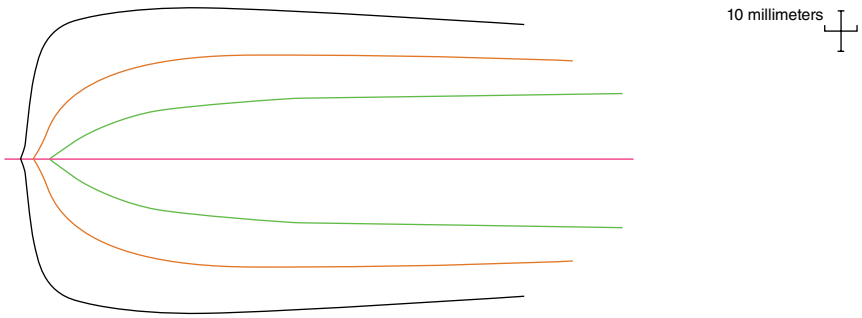
Increased plasma D-dimer concentrations indicate plasmin-mediated cleavage of factor XIII cross-linked fibrin. Since D-dimers require activation of both thrombin and plasmin for their formation, they are considered more specific for thrombosis than fibrin degradation products (FDPs). Rapid, accurate, bedside D-dimer assays are integral to decision making in humans with possible PTE. People with high clinical probability scores (previous TE disease, deep vein thrombosis, dyspnea) undergo thoracic imaging without a D-dimer test. For all other people presenting with compatible clinical signs, rapid, quantitative D-dimer enzyme-linked immunosorbent assays (ELISAs) are performed prior to selection of further diagnostic testing. Positive D-dimer tests prompt thoracic imaging, while negative tests suggest no further investigation for PTE is required.

Similar guidelines for small animals cannot be formulated currently because we lack sufficient data and, more fundamentally, a convenient and highly accurate D-dimer assay is not available for small animals. Although semiquantitative latex agglutination D-dimer assays perform well for disseminated intravascular coagulation (DIC) in dogs, their sensitivity and specificity for thrombosis vary widely depending on the cut-off used. As such, this assay may be best suited to testing patients with a high index of suspicion for PTE, and a cut-off of >1000 ng/mL to minimize false positives. Unfortunately, the latex agglutination assay has limited availability and is laboratory based.

Point-of-care (POC) tests allow determination of analyte values at the bedside, enabling them to be used for clinical decision making in unstable patients. Several canine D-dimer POC tests have been evaluated for the detection of D-dimers in patients with thromboembolic disease. Of these, the NycoCard system performed the best, but all of these assays suffer from a lack of specificity for thromboembolic disease. Irrespective of the assay chosen, D-dimers should be evaluated within 1–2 hours of the suspected embolic event because in experimental canine PTE, D-dimers were increased by 30 minutes, peaked at >2000 ng/mL at 1–2 hours before falling back to control levels after 24 hours.

Viscoelastic Coagulation Testing

Whole-blood tests of coagulation such as thromboelastography (TEG), thromboelastometry (ROTEM), and the Sonoclot system graphically represent the



Events at time of trace	R time (min) 3.0–8.0	K time (min) 3.1–6.7	α angle (°) 28.0–58.9	MA (mm) 38.8–59.0	G (d/s) 3.2–7.2 k
At time of PTE	2.3	0.8	78.6	77.1	16.8 k
On LMWH	7.2	9.5	26.1	29.8	2.1 k
PLE stable on Tx	4.2	2.8	54.9	51.4	5.3 k

Figure 32.3 Tissue factor-activated thromboelastography tracings from a patient with PTE secondary to PLE. The black tracing is a markedly hypercoagulable TEG run at the time of the patient's PTE. Note the shortened reaction (R) and clot formation (K) times and the increased alpha angle (α), maximum amplitude (MA), and clot elasticity (G) values. The patient was treated with low molecular weight heparin, which significantly prolonged the R and K times and reduced the alpha and MA values (*green tracing*). A baseline (pink) is displayed for comparison. After stabilizing on therapy, a normal-looking TEG tracing was produced (*orange tracing*).

viscoelastic properties of clotting blood during clot formation and lysis. These different systems produce comparable but not interchangeable results. These techniques have been validated in small animals and are now commonly used in veterinary medicine. Using TEG/ROTEM, hypercoagulability has been identified in multiple settings in veterinary patients.

Hypercoagulable patients produce characteristic TEG/ROTEM tracings (Figure 32.3). These patients typically have short reaction and clot formation times, steep alpha angles, and large maximum amplitudes. In people, MA values derived from conventional TEG and from a rapid-TEG assay have been demonstrated to predict thrombotic risk in human surgical patients, and risk of PTE following trauma. It is unclear which (if any) of these parameters best relates to thrombotic risk in veterinary patients. It is also essential to recognize that preanalytical variables such as patient hematocrit and fibrinogen concentration in addition to sample handling and assay parameters contribute to the final TEG/ROTEM tracings.

To date, only one study has reported viscoelastic coagulation testing in small animal PTE. That study did not identify any correlation between TEG variables and PTE, but the sample size was limiting. A recent study evaluated TEG in dogs with thrombosis in various anatomic locations. This study found that although the TEG G-values of dogs with thrombosis were significantly greater than controls, half of the dogs' TEG tracings were classified as normocoagulable, suggesting that TEG may not have the discriminant power necessary to diagnose PTE. These tests likely have a place in the diagnostic work-up of possible PTE patients, but more work is needed to identify which test protocols and which parameters are most predictive of thrombotic risk. The ability of these tests to identify hypercoagulability at the point of care suggests they help identify at-risk patients who require further investigation, particularly once properly integrated into diagnostic algorithms.

Plasma-Based Coagulation Assays

Tests including the prothrombin time (PT), activated partial thromboplastin time (aPTT), activated clotting time (ACT), and fibrinogen concentration are of limited value in PTE because they may be normal, and any abnormalities are nonspecific. Similarly, abnormalities of FDPs have not been widely identified in small animals with PTE. These molecules indicate plasmin-mediated degradation of fibrinogen or fibrin has occurred. Increased FDP concentrations are present in thrombosis, but also occur in liver failure, dysfibrinogenemia, excessive fibrinolysis, and DIC, making FDPs less specific than D-dimers.

Complete Blood Counts/Serum Biochemistry

These tests are not discriminating for PTE, but serum biochemical testing may help identify predisposing conditions such as hyperadrenocorticism, protein-losing nephropathy, diabetes mellitus, or hypothyroidism. Complete blood counts may help identify a nonspecific inflammatory leukogram or myeloproliferative disorders such as polycythemia or essential thrombocytosis that can predispose to thrombosis. Secondary thrombocytosis does not predispose to PTE, although primary essential thrombocythemia may, particularly if other risk factors exist. Thrombocytopenia or schistocytosis, as markers of DIC, may increase the index of suspicion for PTE.

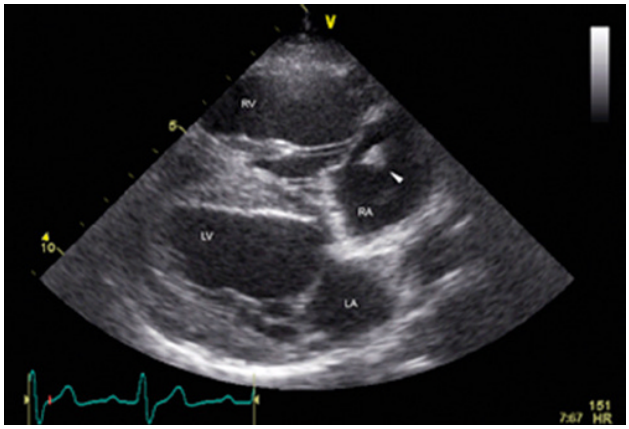


Figure 32.4 Long-axis four-chamber echocardiographic view showing a pendulous thrombus (*arrowhead*) adherent to the roof of the right atrium in this patient. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Cardiac Function Testing

Echocardiography

In people, echocardiography is not a routine diagnostic test for PTE, although case registries report echocardiography is performed in 47–74% patients. Although many echocardiography studies are normal in PTE, they may be diagnostic if cardiac or RV outflow tract thrombi are present (Figure 32.4). Where PTE is present, echocardiography can quantify the hemodynamic consequences of PTE and provides valuable prognostic information to guide patient management. Echocardiography can also identify differential diagnoses such as cardiomyopathy, endocarditis or pericardial tamponade noninvasively.

Typical echocardiographic findings in humans with PTE include right ventricular dilation and hypokinesis, septal flattening and paradoxical septal motion, diastolic left ventricular impairment, pulmonary arterial hypertension, right ventricular hypertrophy, and patency of the foramen ovale. The degree of right ventricular dysfunction is related to the cross-sectional area of the pulmonary vasculature affected; occlusion of >30% is frequently associated with RV hypokinesis. In people with severe PTE, the apex of the RV appears to be spared the hypokinesis that affects the remainder of the right ventricular free wall (RVFW). This apical sparing (the McConnell sign) is highly specific for the diagnosis of PTE in people.

There are currently few data regarding echocardiography in canine PTE because in recent retrospective studies <20% of dogs underwent echocardiography. However, it is reasonable to suspect many small animals with PTE will have abnormal echocardiograms. Typically reported findings in small animals include right atrial and ventricular enlargement, paradoxical septal motion, pulmonary hypertension, and thrombi in the heart or pulmonary artery (PA). To date, RV hypokinesis (apical sparing) has not been confirmed in dogs or cats with PTE.

Cardiac Biomarkers

In humans, echocardiographic RV dysfunction secondary to PTE is associated with elevated cardiac troponin (cTn) concentrations. A recent metaanalysis of 20 studies suggested that humans with PTE and an increased cTn level are at high risk of short-term death and adverse events. Cardiac troponins are increased in veterinary patients with primary, ischemic, congenital and degenerative cardiac and pericardial diseases, but also in gastric dilation-volvulus (GDV) syndrome, sepsis, trauma, uremia, and hyperthyroidism. Serum cTn concentrations are related to the magnitude of myocardial injury in myocarditis, GDV syndrome, and blunt chest trauma. In dogs with PTE secondary to dirofilariasis, cTnI values were significantly higher than in controls, and in dogs with experimental PTE, cTnI levels increase in proportion to the severity of occlusion as indicated by PVR and mean pulmonary artery pressure (MPAP). There is only one report on cTnI in dogs with PTE. In that small study, patients with CT-confirmed PTE did not have significantly increased cTnI values compared to dogs without PTE, but the sample size was limiting.

It seems unlikely that cTn values will be sufficiently specific to enhance the diagnosis of PTE and they may prove most valuable in assessing PTE severity and predicting complications, rather than differentiating PTE from other disease processes. In contrast to D-dimers, which peak at 1–2 hours after PTE, cTnI levels peak at eight hours post embolism in people and are most diagnostically accurate at this time point. The availability of POC tests for cTn in dogs makes accurate timing of this assay a viable proposition.

Atrial and B-type natriuretic peptides are produced by cardiac muscle and released in response to volume overload, hypertrophy, and hypoxia to elicit natriuresis and vasodilation. Assays of BNP or the metabolic by-product NT-proBNP are used to diagnose cardiac disease, differentiate respiratory from cardiac disease, assess severity, and guide management. In PTE, NT-proBNP concentrations are closely related to the degree of RV dysfunction, and this likely underpins their relationship with adverse events and outcome in people with PTE. No studies on NT-proBNP measurement in small animal PTE have been reported to date. As with cTn, it is likely that concentrations of NT-proBNP will be increased. The discriminant ability of this test in small animal PTE remains an open question. Currently, the principal limitations of the NT-proBNP test are the *ex vivo* stability of the analyte which is time and temperature dependent, and the lack of a POC test for dogs. Once a bedside test for dogs

becomes available, NT-proBNP may become integral to the evaluation of these patients.

Electrocardiography

Electrocardiographic abnormalities are likely uncommon in acute PTE. The most likely alteration is sinus tachycardia secondary to sympathetic stimulation associated with hypotension or hypoxemia. Myocardial hypoxia or cardiac hypertrophy may cause ST segment depression or slurring. Only with chronic pulmonary hypertension will ECG morphology changes occur, reflecting right ventricular compromise (right axis deviation, increased amplitude of S-, T- or P-waves).

Definitive Diagnostic Imaging

Computed Tomography Pulmonary Angiography

Rapid, multislice helical CTPA is key to diagnosis of PTE in human medicine, and is now integral to PTE diagnosis in small animals too. These studies are obtained by performing rapid, spiral thoracic CT concurrent with bolus injection of contrast media. The contrast agent is infused through a peripheral catheter using a pressure injector, linked electronically to the scanner to ensure peak enhancement of the pulmonary arteries.

Diagnostic criteria for PTE using CTPA are failure to enhance the entire arterial lumen due to occlusive filling defects, partial filling defects surrounded by contrast material, producing the "polo mint" or "railway track" signs, and peripheral intraluminal filling defects that form acute angles with the arterial wall (Figure 32.5). A normal CTPA study essentially rules out PTE as the cause of the patient's respiratory distress, unless the index of suspicion is very high.

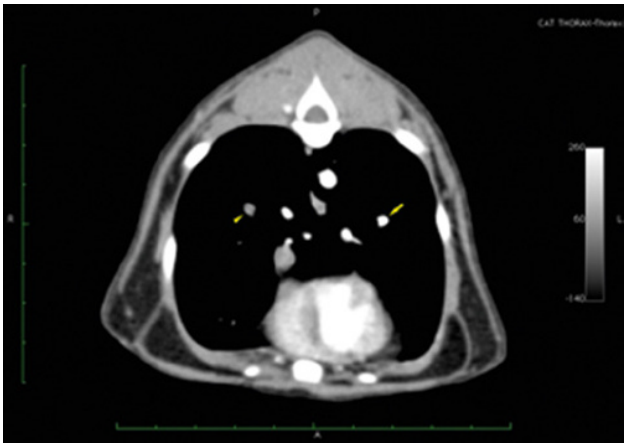


Figure 32.5 A transverse CT angiographic image of the heart and main pulmonary arteries from a cat with PTE. Right is on the left of the image. There is a strongly attenuating signal from contrast medium in the heart and in the left pulmonary artery (*arrow*), but there is substantially lower attenuation by the right pulmonary artery (*arrowhead*) due to an occlusive thrombus, which has prevented the entry of contrast material.

Single-channel CTPA has been used for experimental PTE diagnosis and investigation of PTE following total hip arthroplasty. No emboli were identified in the arthroplasty patients, but the authors stated that the CTPA protocol enabled consistent diagnostic quality acquisition visualization down to fifth-generation PA branches.

Multidetector row CT is also increasingly available in veterinary medicine. These multislice CT scanners permit imaging of the whole thorax in sedated patients without the need for breath-hold techniques to eliminate motion artifact. Multidetector CTPA has been reported in dogs using 16-slice and 64- slice scanners, and protocols to maximize PA contrast enhancement have been published. Although the majority of publications to date have focused on normal patients, multidetector CT angiography has been successfully used to detect PTE in experimental dogs, to identify a descending aortic thrombus secondary to spirocercosis in a dog and in dogs with PTE secondary to immune-mediated hemolytic anemia (IMHA).

MRI and Clot-Labeling Techniques

The use of magnetic resonance imaging (MRI) in the diagnosis of PTE is still in its infancy, but recently this technology has been used for angiography in dogs. The safe, noninvasive nature of MRI offers potential advantages over CT – lack of ionizing radiation and no need for iodinated contrast material. However, the need for cardiac gating and, more importantly, a requirement for general anesthesia limit the utility of MRI-based techniques in unstable veterinary patients. Nevertheless, MR angiography appears comparable to CTPA in experimental studies in dogs.

Direct thrombus imaging techniques have also been developed. Clots can be imaged by identifying the thrombus degradation product methemoglobin via a heavily T1-weighted image. Clot-labeling techniques utilizing radiolabeled antibodies against P-selectin, D-dimers or GPIIIa have been performed experimentally in dogs. The feasibility and utility of these techniques remain uncertain and they may be best suited to more stable patients, patients in whom CTPA is equivocal or those with specific contraindications to iodinated contrast material use.

Other Imaging Modalities

Selective pulmonary angiography is now largely obsolete in human medicine. Since selective pulmonary angiography involves the risk of general anesthesia and

the technical difficulty of PA catheter placement, it has been largely supplanted by CTPA in small animals.

Ventilation–perfusion (V–Q) scanning has been used for the detection of PTE in small animals. Perfusion scanning is performed after IV injection of technetium-labeled macroaggregated albumin (^{99m}Tc-MAA). Inhomogenous pulmonary vascular distribution of activity from the decay of ^{99m}Tc-MAA is consistent with PTE. Although radionuclide labeling of inspired air to assess ventilation is possible, typically perfusion scans are compared against thoracic radiographs to identify pulmonary pathology. Photopenic wedge-shaped, pleural-based defects with a lobar or segmental distribution are classic for PTE, but entire lung lobes may appear photopenic, or if multiple small emboli are present, then a mottled pattern may result.

Computed tomography pulmonary angiography has largely replaced V–Q scanning in human medicine. A prospective evaluation of PTE diagnosis (PIOPED II) suggested that V–Q scanning was indicated for just a small subset of the population presenting with suspected PTE. In light of this, and the limited availability of equipment and expertise, it is likely few V–Q scans will be performed in small animals in future.

Management

In people, risk stratification based on clinical assessment, oxygenation status, anatomic clot size, cardiac function, and biomarkers underpins successful treatment. Anticoagulant therapy alone is recommended for low-risk patients, while patients with hypotension secondary to PTE are treated with thrombolytics followed by anticoagulation. The optimal strategy for management of PTE in small animals is not known because of the scarcity of specific information in the veterinary literature. Tailored supportive treatment for PTE patients is easy to recommend. When PTE is definitively diagnosed or the index of suspicion is sufficiently high then antithrombotic therapy is also warranted. Successful treatment for acute PTE is typically followed by chronic antithrombotic therapy and should be accompanied by management of any underlying predisposing disorder.

Supportive Therapy

For some patients, PTE is rapidly fatal irrespective of therapy. In normal dogs, thrombi lyze rapidly so supportive therapy buys time for fibrinolysis to occur. All dyspneic patients should receive oxygen therapy. Positive pressure ventilation (PPV) should be considered as a last resort if oxygen therapy cannot resolve hypoxemia, with efforts made to minimize the detrimental impact of PPV on PVR, which will already be increased in these patients. Caution must be exercised with fluid therapy, because RV overdistension impairs coronary perfusion and LV preload. Echocardiography to determine RV filling may help determine if fluid administration is likely to be beneficial.

Theophylline may be beneficial as a bronchodilator and through pulmonary vasodilation, improved diaphragmatic contractility, and reduced respiratory muscle fatigue. Positive inotropes such as dobutamine may be necessary in cardiogenic shock, but can increase MPAP and cause arrhythmias. Reflex pulmonary vasoconstriction increases PVR in PTE. Inhaled nitric oxide (NO) acts as a vasodilator, decreasing MPAP and improving hemodynamics in PTE, but has not been used clinically in small animals as yet, and is cost-prohibitive. In dogs, sildenafil has beneficial effects in pulmonary hypertension, and in canine PTE models it reduces MPAP through selective pulmonary arterial vasodilation. In people, sildenafil has beneficial effects in both acute PTE and the treatment of chronic PTE-induced pulmonary hypertension. Although sildenafil has not been reported in small animal PTE to date, it should be considered if pulmonary hypertension is documented echocardiographically. Potential side-effects include vomiting and systemic hypotension, and co-administration with heparin may increase the risk of hemorrhage.

Thrombolysis

Therapeutic thrombolysis is the administration of supraphysiologic doses of plasminogen activators systemically or directly at the thrombus site to accelerate plasmin generation and induce thrombus dissolution. Thrombolysis in PTE aims to reverse right heart failure, improve systemic and pulmonary hemodynamics, limit neurohumoral activation, and reduce recurrence. Available drugs include alteplase, reteplase, and tenecteplase. These drugs have distinct pharmacokinetics, thrombolytic activities, and fibrin specificities. Veterinary experience with thrombolytics is limited and is predominantly in the field of feline aortic thromboembolism (ATE). A recent prospective clinical trial of tissue plasminogen activator (t-PA) in cats with ATE highlighted the risks of side-effects associated with these agents. Although efficacious in >50% cats, all 11 patients in the study suffered side-effects, many attributable to reperfusion injury.

The t-PA products are fibrin specific, activating fibrin-bound plasminogen more rapidly and more effectively than plasminogen in circulation. At pharmacologic concentrations, however, a systemic lytic state can still occur and all t-PA products are associated with a risk of hemorrhage in humans. Alteplase has the shortest half-life of the available recombinant thrombolytics.

Alteplase has been successfully used in one dog with ATE, and experimentally induced canine PTE has been treated with t-PA therapy.

Currently, the American College of Clinical Pharmacology (ACCP) recommends thrombolytic therapy for people with hypotension secondary to acute PE. Thrombolysis in PTE in the absence of hypotension is not currently recommended, but could be considered in patients with echocardiographic evidence of cardiac dysfunction or in those with high cTnI or NT-proBNP concentrations. A recent trial of normotensive PTE patients with biomarker and echocardiographic evidence of myocardial damage and dysfunction evaluated thrombolysis with tenecteplase. Thrombolysis in these patients significantly reduced the rate of death due to hemodynamic collapse, but at the cost of a significant increase in major bleeding events.

Where thrombolytic agents are used, the ACCP recommend they be administered over a short time period via a peripheral catheter rather than a PA catheter. Case registry data suggest thrombolytics are used in only 30% of people with massive PTE. In veterinary medicine, no consensus on their administration exists and clinicians must determine the potential benefits and risks of administration for individual patients. Recent advances in small animal interventional radiology may provide novel methods or routes for thrombolysis in future. Based on the ACCP guidelines, thrombolytic therapy should only be considered in veterinary patients with hemodynamically unstable acute PTE and where continuous hemodynamic monitoring is available. In appropriate cases, fibrin-specific drugs with short half-lives (e.g., alteplase) are preferred.

Antithrombotic Strategies

In PTE anticoagulants and antiplatelet agents are administered to minimize thrombus propagation, which can be stimulated by embolization, and to reduce risk of recurrence. However, the optimal antithrombotic strategy for small animals is not known. Some suggest that PTE should be managed with anticoagulant drugs and that antiplatelet agents are not appropriate. Viewing arterial and venous thrombosis as separate pathophysiologic entities is likely an oversimplification, however, and there is evidence of overlapping efficacy of antiplatelet and anticoagulant agents in the treatment of both venous and arterial thromboembolic conditions. Platelets are integral to the cell-based model of hemostasis, and thrombocytosis is associated with an increased risk of PTE in people. In venous thrombosis, tissue factor-mediated secondary coagulation precedes platelet activation, but both arms of the hemostatic system are activated, which correlates with the architectural and pathophysiologic features shared by both venous and arterial thrombi.

Anticoagulants remain the mainstay of antithrombotic therapy for people with PTE, however. In people with PTE, the ACCP recommends initial parenteral anticoagulation with low molecular weight heparin (LMWH) or fondaparinux except where renal insufficiency, thrombolytic therapy or poor perfusion mandate the use of IV unfractionated heparin (UFH). Ongoing anticoagulation for people with PTE is recommended for three months, although this may be extended in certain cases. Since the advent of the orally active direct Xa inhibitors and direct thrombin inhibitors, most people are now maintained on these newer medications. The direct oral anticoagulants (DOACs) have equivalent efficacy to warfarin but are associated with significantly lower bleeding risk.

To date, there are no clinical trials of anticoagulants in PTE in small animals on which to base recommendations. Although there is not universal consensus on dosage, frequency of administration or monitoring strategy for antithrombotics in small animals, ongoing efforts by the American College of Veterinary Emergency and Critical Care led to guidelines being published in January 2019. As a result of improved understanding and the availability of the DOACs, long-term anticoagulation in veterinary medicine is becoming increasingly common. The narrow therapeutic index of warfarin has led to increasing use of the DOACs in dogs and cats. Individual patient monitoring and dose adjustment of UFH and LMWH may enhance efficacy and improve safety and is possible using commonly available assays.

Anticoagulants

Unfractionated heparin, a heterogenous mixture of polysaccharides, complexes with and amplifies the inhibitory activity of AT against factor IIa (thrombin) and factor Xa, although factors IXa, XIa, XIIa, and XIII are also inhibited. Thrombin inactivation prevents fibrin formation and reduces thrombin-induced platelet activation. Variation in the size distribution of heparin molecules in UFH and unpredictable bioavailability in critical illness cause variation in heparin dose–responses, necessitating therapeutic monitoring since severe bleeding complications can result from exceeding the therapeutic range. Therapeutic monitoring can be performed using the ACT, aPTT, thrombin generation, viscoelastic testing, or anti-FXa levels. This need for therapeutic monitoring reduces the cost benefit of UFH, but individually adjusted dosing may offer benefits over fixed dosing.

Low molecular weight heparins derive from depolymerization of UFH and were developed to provide more consistent pharmacokinetic/pharmacodynamic (PK/PD) profiles than UFH. The reduced size of the LMWH polysaccharides limits their ability to simultaneously bind AT

and thrombin. Thus, LMWHs are principally anti-FXa agents and are probably best monitored with anti-Xa assays, although tissue factor (TF)-activated TEG can also be used. LMWHs are less protein bound than UFH, and have more predictable PK profiles and better bioavailability after SC injection. The PK profiles of distinct LMWHs preparations are not interchangeable, however. LMWH PKs have been evaluated in normal healthy dogs and therapeutic anti-Xa levels extrapolated from people are achievable. LMWH PKs in cats are less predictable, however, with frequent administration of high dosages necessary to achieve target anti-FXa activities. A recent study evaluated the *ex vivo* antithrombotic effect of enoxaparin in a venous stasis model in cats, comparing it to anti-Xa activity. The study found that at peak (but not at trough) plasma levels, enoxaparin significantly reduced thrombus formation, but in this model there was little correlation between antithrombotic effect and anti-Xa activity. Clearly, well-designed clinical studies evaluating LMWH in naturally occurring PTE in dogs or cats are urgently needed.

Fondaparinux is a synthetic, AT-dependent selective FXa inhibitor with no anti-FIIa activity. In people with acute PTE, fondaparinux administration reduces PTE recurrence rate compared with UFH without increases in major bleeding, and is at least as effective as enoxaparin in this setting. In dogs to date, fondaparinux has only been studied in experimental settings. In cats, a recent dose-finding study found that SC administration of 0.06–0.20 mg/kg q12h was sufficient to achieve peak plasma anti-Xa activity deemed therapeutic in humans.

Warfarin is an oral anticoagulant that inhibits vitamin K epoxide reductase, interrupting the recycling of vitamin K epoxide to hydroquinone and depleting the supply of carboxylated clotting factors II, VII, IX, and X. Warfarin is the mainstay for oral anticoagulation in people but maintaining adequate anticoagulation without hemorrhagic complications is challenging. The drug has a narrow therapeutic index, variable patient dose–response and numerous interactions with other drugs, necessitating close therapeutic monitoring. As a result, the Consensus on the Rational Use of Antithrombotics in Veterinary Critical Care (CURATIVE) guidelines published in January 2019 advise against the use of warfarin in small animals.

The difficulties associated with the clinical use of vitamin K antagonists generated a need for effective, safe, novel oral anticoagulants. Rivaroxaban is an oral, small molecule, direct FXa inhibitor that can inhibit both free and prothrombinase complex-associated FXa. This drug can be monitored using the PT or aPTT. Rivaroxaban was recently approved by the FDA for PTE following demonstration of equivalent efficacy to standard therapy with enoxaparin and warfarin. The pharmacokinetics of rivaroxaban has been studied in dogs, and it is reported to be an effective anticoagulant in healthy dogs. Its clinical use has been reported in a small case series, but it has not been evaluated in a randomized clinical trial.

The oral prodrug dabigatran etexilate is a potent, reversible direct thrombin inhibitor. This class of drugs do not require AT as a co-factor for their anti-IIa activity and are also able to inhibit thrombin bound to formed clot. Dabigatran can be monitored with the PT, aPTT or the preferred ecarin clotting time (ECT) in canine plasma. Dabigatran is FDA approved for thromboembolism in AF and in other countries for VTE and has a similar efficacy and safety profile to warfarin for the treatment of acute symptomatic VTE. To date, no studies have examined the effects of dabigatran in small animals.

Antiplatelet Agents

In small animals, antiplatelet agents are principally used for long-term oral maintenance therapy or as thromboprophylaxis for at-risk patients. Oral antiplatelet agents available for small animals include aspirin, ticlopidine, and clopidogrel, although concerns over myelotoxicity associated with ticlopidine have led to it being largely superseded by clopidogrel. There is limited evidence of efficacy for either aspirin or clopidogrel in veterinary medicine, however.

The COX-1 inhibitor aspirin irreversibly inhibits platelet thromboxane A_2 (TXA_2) synthesis, inhibiting platelet function. Aspirin is the primary antithrombotic therapy for people with atherosclerotic disease, but the populations of small animals which would most benefit from aspirin therapy are unknown. Aspirin has been recommended for dogs with protein-losing nephropathy, nephrotic syndrome, and IMHA. The use of aspirin in IMHA is contentious, however.

To date, no studies have been performed in veterinary medicine evaluating the efficacy of aspirin against objective measures of thrombosis or comparing the efficacy of aspirin against other antithrombotic therapies, but one such study is reportedly under way. The dose required to cause *in vitro* or *ex vivo* inhibition of canine platelet function varies with the assay used, but is in the range of 0.5–20 mg/kg. This wide range may be related to heritable variability in canine thromboxane responsiveness. A recent study suggested that 1 mg/kg/day aspirin consistently inhibited platelet function in only a third of dogs and higher dosages may be required to obtain a consistent effect.

The thienopyridines ticlopidine and clopidogrel are both produgs that rely on active metabolites for their *in vivo* efficacy. The active metabolite of clopidogrel causes cumulative inhibition of platelet function following repeated daily administration. In humans, clopidogrel may be marginally more effective than aspirin,

while combining both agents may produce beneficial additive effects. The clinical activity and pharmacodynamics of clopidogrel have been evaluated in cats and in dogs and significant antiplatelet effects are achievable in both species. A recent multicenter double-blinded prospective study comparing aspirin with clopidogrel in cats with ATE demonstrated superior efficacy for clopidogrel compared to aspirin, suggesting that clopidogrel should be the first-choice antiplatelet agent in cats.

The parenteral GPIIb/IIIa inhibitors abciximab, eptifibatide, and tirofiban, which antagonize the platelet fibrinogen/vWF receptor, have been used in canine experimental model settings of myocardial infarction and coronary stent thrombosis. Of these agents, only abciximab has been used safely in cats. Eptifibatide causes fatal cardiotoxicity in cats and should be avoided. All three drugs effectively inhibit canine platelet aggregation, but none has been used in veterinary medicine. Barriers to their clinical use include cost, risk of hemorrhage, and the need for administration by continuous infusion.

Conclusion

Despite recent advances in human and veterinary medicine, PTE remains a challenging diagnosis to confirm. A thorough, logical diagnostic approach should incorporate assessment of clinical probability, identification of risk factors and disease biomarkers, and appropriate application of diagnostic imaging, principally echocardiography and multislice CTPA. Many of these diagnostic steps remain to be prospectively investigated in veterinary medicine.

Since PTE carries a poor prognosis and is potentially fatal, the importance of early detection cannot be overstated. Once we can more consistently confirm the diagnosis of PTE in small animals, therapeutic clinical trials of thrombolytics, anticoagulants, and antiplatelet agents will be essential in order to improve our treatment of this condition. Until such time, therapy for PTE should consist of close monitoring, good supportive therapy and judicious, individualized empiric use of thrombolytics and antithrombotic agents.

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33

Surgical Approaches to Thoracic Disease

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Thoracotomy is commonly performed in critically ill small animal patients with disease of the pulmonary parenchymal structures, intrathoracic cardiovascular system, pleural space, thoracic wall, mediastinum, or esophagus. Aside from the underlying disease process, the thoracotomy procedure has the potential to induce several negative effects that can be detrimental without appropriate intensive monitoring and care. This chapter discusses the pathophysiologic effects of thoracic surgery, thoracostomy tube care, postoperative monitoring, overall case management strategies, and potential complications incurred in postoperative thoracotomy patients.

Pathophysiology of Thoracotomy

The most common surgical approaches to the thoracic cavity include intercostal thoracotomy, median sternotomy, and transdiaphragmatic incisional thoracotomy. Regardless of technical approach, some pathophysiologic consequences of entering the thoracic cavity may include atelectasis, hypoxemia, hypoventilation, hypotension, hypothermia, cardiac arrhythmias, pain, and continual pneumothorax or effusion.

The four distending forces of the lungs that prevent collapse under normal conditions are transpulmonary pressure (the difference between alveolar and pleural pressure), tethering of the lungs to the surrounding structures, pulmonary surfactant, and the nitrogen skeleton. During thoracotomy, there is disruption of the natural subatmospheric pleural and transpulmonary pressure. Thoracotomy induces a positive pleural pressure which exceeds the alveolar pressure and this alteration from normal physiology rapidly leads to atelectasis. Nitrogen wash-out occurs secondary to oxygen supplementation, which results in absorption atelectasis. This occurs as the native nitrogen skeleton is washed out by the greater than 21% FiO_2, leading to a loss of the natural nitrogen skeleton that helps maintain normal alveolar distension. It is important to emphasize that oxygen supplementation is necessary during the thoracotomy procedure, and strongly recommended in the postoperative period. Nitrogen wash-out is, however, an important pathophysiologic contributing factor to atelectasis in the thoracotomy patient. Prolonged lateral recumbency may lead to pressure atelectasis, which results in significant low ventilation–perfusion (V–Q) mismatching and intrapulmonary shunting. Hypoxemic pulmonary vasoconstriction is the natural defense mechanism to improve V–Q mismatching under such conditions. This emphasizes the importance of body positioning and frequent rotation of recumbent patients in the immediate postoperative period.

Hypoxemia and Hypoventilation

Postthoracotomy hypoxemia can result from many etiologies, including hypoventilation, V–Q mismatching, and diffusion impairment. Delivery of oxygen (DO_2) is the product of arterial oxygen content (CaO_2) and cardiac output. In relation to hypoxemia, arterial oxygen content is dependent upon hemoglobin concentration (g/dL) and saturation as well as the partial pressure of dissolved oxygen (PaO_2).

Hypoventilation is defined as a $PaCO_2$ greater than 45 mmHg in the dog or 40 mmHg in the cat. Common causes of hypoventilation in postthoracotomy patients include pain, residual anesthetics, respiratory fatigue, loss of chest wall elasticity, decreased total pulmonary compliance, increased airway resistance, and increased dead space ventilation. There is an approximate 1:1 ratio to explain hypoxemia due to hypoventilation. That is, for every 1. mmHg elevation in $PaCO_2$, there is a corresponding 1.0 mmHg decrease in PaO_2. Calculation of the alveolar to arterial oxygen gradient can be performed to rule out pulmonary pathology as the cause for hypoxemia.

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Decreased transpulmonary pressure, pain, and recumbency impede proper ventilation via atelectasis and decreased tidal volume. As previously mentioned, gravitational forces may cause significant atelectasis and decreased alveolar ventilation within the dependent lung, but perfusion is maintained (or even increased) within these pulmonary segments. The overall net result in this situation is moderate to low V–Q mismatching and hypoxemia.

Finally, hypoxemia following thoracotomy may also result from a combination of diffusion impairment and low V–Q mismatch secondary to reexpansion pulmonary edema or increased pulmonary vascular hydrostatic pressure. The pulmonary vasculature possesses significant permeability to protein compared to the extrapulmonary blood vessels. Since there is less intravascular oncotic pressure within this vascular circuit, elevated intrapulmonary hydrostatic pressure will favor the movement of fluid into the alveolar and interstitial space relatively quickly. Thus, pulmonary hydrostatic pressure is the main determinant for the development of pulmonary interstitial fluid accumulation and subsequent edema.

Net filtration in the pleural cavity (pleural effusion) is dependent upon the capillary hydrostatic pressure of the visceral and parietal pleura, intrapleural hydrostatic pressure, plasma oncotic pressure, and intrapleural oncotic pressure. Unlike the low pulmonary interstitial to vascular space oncotic gradient, a substantial gradient is generated within the pleural space. The normal colloid osmotic pressure (COP) of the pleural space is 3.2 cmH_2O (compared to 24.5–27.0 peripherally) with the average pleural pressure being –5 cmH_2O.

Hypothermia

Hypothermia is a common occurrence during and immediately following thoracotomy. With either median sternotomy or lateral thoracotomy, the pleural (visceral and parietal) body surface area is exposed to relatively cool ambient temperatures. This results in loss of body heat via evaporation and to some extent convection. Unimpeded hypothermia can have serious detrimental cardiovascular, respiratory, acid–base, and coagulopathic effects.

Arrhythmias

Cardiac arrhythmias may be observed during and subsequent to thoracotomy. Intraoperative cardiac arrhythmias may result from manual cardiac manipulation and are typically ventricular in origin. Postoperative arrhythmias, however, are classically secondary to underlying pathophysiology including pain, hypoxemia, or physical irritation from thoracostomy tube(s). Common arrhythmias include sinus tachycardia, accelerated idioventricular rhythm, bundle branch blocks, and ventricular tachycardia.

Hypotension

Postoperative hypotension is a common challenge for clinicians caring for patients following thoracotomy. Similar to the transpulmonary pressure gradient, subatmospheric pleural pressure is also important to maintain vascular distension within the thoracic cavity.

During a normal breath, the elastic recoil of the lungs upon inhalation allows distension of the large intrathoracic vessels (caudal and cranial vena cava), promoting venous return and thus increasing preload. Positive intrathoracic pressure exerted during exhalation causes mild collapse of these vessels, resulting in slight changes in pulse pressure between inspiration and expiration. During mechanical ventilation, the opposite effect occurs. With positive pressure ventilation, the majority of venous return occurs during expiration, not inspiration. Anesthesia along with underlying pulmonary pathology often necessitates the use of positive end-expiratory pressure (PEEP). Baseline PEEP is generally set at 5.0 cm H_2O, but decreased pulmonary compliance and atelectasis often require higher values of PEEP. Constant, low-grade, positive intrathoracic pressure, as PEEP increases, further impedes venous return, resulting in significant reductions in cardiac preload. Decreased preload leads to compromised stroke volume, cardiac output, and subsequent reduced delivery of oxygen. Positive pressure ventilation also has beneficial effects as it decreases afterload during inspiration, although this can be offset by dramatic decreases in preload.

Pain

Postoperative pain control is of critical importance following median sternotomy or lateral thoracotomy. Both of these procedures induce pain. In addition to surgical trauma, all postthoracotomy patients have an indwelling thoracostomy tube(s) that is a frequent source of pain. Hypoventilation and hypoxemia may be a direct result of pleurodynia, incisional pain, or thoracostomy tube-induced discomfort. Some patients are unwilling or unable to maintain an adequate tidal volume due to painful thoracic expansion. Hypoventilation secondary to pain may also contribute to significant atelectasis resulting in hypoxemia secondary to V–Q mismatching.

Continual Effusion and Pneumothorax

The goal of thoracic surgery is generally to palliate or resolve the underlying disease process to improve cardiopulmonary, vascular, or esophageal function. Often, the underlying disease process may not be immediately terminated post thoracotomy, such as chylothorax,

pyothorax, or pneumothorax. In such cases, thoracostomy tubes remain in place for several days following surgery for continual thoracic evacuation and fluid sampling. Occasionally, continual effusion or pneumothorax occurs postoperatively, exceeding expected volumes.

Predictable pleural effusion secondary to an indwelling thoracostomy tube should approximate 2.0 mL/kg/day. Fluid production above this may represent continual disease. Fluid analysis, including cell counts and cytology, can help the clinician assess if the fluid is reflective of ongoing disease. If cell counts and cytology do not support ongoing inflammation, infection or neoplasia, then it is possible that the ongoing fluid production is related to a systemic vasculitis, low oncotic pressure or elevated hydrostatic pressure. The pleural space volume is approximately 100–140 mL/kg in small animals. As such, when volumes of air or fluid exceed this value, it can be classified as a continuous process (e.g., continuous pneumothorax).

Thoracostomy Tubes

Thoracostomy tubes are a mainstay in the management of postthoracotomy patients. Depending on patient stability, a thoracostomy tube may be placed preoperatively or intraoperatively. Patients with viscous thoracic effusions or large-volume pneumothoraces may require bilateral thoracostomy tube placement.

Conventional thoracostomy tubes consist of large-bore plastic tubing made from silicone or polyvinyl chloride. Soft, small-bore thoracostomy tubes (e.g., Mila®, Mila International) that can be placed using a percutaneous catheter and guidewire are preferred by many emergency and critical care clinicians. The small bore tubes can be placed with ease and minimal risk to the patient either pre or intra-operatively. The smaller diameter low profile thoracostomy tubes are effective for all disease processes, including viscous effusions such as pyothorax. A cadaver study evaluating traditional large bore chest tubes to small bore tubes in efficiency to remove air, low viscosity fluid and high viscosity fluid found that small bore tubes were as effective as large bore tubes. It is the authors' opinion that the more traditional larger diameter tubes should be very rarely utilized, and that these tubes contribute to patient discomfort without providing any significant advantage with regards to evacuating the pleural space.

Postoperative Monitoring

Intensive postoperative monitoring is imperative following thoracotomy. Ideal monitoring would include electrocardiography, direct arterial blood pressure measurement, pulse oximetry, and arterial blood gas analysis, as well as end-tidal CO_2 and tidal volume in patients requiring continued mechanical ventilation.

Electrocardiography

Electrocardiographic monitoring provides early detection and continuous monitoring of cardiac arrhythmias. Postoperative arrhythmias may be observed primarily as a result of surgical trauma, prior manual cardiac manipulation, or direct pericardial or epicardial irritation from the indwelling thoracostomy tube. Arrhythmias may also occur secondary to pain, hypoxemia, hypovolemia, or electrolyte imbalances. Observation of hemodynamically significant postoperative atrial or ventricular arrhythmias necessitates therapeutic intervention including supplemental oxygen therapy, aggressive analgesia, correction of hypovolemia and electrolyte imbalance, and possibly antiarrhythmic medications. Diagnostic evaluation of postoperative arrhythmias may include electrolyte measurement, arterial blood gas analysis, and echocardiography.

Arterial Blood Pressure

As mentioned, changes in transpulmonary and pleural pressures can have significant hemodynamic effects. Direct arterial blood pressure measurement is the gold standard for monitoring patient stability and diagnosing changes in intrathoracic pressure. A sudden reduction in blood pressure may indicate an acute increase in pleural pressure, such as pneumothorax, warranting immediate investigation. Central venous pressure (CVP) monitoring can guide fluid therapy for postthoracotomy patients, but CVP is known to be affected by changes in intrathoracic pressure due to respiration, PEEP, and abdominal hypertension as each of these is known to decrease right ventricular compliance and thus artificially augment CVP. For these reasons, routine measurement of CVP in the postoperative patient with significant pleural space disease is not recommended.

Pulse Oximetry and End-Tidal CO_2

Pulse oximetry can provide valuable information regarding arterial hemoglobin saturation but it can also be affected by multiple patient factors. End-tidal CO_2 ($ETCO_2$) and tidal volume are helpful monitoring tools in the postthoracotomy patient requiring extended intubation and mechanical ventilation. Changes in $ETCO_2$ may be the first indicator of acute deterioration such as a large pulmonary thromboembolism or cardiopulmonary arrest in these critical patients, emphasizing the importance of capnography.

Arterial Blood Gas Analysis

Arterial blood gas analysis is paramount in patients with pulmonary dysfunction, as it will provide rapid identification of hypoxemia, hypoventilation, and respiratory failure. When arterial access is unobtainable, central venous ($S_{cv}O_2$) or mixed venous (S_vO_2) oxygen saturation as well as venous CO_2 ($PvCO_2$) can be extrapolated to evaluate respiratory function. Normally, $S_{cv}O_2$ is 10–15% higher than S_vO_2 but in states of circulatory shock or failure, these two measurements closely parallel one another. The normal arterial-venous gradient for PCO_2 is 4–6 mmHg, but it may approach 10 mmHg in some patients. This allows for serial ventilatory monitoring via venous blood sampling.

Postoperative Management

Intense postoperative management following thoracic surgery comprises adequate analgesia, appropriate thoracostomy tube care, intravenous fluid therapy, and intensive nursing care. Supplemental oxygen therapy is often implemented in the immediate postoperative period and occasionally continued mechanical ventilation is required.

Analgesia

Optimal analgesic protocols are critical for the postthoracotomy patient to prevent secondary hypoxemia, hypoventilation, and cardiac arrhythmias. Multimodal analgesia is preferred to avoid noxious effects of single-agent protocols. Combination therapy of systemic analgesics allows for synergistic analgesia and lower dosing of each chosen drug. Local analgesia including intercostal nerve blocks, incisional diffusion catheters, and intrapleural infusion of local anesthetics via the thoracostomy tube provides effective adjunctive analgesia. Intercostal nerve blocks can provide very effective analgesia when utilized for lateral thoracotomy. It is recommended to perform the procedure at the intercostal space of the incision, one space cranial and one space caudal to the incision. As discussed later, much of the postoperative pain seems to be associated with large-bore thoracostomy tubes.

Thoracostomy Tube Management and Pleural Drainage

Thoracostomy tubes generally remain in place for 12–24 hours post thoracotomy in patients without ongoing pleural space disease, but certain circumstances may necessitate maintenance beyond this timeframe due to continual effusion, residual pneumothorax, and for therapeutic lavage or delivery of chemotherapeutics. Pleural drainage may be passive or active, but active drainage is more commonly implemented in veterinary patients. The normal transpulmonary pressure is 4–8 mmHg, which is equivocal to 5–10 mL of suction in a syringe. Intrapleural infusion, via the thoracostomy tube, of lidocaine and bupivacaine (1.0 mg/kg each) provides local analgesia following intermittent suction and may be performed every 4–6 hours. The rationale behind using both lidocaine and bupivacaine is that the lidocaine provides immediate relief and allows for a more comfortable infusion of the longer-acting bupivacaine. This method of analgesia delivery has been investigated and deemed safe in patients following pericardectomy.

Intermittent active suction is applied often postoperatively, but continuous active suction may be necessary for larger volumes of air or effusion which compromise ventilation. The pleural space in small animals can accommodate approximately 100–140 mL/kg of fluid or air. Beyond this volume, continuous pneumothorax or hydrothorax (usually hemothorax) should be suspected. Obstruction of the thoracostomy tube may rarely occur, depending on tube diameter and viscosity of the thoracic effusion. The Mac technique consists of turning the thoracostomy tube 180° in each direction and observing whether the tube returns to the prior position. This method can be used to evaluate kinking of the tube when persistent negative pressure is observed despite evidence of significant pleural effusion or pneumothorax. If the tube consistently spins back into the initial position, tube kinking should be suspected.

The thoracostomy tube itself will induce approximately 2.0 mL/kg/day of pleural effusion. Once the volume of pleural effusion drops below this value, removal of the thoracostomy tube may be considered. Ideally, consistent negative pressure should be observed for 24 hours following pneumothorax prior to thoracostomy tube removal.

Fluid Therapy

Fluid therapy is a mainstay of postthoracotomy therapy. Most postoperative patients will require, at minimum, maintenance fluid therapy, as they may be unwilling to drink following surgery. Of further importance, continual fluid losses via the thoracostomy tube should be accounted for, and at least a percentage of this loss should be replaced with IV fluids to avoid hypovolemia due to third spacing. Postthoracotomy patients may experience significant protein loss with pleural effusion. The ideal

therapy for protein replacement in critically ill patients is to provide enteral nutrition in order for the patient to synthesize albumin.

Oxygen Therapy

Oxygen therapy may be provided intermittently via facemask or continuously by nasopharyngeal insufflation, nasal prongs, oxygen cage, or intubation and mechanical ventilation. Provision of intermittent supplemental oxygen at an FiO_2 of 50–60% can be achieved via facemask with oxygen flow rates of 8.0–12.0 L/min. Nasopharyngeal insufflation or nasal prongs may be utilized with oxygen flow rates of 50–150 mL/kg/min to achieve an FiO_2 of 30–70%. More commonly, postoperative thoracotomy patients are maintained in an oxygen cage with flow rates of 0.5–1.0 L/min to maintain a FiO_2 of 40–60%. Patients requiring an FiO_2 above 60% to maintain normoxemia will likely require intubation and mechanical ventilation. Caution must be exercised to avoid oxygen toxicity when supplemental oxygen levels are maintained above 60% for more than 24 hours.

When mechanical ventilation is utilized, PEEP ventilation can be beneficial to prevent atelectasis and augment work of breathing. In contrast to the spontaneously breathing patient, permissive hypercapnia is tolerated in mechanically ventilated postthoracotomy patients. Arterial PCO_2 may rise to 50 mmHg before intervention is necessary, as long as normoxemia is maintained. Proper humidification is an important component of oxygen therapy for preservation of proper mucociliary function and clearance of respiratory secretions.

Dyspnea

Dyspnea is the perceived feeling of breathlessness. The pathophysiology of dyspnea is multifactorial and is described elsewhere. Multiple therapeutic targets have been investigated to decrease the perception of dyspnea in human patients. In human studies, nebulized or aerosolized furosemide has been found to prevent bronchoconstriction and inhibit the cough reflex in addition to reducing pulmonary vascular hydrostatic pressure and edema when absorbed systemically. Furosemide has been shown experimentally and clinically in people to reduce bronchial slow-acting receptors (SARs), thereby reducing the sensation of dyspnea. Furosemide exerts a diuretic effect when administered by the enteral or parenteral route via inhibition of the Na:K:2Cl co-transporter within the thick ascending loop of Henle. A similar mechanism is postulated for the antidyspneic effect of nebulized furosemide causing a local increase in sodium ion concentration within the airways, increasing pulmonary stretch receptor activity.

Hypothermia

Hypothermia is an inevitable occurrence during and immediately following thoracic surgery. Warming IV fluids prior to administration can help diminish large reductions in intraoperative body temperature. Postoperative temperature monitoring, either intermittent or continuous, is recommended to ensure euthermia and active warming using warming blankets or heat lamps should be performed until the patient's temperature has reached 99.5 °F.

Arrhythmias

For hemodynamically significant, multifocal, sustained, or R-on-T phenomena ventricular arrhythmias, lidocaine remains the mainstay therapy. Lidocaine may also be useful to slow the heart rate, allowing differentiation of ventricular tachycardia from sinus tachycardia with bundle branch block. The waveform of the latter often will not change following lidocaine bolus (2.0 mg/kg IV), but P-waves may be appreciable once the heart rate has decelerated. For lidocaine-responsive arrhythmias, a constant rate infusion of 60–80 μg/kg/min may be implemented postoperatively. A beta-blocker may also be considered for patients that do not have known underlying cardiac disease with compromised contractility. Anecdotally, sotalol 2.0 mg/kg PO BID has favorable postoperative antiarrhythmic properties for patients with supraventricular and ventricular tachyarrhythmias.

Nursing Care

Nursing care is a critical yet often underemphasized aspect of postthoracotomy care. Patients undergoing median sternotomy often prefer lateral recumbency in the immediate postoperative period due to incisional pain. Turning or rotating the patient every 4–6 hours prevents atelectasis and V–Q mismatching secondary to gravitational forces in lateral recumbency. Turning the patient also promotes patient comfort and hygiene. Optimal analgesia aids in patient well-being and may promote tolerance of sternal recumbency and therefore improved oxygenation and ventilation.

Complications

Complications post thoracotomy may include edema formation, hypoproteinemia, continual pleural effusion,

secondary infection, hemorrhage, residual or continuous pneumothorax, seroma formation, sternal osteomyelitis, pyrexia, iatrogenic chylothorax, fibrosing pleuritis, surgical dehiscence, and ipsilateral thoracic limb lameness (lateral thoracotomy). Crystalloid fluid therapy, anorexia, vasculitis, and postoperative inflammation can contribute to peripheral edema formation.

The most common complication involving the thoracostomy tube is improper placement. Insufficient subcutaneous tunnel formation with large-bore thoracostomy tubes can lead to continuous air leakage and pneumothorax. The thoracostomy tube percutaneous insertion site should be inspected carefully when continuous pneumothorax is observed. Continual pleural effusion may be primary or secondary in origin, depending on the etiology requiring thoracotomy. Pyothorax, chylothorax, and neoplastic effusion represent sources of continual pleural effusion during the postoperative period. Pleural drainage is important to maintain proper ventilatory function as well as oxygenation. However, excessive pleural effusion can lead to significant systemic protein and fluid loss with subsequent intravascular volume depletion. Vasculitis and surgical inflammation are contributors to this protein-losing pleuropathy and third spacing, which may encourage perpetual effusion. Resolution of the underlying disease process will likely terminate the cause of effusion.

Infection is an undesirable complication in any postoperative patient. Preoperative infection may be present in some patients, such as pyothoraces, in which septic effusion necessitated surgical intervention. Continual monitoring of thoracic fluid cytology and cell counts aids in determining resolution of pyothorax. Responsible antimicrobial administration is of paramount importance in the care of critically ill patients. A full discussion on this topic can be found elsewhere. Generally speaking, clinicians should be familiar with antibiotic sensitivity patterns of common bacterial isolates from their hospitals and deescalate coverage to single-agent therapy as soon as possible. Infection may be introduced intrathoracically via the thoracostomy tube or surgical incision. This may be due to bacterial contamination associated with prolonged surgical exposure, improper handling of the thoracostomy tube, or bacterial invasion of the thoracostomy tube insertion site and/or surgical incision. Appropriate samples should be obtained for bacterial culture and antimicrobial susceptibility testing when infection is suspected.

Proper intraoperative hemostasis ensures minimal postoperative hemorrhage, therefore significant hemorrhagic pleural effusion is not expected in the postthoracotomy patient. Serosanguinous pleural effusion (PCV <25% of peripheral PCV) is a common and expected occurrence with an indwelling thoracostomy tube(s). However, hemothorax is diagnosed when the pleural PCV exceeds peripheral PCV by 25% and warrants immediate investigation. When the volume of thoracic hemorrhage exceeds 10 mL/kg, autotransfusion should be considered.

Proper postoperative incisional care can reduce patient discomfort and surgical inflammation while minimizing risk of infection. During the initial postoperative period, the thoracotomy incision as well as thoracostomy tube insertion site(s) should be covered with an impermeate adhesive dressing. This provides a seal preventing air leakage with resultant pneumothorax while protecting against environmental contamination. Cold and warm compresses following surgery can reduce incisional pain, swelling, and inflammation. Cold compresses are usually applied during the immediate postthoracotomy period for 24–48 hours, with warm compresses used thereafter.

An elevation in body temperature above normal in any postoperative patient warrants immediate concern and investigation. Hyperthermia may be secondary to decreased heat dissipation (inability to pant due to pain, excessive cage bedding), pharmacologic (mu opioid use in cats), or pain induced. Postthoracotomy pyrexia may be observed with infection, inflammation, or neoplasia. Indwelling catheter sites should be inspected for hyperemia, warmth or discomfort upon palpation. Thoracostomy tube insertion sites should also be interrogated in a similar fashion. Complete blood count and thoracic radiographs may also be considered when an obvious etiology of pyrexia cannot be determined from physical examination.

Surgical reexploration is rarely necessary following thoracotomy, but is required for continuous pneumothoraces or hemothoraces that do not respond to medical management. Pneumothoraces, which fail to seal despite continuous active suction, are an indication for prompt reexploration to evaluate the pulmonary parenchyma (bullae or pneumatocele rupture) and previous surgical sites (complete or partial lobectomy). Chronic pleural effusion, despite prior thoracotomy, may also necessitate a second surgery due to fibrosing pleuritis or restrictive fibrin plaque formation on the surface of the visceral pleura of the lung. Decortication may be necessary if significant inelastic fibrin plaque formation has occurred restricting lung expansion. For perpetual pleural effusion, pleurodesis may also be considered.

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34

Pleural Effusion

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Pleural effusion is the pathologic collection of fluid within the pleural space resulting from one of three primary mechanisms: disruption of pleural pressure homeostasis, diminished lymphatic drainage, or increased mesothelial and capillary endothelial permeability. Given the dynamic state of the pleural space, overlap can occur between the mechanisms of effusion, depending on the underlying disease. Dogs and cats with pleural effusion present with various clinical signs including lethargy, hyporexia, tachypnea, dyspnea, and a paradoxical breathing pattern, regardless of precipitating cause. History and physical examination may help to formulate a differential diagnosis for pleural effusion, but ultimately collecting a sample of the effusion for cytologic analysis and additional tests provides the most important information to obtain an accurate diagnosis. Treatment options and prognosis are dependent on the underlying cause of pleural effusion.

Anatomy and Physiology

The pleura lines the thoracic cavity and is a thin, serous membrane with five layers: an outer fibroelastic layer, an extensively vascularized subpleural loose connective tissue layer, an elastic superficial tissue layer, a loose connective submesothelial tissue layer, and a mesothelial layer. The visceral pleura line the lungs, whereas the parietal pleura line the thoracic wall with the potential space between the two known as the pleural space. The visceral pleura functions to provide mechanical lung support, limit lung expansion, and contribute to elastic recoil and deflation of the lung. The parietal pleura is subdivided into the costal, mediastinal, and diaphragmatic parietal pleura and contains numerous lymphatic vessels that form stomas between mesothelial cells for lymphatic drainage. Lacunae are dilated lymphatic vessels in the submesothelial parietal pleura where stomas form and transport fluid back through the lymphatic system. Compared to other species, dogs and cats have a thin pleural surface, approximately 15 μm thick. The mediastinum divides the pleural space into a right and left pleural cavity, although in dogs and cats the mediastinum may not be complete, allowing for bilateral disease from a unilateral origin. The highly metabolically and immunologically active multipotent mesothelial cells line the entire pleural cavity and play an active role in pleural fluid production and reabsorption. Sialomucins are negatively charged glycoconjugates which coat the free mesothelial surface, functioning to repel opposing membranes as well as organisms, abnormal cells, and particles.

In healthy animals, a small volume of fluid is present in the pleural space which facilitates smooth gliding of the lung over the thoracic wall and transmission of forces during normal respirations. Normal pleural fluid is low in protein (<1.5 g/dL) and cellular content (1500–2500 cells/μL), consisting of mesothelial cells (9–30%), monocytes (61–77%), lymphocytes (7–11%), and neutrophils (<2%). Healthy dogs and cats produce approximately 0.01–0.02 mL/kg/h of pleural fluid via microvascular filtration from pleural capillaries. Fluid crosses the pleural capillary endothelium followed by the interstitium. Pleural capillary endothelium imparts most of the resistance to flow; however, the resistive properties of the endothelium and interstitium are additive, which becomes significant during some disease processes that interfere with the resistive properties of these layers. The production and reabsorption of pleural fluid are multifactorial, dependent on Starling forces, solute flux, hydraulic conductivity (the resistive properties of the two pleural surfaces), total surface area, the solute reflection coefficient (ability of the surface to restrict larger molecules), membrane diffusive permeability, pleural lymphatic drainage via stomata in the parietal pleura, and cellular mechanisms of transport by mesothelial cells (Table 34.1).

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Table 34.1 Starling Law applied to pleural membrane

$$Q_b = LA[(P_c - P_{pl}) - \sigma_o(\pi_c - \pi_{pl})]$$

Q_b	Filtration rate across the capillary endothelial barrier in series with the pleural membrane (interstitium)
LA	Filtration coefficient = [hydraulic conductivity (L) * surface area (A)]
σ_o	Reflection coefficient to protein of the combined endothelial-interstitial barrier
P_c	Capillary hydrostatic pressure
P_{pl}	Pleural hydrostatic pressure
π_c	Capillary oncotic pressure
π_{pl}	Pleural oncotic pressure

Source: Adapted from Lai-Fook 2004.

Normal pleural pressure is approximately −3 to −5 cmH_2O at functional residual capacity, becomes greater (more negative) with deeper breaths, and is more negative in the dorsal space compared to the ventral space, decreasing by 0.5–0.7 cmH_2O/cm in dogs. This subatmospheric pleural pressure results from elastic recoil forces of the lung exerting a force inward with the propensity of the chest wall to expand outward and serves to maintain lung inflation while decreasing the work of breathing. Although reported as a single number, pleural pressure is a result of the dynamic nature of the pleural space and represents a summation of the pressure exerted by pleural fluid, regional pleural surface deformation, and weight of the lung in dependent areas of the thoracic cavity.

Pathophysiology of Pleural Fluid Accumulation

Pleural fluid volume depends on Starling forces, mesothelial cell activity, and lymphatic drainage; however, the exact contribution of each of these mechanisms remains somewhat elusive and varies during disease processes. Starling forces which favor the formation of pleural fluid include increased capillary hydrostatic pressure, decreased capillary oncotic pressure, and increased capillary permeability. Mesothelial cells have apical microvilli that increase the surface area for exchange and vesicles that allow for transcytosis of proteins from the pleural space to the pleural interstitium. In addition, indirect evidence suggests mesothelial cells are involved in solute-coupled liquid transport across the pleural surface. Lymphatics communicate directly with the pleural cavity through openings between the mesothelial layer in the parietal pleura, called stomas, and allow cells, protein, and larger particles to be absorbed into the lymphatic system through channels called lacunae. The maximal reabsorption rate through pleural lymphatics is estimated to be 0.2–0.3 mL/kg/h, which is considerably more than the normal daily rate of fluid accumulation. Therefore, the accumulation of pleural fluid occurs when the disease process overwhelms fluid reabsorption capacity, reduces the ability of lymphatics to reabsorb fluid, or increases production of fluid while simultaneously decreasing lymphatic clearance.

Pathologic fluid effusions are classified in two broad categories: transudates and exudates. Transudative effusions typically accumulate secondary to an increase in hydrostatic pressure or a reduction in plasma oncotic pressure while the pleura remains normal, whereas exudative effusions typically accumulate secondary to various pleural pathologic conditions leading to increased vascular permeability and/or diminished lymphatic fluid reabsorption. Mesothelial cells play a pivotal role in the development of exudative effusions by synthesizing inflammatory cytokines, growth factors, and extracellular proteins. A classic example of increased systemic venous hydrostatic pressure leading to a transudative effusion is congestive heart failure. In addition, pulmonary thromboembolism, cardiac tamponade, heartworm disease, and neoplasia can all lead to increased venous hydrostatic pressure and therefore transudative pleural effusion. In comparison, a classic example of an exudative effusion is pyothorax with an influx of inflammatory cells, which can increase vascular permeability and decreased lymphatic drainage (Table 34.2).

Regional changes in pleural pressure occur with the accumulation of pleural effusion and the mechanism of pressure change is controversial. Proposed theories to explain the pressure difference center around the hydrostatic pressure contribution of a column of fluid in the thorax and the changes in deformation forces as the lung and thoracic wall become separated by fluid. The hydrostatic theory divides the pleural space into three distinct pressure zones: the upper (dorsal) zone, middle zone, and lower (ventral) zone. In the upper (dorsal) zone, the pleural liquid thickness is normal and the pleural liquid pressure is less than the pleural surface pressure. In the middle zone, the pleural liquid thickness increases and pleural liquid pressure equalizes with pleural surface pressure at zero. In the lower (ventral) zone, the pleural fluid thickness increases substantially and the pressure becomes positive, displacing the lung from the thoracic wall. In the other predominant theory, the pleural liquid pressure is always equal to pleural surface pressure such that pressure gradients caused by gravity and regional differences in pleural surface pressure drive a small viscous flow of fluid in the normal pleural space and surfaces are never in contact. As pleural effusion

Table 34.2 Causes of pleural effusion in dogs and cats

Physical agents
- Thoracic trauma
- Electrical burn
- Radiation therapy
- Iatrogenic
- Foreign body (e.g., grass awn)

Lymphatic or venous obstruction
- Lung lobe torsion
- Diaphgragmatic hernia

Decreased oncotic pressure
- Protein-losing nephropathy
- Protein-losing enteropathy
- Liver failure

Increased hydrostatic pressure
- Congestive heart failure
- Heartworm disease
- Thrombosis
- Neoplasia

Neoplastic disease
- Mesothelioma
- Lymphoma
- Adenocarcinoma
- Lymphoproliferative syndromes
- Mesenchymal tumors

Infectious disease
- Pyothorax (bacterial, fungal)
- *Mycoplasma*

Extrathoracic disease
- Pancreatitis
- Peritonitis
- Esophageal rupture
- Uroabdomen

Others
- Feline infectious peritonitis
- Coagulopathy (rodenticide or factor deficiency)
- Allergic hypersensitivity conditions
- Cholecystectomy

accumulates, the viscous resistance to flow quickly decreases and the pleural pressure gradient approaches the hydrostatic pressure gradient. Both theories contend that pleural effusion increases pleural pressure by 1 cm H_2O/cm effusion height.

Measuring pleural liquid pressure and pleural surface can be challenging because the space is small and the insertion of any device will cause an artifact by deforming the surface. In the diseased thorax with an appreciable amount of pleural effusion, these challenges become less significant and pleural pressure measured is an accurate representation of hydrostatic pressure at the level of the catheter or transducer. During thoracocentesis or if an indwelling thoracostomy tube is in place, pleural pressure can be monitored in veterinary patients with a minimal amount of equipment using a water manometer or pressure transducer. If using a pressure transducer, measurements are recorded in mmHg and should be converted to be interpreted appropriately (1 mmHg = 1.36 cmH_2O). Pleural pressure monitoring may be beneficial with chronic effusions when draining the effusion does not necessarily equate to return to normal pleural physiology because the pleural surface remains diseased. If the lungs cannot expand appropriately after thoracocentesis, creating a situation of entrapped lung, the supraphysiologic negative pressure created in the pleural cavity by removing the fluid may increase the risk of pneumothorax.

Clinical Signs and Physical Examination

Rapid intervention with minimal patient stress is paramount in patients with respiratory distress so it is important to be familiar with clinical signs and physical examination findings indicative of certain disease processes. Time of onset, volume of fluid accumulation, and inciting cause of pleural effusion all contribute to the patient's history and clinical signs.

Pleural effusion is a consequence of an underlying disease and vague historical clinical signs are often reported including lethargy, exercise intolerance, weight loss, and hyporexia or anorexia. In a retrospective study, tachypnea and dyspnea were the most commonly reported complaints by owners, present in 95% of dogs with pleural effusion. Additional complaints, which may or may not be an indication of the underlying disease, include cough, polydipsia, vomiting, fever, collapse, diarrhea, restlessness, reluctance to lie down, cervical extension, hemoptysis, abdominal distension, melena, hematemesis, and halitosis. Severe pleural effusion may present as open mouth breathing and cyanosis, especially if onset is acute.

On physical examination, a restrictive breathing pattern seen as rapid and shallow breathing has historically been reported but recent literature suggests an asynchronous (paradoxical) or inverse breathing pattern and decreased lung sounds on auscultation are more common clinical findings in dogs and cats. Paradoxical breathing refers to increased inspiratory effort strong enough to pull the abdominal contents toward the thorax, leading to a sunken flank appearance during inspiration and a bulging flank appearance on expiration. Additional physical examination findings include muffled heart sounds, decreased ventral lung sounds, shallow breathing, and inspiratory dyspnea. Patients with cardiac disease, such as heart failure, pericardial effusion, or caval syndrome, may have a murmur or crackles on thoracic auscultation, jugular pulses, a positive hepatojugular reflex, and/or pulse deficits. Patients with a coagulopathy causing pleural effusion, such as anticoagulant rodenticide toxicity, may have bruising, pale mucous membranes, weak pulses, or tachycardia on physical examination. Masses found on abdominal palpation, oral or dermatologic examination may indicate a neoplastic cause for pleural effusion. Mediastinal neoplasia should be suspected with an incompressible cranial thorax in cats or Horner syndrome in cats or dogs. Pain in the right cranial abdominal quadrant with gastrointestinal signs may be suggestive of pancreatitis as an underlying cause of pleural effusion (Table 34.3).

Table 34.3 Classification of effusions in dogs and cats

	Total protein (g/dL)	Cells per microliter	Cell types	Special features
Transudate	<2.5	<1500	Mononuclear	Low cellularity
Modified transudate	2.5–7.5	1000–7000	Mononuclear	Cell type varies with etiology
Exudate	>3.0	>3000	Neutrophils or specific to underlying disease	Subcategories: hemorrhage, bile, chyle, septic, aseptic

Diagnostics

Patient presentation, stability, and available resources will often guide the diagnostic approach in patients with pleural effusion. The cyanotic cat with open mouth breathing will have a different initial diagnostic and treatment plan from a dog presenting for vomiting or diarrhea with scant pleural effusion found during routine testing for underlying gastrointestinal disease. Regardless of the underlying pathology, the goal should be patient stabilization first followed by a thorough investigation into the inciting cause of pleural effusion using imaging techniques, pleural fluid tests, and, if necessary, histopathology.

Imaging

Ultrasonography, radiography, and computed tomography (CT) are currently available imaging techniques in dogs and cats with pleural effusion. In general, the patient requiring emergent treatment for respiratory distress due to pleural effusion is likely to have an ultrasound in the emergency department initially followed by thoracocentesis prior to the pursuit of additional imaging techniques whereas a stable patient will likely have thoracic radiographs with or without a thoracic ultrasound followed by advanced imaging if necessary.

Although the name implies a single subset of patients, which benefit from the test, the thoracic focused assessment with sonography for trauma (TFAST) is the most common initial test in an emergency situation due to pleural space disease because it allows for rapid assessment of the thoracic cavity with a therapeutic goal. TFAST is performed with the patient in sternal or right lateral recumbency and assessing five areas of the thoracic cavity: the right and left chest tube site (dorsolateral 7th–9th intercostal spaces), right and left pericardial site (ventrolateral 5th–6th intercostal space), and the diaphragmatico-hepatic (subxiphoid) site. Pleural effusion is recognized as anechoic or echogenic fluid in the pleural space and its presence may allow better visualization of some mediastinal masses. In people, the diaphragmatico-hepatic site is the most sensitive and specific area to diagnose pleural effusion because it has less air interface than the pericardial sites; however, with breed conformation and size variation of veterinary patients, this has yet to be prospectively evaluated. Thoracic ultrasound is useful for the detection, characterization, and subjective quantification (by depth) of pleural fluid, in addition to guiding therapeutic intervention. Abdominal ultrasound and echocardiogram may also help determine the cause of pleural effusion.

Thoracic radiographs are useful to evaluate for the presence of pleural effusion and survey the thoracic cavity for an underlying etiology. Radiographic signs of pleural effusion include retraction of the lung margins from the thoracic wall and sternum with increased opacity in the pleural space, widened interlobar fissures, rounding of lung margins, pleural thickening, and obscuring of the diaphragm and cardiac silhouette by radiopaque fluid. Pleural fluid will often obscure structures in the thoracic cavity, including the heart, mediastinum, and diaphragm; therefore, in patients with significant pleural effusion it is advantageous to perform thoracocentesis, ideally ultrasound guided, prior to radiographs to allow better evaluation of intrathoracic structures. Since the pleura cannot normally be seen on radiographs, if pleural lines are seen, horizontal beam radiographs, in addition to the standard three-view series, may help differentiate pleural thickening from pleural effusion because vertical beam projections are limited by superimposition of fluid and soft tissue structures. In addition, more pleural effusion is present than predicted based on vertical beam (standard-view) radiographs because large fluid pockets are not struck head-on by the X-ray beam; however, a horizontal beam allows fluid to collect ventrally such that the X-ray beam strikes the fluid–lung interface tangentially. However, ultrasound remains the most sensitive test for detection of small amounts of fluid.

Thoracic CT has become increasingly available in veterinary practice; CT allows better lesion delineation and characterization than conventional radiography for many thoracic disorders. Prior to thoracic CT,

thoracocentesis should be performed to remove as much fluid as possible to enhance visualization of intrathoracic and extrathoracic structures. Patients are maintained in dorsal or ventral recumbency, manually hyperventilated immediately preceding the helical scan to decrease respiratory drive during a forced breath hold, and the entire thorax is acquired using a slice collimation of 3–7 mm, depending on patient size. During a single inspiratory hold not exceeding one minute, the entire thorax is scanned which determines the slice thickness of the images, reserving the ability to make thinner slices of areas of pathologic importance if needed. Both ultrasound and conventional radiographs are poorly sensitive to determine vascular invasion, displacement of normal anatomic structures, or invasion of adjacent structures by mediastinal masses; however, CT enhances the ability to determine the aggressiveness of the tumor prior to surgical exploration. Regarding chylothorax, CT may be superior to traditional radiographic lymphangiography to show contrast enhancement of the thoracic duct. Thoracic CT may also be indicated in dogs and cats with pyothorax not responding to conventional management or if a pleural or pulmonary foreign body or abscess is suspected because this imaging technique eliminates superimposition and silhouetting of intrathoracic structures. Pleural abscesses on CT often appear as ring-enhancing cystic structures with a fluid-attenuating core. Additional benefits of thoracic CT include identifying pleural thickness, small-volume pneumothorax, parenchymal lung masses, and peripheral bronchopleural fistulae.

Pleural Fluid Evaluation

Thoracocentesis is therapeutic and has the potential to be diagnostic in any dog or cat with pleural effusion. In the emergent respiratory patient, thoracocentesis should be the first step after pleural effusion has been confirmed by TFAST with a goal to remove as much fluid as possible, the exception being the coagulopathic patient. There are no absolute contraindications to perform thoracocentesis but in coagulopathic patients, extreme caution should be used if thoracocentesis is necessary and should be reserved for patients in moderate to severe respiratory distress. In the absence of ultrasound availability, thoracocentesis can be carefully performed in a dyspneic patient prior to radiographs. The small risk associated with thoracocentesis is outweighed by the major risk of prolonged restraint for radiographs of a patient in severe respiratory distress. Unilateral or bilateral thoracocentesis may be needed and is ideally performed with ultrasound guidance.

Gross appearance of aseptically collected pleural fluid should be recorded, as well as protein content and cytologic characteristics. Samples should also be saved in ethylenediaminetetraacetic acid (EDTA, lavender top), serum (red top) tubes, sterile tubes for culture, and/or other tubes for effusion-specific tests such as polymerase chain reaction (PCR). Information gained from protein content and cellularity may help guide future diagnostics or treatment. Gram stain should be performed if pyothorax is suspected on preliminary diagnostics to guide antimicrobial therapy while cultures are pending. Sterile samples can be stored for bacterial, fungal, and/or *Mycoplasma* culture followed by antimicrobial susceptibility. Fluids are typically divided into three categories based on protein content and nucleated cell count: transudate, modified transudate, and exudate. Subcategories of exudative effusions include hemorrhage, bile, chyle, septic and aseptic (Table 34.4).

Pure transudates are low in protein (<2.5 g/dL) and total nucleated cell count (<1500 cells/μL) with a clear, colorless, or straw-colored appearance. Cytologic examination shows predominantly mononuclear cells such as lymphocytes, macrophages, and mesothelial cells with low to absent numbers of nondegenerate neutrophils. Transudative pleural effusion is a consequence of either increased hydrostatic or decreased oncotic pressure. Liver disease, protein-losing enteropathies and nephropathies, malnutrition, maldigestion, and malabsorption can cause profound hypoalbuminemia with or without hypoglobulinemia, leading to decreased oncotic pressure. In addition, chronic blood loss, intestinal parasitism, and

Table 34.4 Pyothorax bacterial isolates

Organism	Dogs	Cats
Aerobic	*Escherichia coli* *Enterobacter cloacae* *Klebsiella pneumoniae* *Pasteurella* spp. *Actinomyces* spp. *Streptococcus canis* *Streptococcus intermedius* *Mycoplasma* spp. *Nocardia* spp.	*Pasteurella* spp. *Actinomyces* spp. *Escherichia coli* *Enterococcus faecalis*
Anaerobic	*Peptostreptococcus anaerobius* *Bacteroides* spp. *Fusobacterium* spp. *Porphyromonas* spp. *Prevotella* spp. *Eubacterium* spp. *Propionibacterium* spp.	*Bacteroides* spp. *Peptostreptococcus anaerobius* *Fusobacterium* spp. *Porphyromonas* spp. *Prevotella* spp. *Filifactor villosus* *Fibrobacter succinogenes*

Source: Adapted from Walker, Jang, and Hirsch 2000.

intestinal neoplasia can also cause significant hypoproteinemia. In general, albumin concentrations less than 1.0 g/dL cause oncotic pressure to be low enough for a transudate to develop; however, if increased hydrostatic pressure is also present, a pure transudate can be seen with a higher albumin concentration.

Modified transudates are variable in protein content (2.5–7.5 g/dL) and cell count (1000–7000 cells/μL). Grossly, they can be tan and slightly turbid, to pink, or opaque and white in appearance depending on the underlying etiology. Most of the nucleated cells are mononuclear (macrophages, lymphocytes, or a combination of both) with a lower number of mesothelial cells and nondegenerate neutrophils. Modified transudates result from increased vascular or lymphatic permeability with or without increased hydrostatic pressure. They are modified by the addition of proteins, cells, or chyle, and classifying a fluid as a modified transudate implies the disease process causing fluid to accumulate is noninflammatory. Most modified transudates are a consequence of obstructed venous or lymphatic drainage secondary to numerous underlying diseases, with right-sided heart failure being most common. Some modified transudates may become exudative effusions, especially with chronicity because fluid in the pleural space is inflammatory. Chylous effusion has been classified as both a modified transudate and an exudate for this reason. Initially, chylous effusions contain a predominant population of mononuclear cells (lymphocytes) and fluid accumulates due to lymphatic obstruction from noninflamed vessels. In cats, chylous effusion can result from congestive heart failure or heartworm disease. Additional causes in veterinary species include lung atelectasis, neoplasia, diaphragmatic or peritoneal-pericardial hernias, lung lobe torsion, lymphangiectasia, cranial vena cava thrombosis, trauma, restrictive pericarditis, pericardial disease, and mediastinal disease. Often, an underlying disease for chylous effusion is not identified and is therefore idiopathic.

Exudates have a high protein concentration (>3.0 g/dL) and nucleated cell count (>3000 cells/μL). Exudates vary in gross appearance from white to amber to pink depending on etiology and are typically turbid. The predominant cell type is the neutrophil, which may be nondegenerate (aseptic) or degenerate (septic), with macrophages, lymphocytes, eosinophils, and mesothelial cells in lesser quantities. Exudative effusions usually result from an inflammatory process in the pleural cavity causing release of cytokines and other vasoactive mediators, leading to increased capillary permeability (filtration coefficient). The initial inflammatory process can be due to endogenous (chyle, neoplastic cells) or exogenous (bacteria, fungi) mediators. Eosinophilic effusions determined cytologically with >10% eosinophils are infrequently reported in veterinary medicine; however, if present, cancer is the most common underlying etiology, followed by thoracic wall trauma, pneumothorax, congestive heart failure, and allergic hypersensitivity conditions. Pyogranulomatous inflammation may indicate fungal or foreign body reaction. Cytologic slides should be closely evaluated for the presence of intracellular bacteria and aerobic and anaerobic cultures with antimicrobial susceptibilities should always be submitted when degenerate neutrophils are present. Nondegenerate neutrophils typically indicate a nonseptic process and may be secondary to neoplasia, chronic diaphragmatic hernia, lymphatic obstruction or leakage, and infectious processes. If the patient has a history of recent cholecystectomy or trauma and yellow, nonseptic exudate is collected, bilothorax should be a differential and further diagnostics performed.

Specific Pleural Fluid Tests

When chylothorax is suspected, triglyceride concentration should be analyzed in the pleural effusion and patient's serum. Diagnosis of chylothorax is confirmed if the triglyceride concentration in the pleural fluid is higher than the triglyceride concentration in the patient's serum. Decreased glucose (<60 mg/dL) in pleural fluid is due to decreased transport of glucose to the pleural fluid or increased utilization of glucose by mononuclear cells, neutrophils, bacteria, or malignant cells. If the effusion appears hemorrhagic, the packed cell volume (PCV) of the pleural effusion should be compared to the PCV of the patient, with hemothorax present if the pleural fluid PCV is at least 25% of the patient's PCV. Bilirubin should be quantified in the pleural fluid and blood if bilothorax is suspected, such as those patients with recent biliary surgery or known/suspected trauma. If bilirubin in the pleural fluid is higher than in the patient's blood, bilothorax is diagnosed.

Pleural Pressure Monitoring

Normal pleural pressure in a dog or cat is negative with respect to the atmosphere and functions to facilitate lung inflation and reduce the work of breathing. Negative intrapleural pressure is generated by the lymphatic system as it drains the normal, physiologic small volume of pleural fluid present. As pleural effusions accumulate, lung parenchyma collapses and intrathoracic pressure increases. Dyspnea and tachypnea result due to collapsed parenchymal lung tissue and pleural pressure becomes less negative, or positive to the atmosphere. When the fluid is removed by thoracocentesis, the expectation is that intrapleural pressure returns to its normal negative pressure and the lungs can reexpand but this is not always the case, especially with chronic effusions. The pleural surface can become fibrinous,

thickened, and inflamed by chronic effusions, thus inhibiting reexpansion of the lungs once the effusion is removed. In humans, this is termed lung entrapment as the intrapleural pressure has become negative, but the lungs cannot expand due to the formation of a visceral pleural peel and persistent pleural effusion. This imparts a large negative pressure on the diseased visceral pleural surface, which may cause pain or increase risk of spontaneous pneumothorax.

Intrapleural pressure can be measured during thoracocentesis with several techniques, including a U-shaped water manometer, an "overdamped" water manometer, or electronic pressure transducer systems such as those used for invasive blood pressure monitoring. The role of intrapleuaral pressure monitoring in veterinary medicine is an expanding area of interest and research.

Thoracoscopy

Thoracoscopy is a minimally invasive technique which is becoming more widespread in veterinary medicine and can be used as both a diagnostic and therapeutic technique in veterinary patients with pleural effusion. Advantages of thoracoscopy include obtaining pleural biopsies, visualization of intrathoracic pathology, and minimally invasive approach (Figure 34.1).

Properly collected thoracoscopic pleural biopsies are adequate in quality and quantity to obtain a definitive histopathologic diagnosis (Figure 34.2). Disadvantages include general anesthesia, risk of pneumothorax, hemorrhage, infection, and potential need for thoracotomy if unable to achieve definitive treatment (depending on underlying disease) with thorascoscopy alone.

Pyothorax

Pyothorax is the accumulation of purulent exudative effusion in the pleural space caused by infection. Young (3–6 years) male dogs are more likely to be diagnosed with pyothorax, with performance breeds being overrepresented. Dyspnea, tachypnea, pyrexia, lethargy, and anorexia are the most common clinical signs in dogs. In cats, pyothorax is more common in young (2–4 years) domestic shorthairs, with no sex predilection, and the most common initial clinical signs include hyporexia or

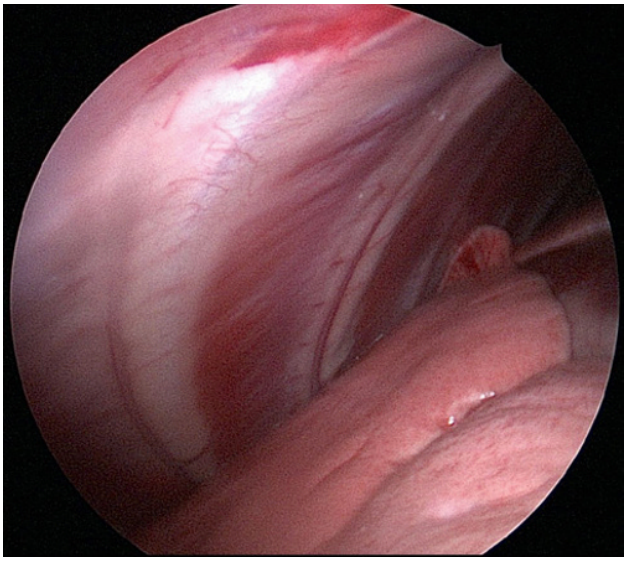
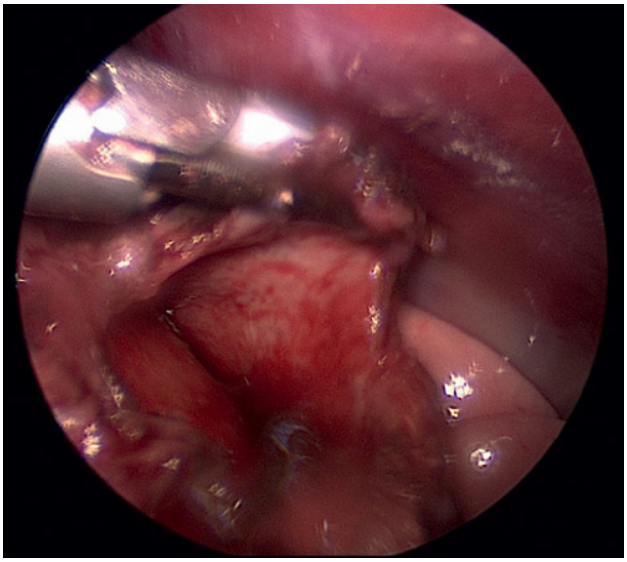


Figure 34.1 Normal pleura visualized via thoracoscopy. *Source*: Photo courtesy of Brad Case, DVM, DACVS, University of Florida CVM.

(a)



(b)

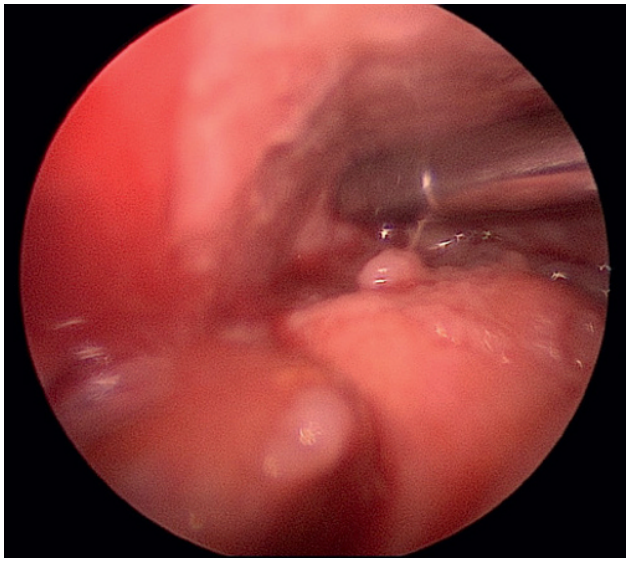


Figure 34.2 (a,b) Thoracoscopic biopsy in a dog with mesothelioma. *Source*: Photo courtesy of Brad Case, DVM, DACVS, University of Floriday CVM.

anorexia, lethargy, and/or dyspnea. Although more common in young animals, pyothorax can occur at any age, with rare reports in neonatal dogs and cats. Additional clinical signs include weight loss, nasal or ocular discharge, hypersalivation, coughing, and exercise intolerance. Clinical signs can be acute or chronic. Physical examination findings often include tachypnea, dyspnea, decreased ventral lung sounds, muffled heart sounds, and restrictive respiratory pattern. Severe sepsis and associated signs could occur in either species, with pyothorax being the most common cause in a retrospective paper on cats with severe sepsis.

In dogs, causes include bite wounds, penetrating thoracic injury, foreign body inhalation, lung abscess, parasitic migration, hematogenous spread, esophageal or tracheal perforation, diskospondylitis, neoplasia with lung abscessation, previous thoracic surgery, and thoracocentesis. In cats, causes include extension from a lung parenchymal infection, foreign body migration, esophageal rupture, and penetrating thoracic wounds. Cats with pyothorax are 3.8 times more likely to live in multiple cat households, *Pasteurella* spp. are the most common bacterial isolate, and 14.5–40% of cases have a history of bite wounds, thus adding support to the theory that bite wounds are a common route of infection. Migrating grass awns can be a common cause of pyothorax in dogs and cats, depending on geographic location, but in many cases the cause of infection is not identified.

Diagnosis is based on presence of an exudate, cytologic slide evaluation, and positive bacterial cultures of aseptically collected pleural fluid. Intracellular bacteria identified on cytologic review confirms the diagnosis but if intracellular bacteria are not seen and degenerate neutrophils are present, then bacterial cultures (aerobic and anaerobic) should be performed (Figure 34.3). If the patient has already been on antibiotics prior to collection of pleural effusion, diagnostic test results may not be reflective of disease and a nonseptic exudate may be seen. Many feline pyothorax infections are due to multiple organisms and common bacterial isolates in feline pyothorax include *Pasteurella* spp., *Clostridium* spp., *Fusobacterium* spp., *Bacteroides* spp., *Peptostreptococcus* anaerobius, *Porphyromonas* spp., *Prevotella* spp., and *Actinomyces* spp. In dogs, enteric organisms are more common than in cats and common bacterial isolates include *Escherichia coli*, *Enterobacter cloacae*, *Pasteurella* spp., *Actinomyces* spp., *Streptococcus canis*, *Peptostreptococcus anaerobius*, *Bacteroides* spp., *Fusobacterium* spp., and *Porphyromonas* spp. Additional clinicopathologic findings seen in patients with pyothorax include elevated liver enzymes, electrolyte disturbances, hypoglycemia or hyperglycemia, hypoalbuminemia, mild anemia, and leukocytosis due to neutrophilia.

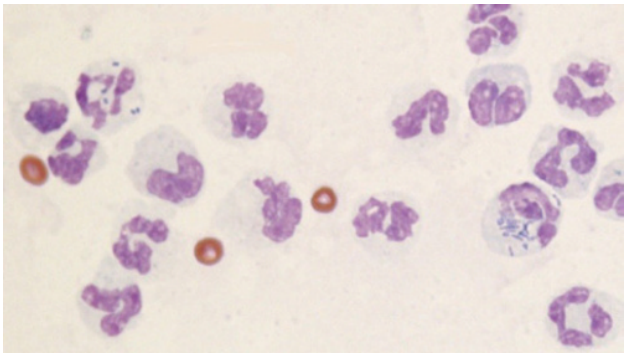


Figure 34.3 Pyothorax cytology. Pyothorax in a dog with a predominance of mature, mildly karyolytic neutrophils that sometimes contain bacilli or coccobacilli forms (Wright-Giemsa stain, 100× objective). *Source: Photo courtesy of Sarah S.K. Beatty, DVM, University of Florida.*

Imaging techniques include thoracic ultrasound, radiographs, and CT. In clinical practice, thoracic ultrasound is typically utilized initially because it is noninvasive, does not require sedation, and can be used rapidly in patients with respiratory disease for diagnosis and to localize an area for therapeutic thoracocentesis. With pyothorax, pleural fluid is often echogenic and wispy, fibrinous strands can be seen along pleural margins. Radiographs may be helpful once fluid has been removed to determine if an underlying cause can be identified, such as a lung mass lesion, focal pulmonary opacity, or foreign body; however, as previously mentioned, an underlying cause is rarely found. The use of CT is becoming more widespread in veterinary medicine but the role of CT in canine pyothorax is controversial. A retrospective study in dogs with spontaneous pyothorax showed that common CT findings include bilateral pleural fluid, pleural gas (due to preimaging thoracocentesis or thoracostomy tube placement), pleural thickening, pulmonary parenchymal abnormalities, and mediastinal involvement. Of the surgically managed dogs in this study, CT correctly predicted the extent of disease in only 62.5% and correctly identified the underlying cause in only 50%; therefore, surgical exploration remains the gold standard to identify underlying pathology.

Treatment includes administration of appropriate antimicrobials, intermittent or continuous thoracic drainage, thoracic lavage, and surgery. Intravenous broad-spectrum antimicrobials with adequate anaerobic coverage should be started once culture samples have been collected and adjusted accordingly based on culture and susceptibility results. Potentiated beta-lactams are reasonable first-line therapy because they have efficacy against *Actinomyces* spp., anaerobes, and some gram-negative organisms. Enrofloxacin is often added to improve gram-negative coverage while awaiting culture results. Deescalation of antimicrobial therapy should be

considered once susceptibility data are available. Medical management involves thoracocentesis alone (repeated as needed) or placement of unilateral or bilateral indwelling thoracostomy tubes with intermittent or continuous suction and thoracic lavage along with appropriate antimicrobial therapy and supportive care. In general, large-bore trocar or surgically placed thoracostomy tubes are preferred in larger patients; however, smaller thoracostomy tubes placed using a modified Seldinger technique have been reported for management of pyothorax in dogs. Surgical management involves exploratory thoracotomy, usually by median sternotomy, to lavage and debride the pleural space, and break down any adhesions causing pocketing of fluid, then insertion of thoracostomy tubes for postoperative care, in addition to appropriate antimicrobial therapy and supportive care.

Appropriate treatment of pyothorax is controversial and there is no consensus on ideal therapy for all cases. Failure of medical therapy or presence of a focal lesion (abscess, tumor, or granuloma), foreign body, or evidence of esophageal rupture found on imaging are indications for surgical management in dogs or cats. In dogs, some advocate for early surgical treatment regardless of whether an underlying cause is identified, with the premise being that any other infectious disease such as peritonitis, septic arthritis, or abscess is best treated by aggressive debridement and drainage. In a retrospective paper on medical versus surgical treatment canine pyothorax, medical management was 5.4 times more likely to fail compared to surgical treatment and more dogs were free of disease at one year if treated surgically. In contrast, other studies have not shown a survival benefit of surgery versus medical management and reported success of medical management has ranged from 29% to 100%. If *Actinomyces* spp. are suspected on cytology or cultured from dogs with pyothorax, surgical management is warranted because medical treatment has a high rate of failure and a grass awn foreign body is a likely underlying cause. In cats, medical management with indwelling thoracostomy tubes is reported to have a survival rate of 73–95%, whereas surgical management has been reported to have a 100% survival rate. Successful management of chronic pyothorax in cats with unilateral pneumonectomy has been reported.

With medical management alone or during the postoperative period, thoracic lavage is often recommended to facilitate drainage of exudative fluid; however, there are no large-scale canine or feline studies to evaluate outcome with this method. Theoretical advantages of lavage include minimizing bacteria and inflammatory mediators in the pleural space and dilution of exudative fluid, which could clog the thoracostomy tube. Potential disadvantages include electrolyte disturbances such as hypokalemia, which has been reported in a cat undergoing thoracic lavage, and nosocomial infection if aseptic technique is not followed. Pleural lavage is performed by slowly infusing 10–20 mL/kg of warmed, 0.9% saline into the pleural space, waiting 10–15 minutes, and then withdrawing the fluid. If bilateral thoracostomy tubes are in place, some advocate for using one side as an infusion port and the opposite side as a withdrawal port. Thoracostomy tubes are generally removed when fluid production decreases to 3–5 mL/kg/day, in addition to clinical improvement of the patient and cytologic confirmation of absence of infectious organisms. Time to resolution of disease is generally 5–8 days and patients should be rechecked frequently as recurrence is possible.

Chylothorax

Chylothorax is a syndrome characterized by the accumulation of chyle, the milky fluid consisting of lymph and emulsified fat formed in the small intestines during digestion, in the pleural space and is often idiopathic in nature. Additional reported causes include traumatic or surgical thoracic duct rupture, cranial vena cava thrombosis, lymphatic obstruction by cancer or fungal granuloma, cardiomyopathy, congenital defect, diaphragmatic hernia, peritoneopericardial diaphragmatic hernia, lung lobe torsion, pericardial effusion, tetralogy of Fallot, tricuspid dysplasia, cor triatriatum dexter, constrictive pericarditis, and heartworm disease. Although trauma has been a reported cause of chylothorax in the literature, it could not be experimentally reproduced in dogs by laceration or transection of the thoracic duct as the effusion resolved within 10 days. Reported neoplasms associated with lymphatic obstruction causing chylothorax include thymoma, lymphosarcoma, lymphangiosarcoma, and aortic body tumors. The rate of chyle production and drainage in normal dogs is approximately 2–4 mL/kg/h.

Most of the body except the right forelimb and right side of the head and neck drain into the thoracic duct in dogs and cats. Intestinal lymphatics drain chyle into the mesenteric lymph nodes, which then form larger ducts that continue on to form the cisterna chyli, which is a lymphatic reservoir located ventral to the first four lumbar vertebrae. The cisterna chyli continues cranially to become the thoracic duct and eventually empty into the brachiocephalic trunk. In dogs, the cisterna chyli and caudal thoracic duct are located on the right side of the mediastinum; however, the duct crosses from right to left in the mid-mediastinum to empty into the brachiocephalic trunk. In cats, the thoracic duct is typically only located to the left side of the mediastinum. Thoracic duct anatomy can vary within the same species. Obstruction of the thoracic duct or cranial vena cava causes lymphatic flow stasis and dilation. It is thought

that increased pressure causes chyle to leak out of dilated lymphatics, as would occur in other parts of the body with lymphedema. With cardiac disease, chylous effusion can develop due to impaired lymph drainage to the venous circulatory system. In addition, hepatic congestion occurs with heart failure, which significantly increases hepatic lymph production and therefore thoracic duct flow. Pathophysiologic mechanisms for idiopathic chylous effusion are not well elucidated.

Chylothorax can occur in any breed or age of dog or cat, with Afghan hounds being overrepresented because of the association between lung lobe torsion and chylothorax. Clinical signs are those typical of pleural effusions, including lethargy, hyporexia or anorexia, weight loss, tachypnea, cough, and paradoxical or restrictive breathing pattern. Diligent cardiothoracic auscultation should be performed because of the association between cardiac disease and chylothorax. Additional physical examination findings include muffled heart sounds, decreased ventral lung sounds, and increased dorsal lung sounds. There are no consistent laboratory findings for dogs or cats with chylothorax.

Diagnosis of chylothorax is based on examination of pleural fluid, which grossly appears milky white to opaque pink-white, but can vary depending on nutritional status of the patient. Pleural fluid from thoracocentesis should be saved in EDTA for cytologic examination and a serum separator tube for triglyceride concentration analysis. The fluid is most often classified as an exudate, but may be classified as a modified transudate depending on the protein and cell count. Cytologic examination shows predominantly lymphocytes, small numbers of macrophages, and nondegenerate neutrophils, which increase in numbers with chronicity of pleural effusion (Figure 34.4).

Definitive diagnosis is made by demonstrating higher triglycerides in pleural fluid than in serum samples, collected at the same time. If the effusion triglyceride concentration is >100 mg/dL, chylomicrons are seen microscopically on a wet-mount preparation, pleural cholesterol concentration is less than serum cholesterol concentration, or Sudan stain verifies lipid in the sample, then it is also classified as chylous. Once the diagnosis of chylothorax has been made, additional diagnostics, including complete blood count, chemistry profile, heartworm test, thoracic radiographs, thoracic ultrasound, echocardiogram, thoracic CT, +/− abdominal imaging, should be considered to determine if an underlying disease can be found. Cats should also be tested for retroviral diseases.

Treatment of chylothorax should be directed at the underlying disease but as the disease is often idiopathic, targeted treatment is rarely possible. Resolution of respiratory distress by removing the pleural effusion should be initial treatment, regardless of etiology. Chylous effusion is rich in lymphocytes, protein, lipid, and electrolytes and removal of large quantities of chylous effusion can cause hypovolemia, hyponatremia, hyperkalemia, hypoproteinemia, lymphopenia, weight loss, and immunosuppression. Conservative medical treatment involves pleural evacuation and nutritional management. Surgical treatment for idiopathic chylous effusion involves ligation of the thoracic duct with or without various adjunctive procedures including subtotal pericardectomy, cisterna chyli ablation, and thoracic omentalization.

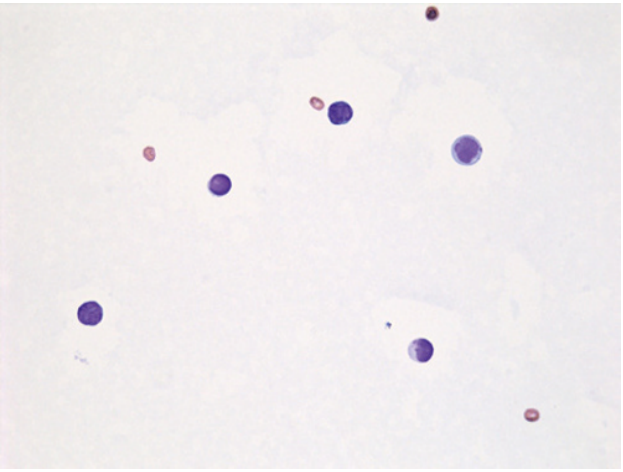


Figure 34.4 Chylothorax cytology. Chylothorax in a cat consisting of a mixture of mostly mature small, well-differentiated lymphocytes and intermediate-sized lymphocytes. One lymphocyte has smudged chromatin (*top, right*), a sign of partial degradation (Wright-Giemsa stain, 50× objective). *Source:* Photo courtesy of Sarah S.K. Beatty, DVM, University of Florida.

Diets low in fat have been recommended for medical management of chylothorax in dogs and cats to decrease the volume of chyle production and therefore flow through the thoracic duct; however, this has not been experimentally validated in dogs or cats. Rutin is a commercially available benzopyrone nutritional supplement used in humans for treating lymphedema and commonly recommended for medical management of idiopathic chylothorax, although no proven beneficial effects have been demonstrated in dogs and cats. Theoretical beneficial actions of rutin include edema uptake by lymphatic vessels, reduction of blood vessel permeability, and enhancement of tissue macrophage number and function to promote phagocytosis of protein in chylous fluid. Octreotide, a somatostatin analogue, inhibits biliary, pancreatic, and gastric secretions, and is recommended in humans with chylothorax to decrease thoracic duct flow; however, use in dogs and cats requires further research.

Prior to surgical treatment, some form of thoracic duct imaging is typically recommended to allow for surgical planning given the anatomic variation within and between species. Mesenteric lymphangiography, or the use of aqueous contrast material injected into a

mesenteric lymph node to highlight the thoracic duct, has been utilized for over 30 years in veterinary medicine to guide surgical planning and assess postoperative success. Mesenteric lymphangiography is an invasive procedure as it requires an exploratory laparotomy and injection of contrast medium into a mesenteric lymphatic vessel or lymph node, followed by radiographs or CT under general anesthesia; therefore less invasive procedures have since been developed for thoracic duct imaging. More recent minimally invasive imaging modalities include percutaneous mesenteric lymphadenography, laparoscopic mesenteric lymphadenography, percutaneous popliteal lymphangiography, and subcutaneous or submucosal lymphography, and CT has largely replaced conventional radiography as the ideal imaging technique.

Surgical treatment is recommended if chylothorax is persistent despite medical therapy because chyle is inflammatory and can cause severe fibrosing pleuritis or pericarditis. Thoracic duct ligation at the entry point of the duct into the thorax is the most commonly performed surgical technique for dogs and cats with idiopathic chylothorax. The premise behind thoracic duct ligation is to create a stimulus for new lymphaticovenous connections to the caudal vena cava or azygous vein outside the pleural space, thereby bypassing the thoracic duct and preventing intrathoracic flow of chyle. Surgical approach to the thoracic duct can be through a caudal intercostal thoracotomy, paracostal or ventral midline celiotomy with transdiaphragmatic extension, median sternotomy, or using thoracoscopy.

Several adjunctive surgical procedures have been combined with thoracic duct ligation in an effort to increase success rate of treatment. Cisterna chyli ablation was developed because hypertension within the cisterna chyli is thought to cause collateral lympathic vessels to form around the thoracic duct ligation site. Adjunctive subtotal pericardectomy is rationalized because chronic chylous effusions can cause pericarditis, which in turn can increase right-sided venous pressure and possibly impede chyle drainage from new lymphaticovenous anastomoses. Other adjunctive or alternative procedures are thoracic omentalization to provide lymphatic drainage, pleurodesis to abolish the pleural space, and cisterna chyli and thoracic duct embolization, with the latter being a salvage procedure if previous surgical attempts have failed. Surgical (conventional or thoracoscopic) success rates vary between 50% and 100% in dogs and 14.3% and 80% in cats. Persistence of chylous or nonchylous pleural effusion is the most common surgical complication. If surgical treatment fails, then implantation of an active pleuroperitoneal shunt or PleuralPort device should be considered to manage long-term effusion.

Hemothorax

Hemothorax is defined as an exudative effusion in the pleural space with a PCV that is at least 25% of peripheral blood. Iatrogenic hemorrhage during thoracocentesis should be suspected if the sample contains platelets and lacks erythrophagocytosis on cytology. In general, causes of hemothorax can be divided into coagulopathic and noncoagulopathic. Anticoagulant rodenticide toxicity is the most common cause of coagulopathic hemothorax in veterinary patients but disorders of primary hemostasis could also result in hemothorax. Reported noncoagulopathic etiologies include neoplasia, thoracic trauma, lung lobe torsion, pancreatitis, pulmonary parasitic disease (*Spirocerca lupi*, *Dirofiliaria immitis*, or *Angiostrongylus vasorum*), esophageal foreign body, and pulmonary infarction. Therapeutic thoracocentesis should only be performed in patients with hemothorax if respiratory distress is present on physical examination because most of the blood will be reabsorbed once the underlying cause is treated. Coagulation tests should be performed prior to thoracocentesis and blood products should be readily available. Fresh frozen plasma should be administered to coagulopathic patients with hemothorax, prior to or during therapeutic thoracocentesis, if this is deemed necessary on patient evaluation. Thoracic ultrasound, echocardiography, and CT may be utilized to determine the underlying cause along with standard blood tests, heartworm test, and fecal examination. Treatment is directed at the underlying cause and emergency surgical treatment may be necessary in some dogs or cats that are nonresponsive to conservative management.

Bilothorax

Bilothorax is the accumulation of a nonseptic, exudative effusion high in bilirubin within the pleural space and is rare in both veterinary and human medicine. It has only been reported in a few veterinary patients, all of which had recent hepatobiliary trauma (gunshot wound or penetrating trauma) or biliary surgery. In one cat, the penetrating trauma was iatrogenic; pleurobiliary fistulae occurred secondary to thoracotomy tube placement. The theorized mechanism of bilothorax formation is from pleurobiliary formation, with a presumptive diaphragmatic incongruity; however, bile can also be carried across an intact diaphragm by way of the lymphatic system. Diagnosis is confirmed if the ratio of bilirubin in pleural fluid to serum is greater than 1:1. Given the rarity of bilothorax, optimal treatment is controversial. Medical management by placing thoracostomy tubes with frequent pleural fluid drainage is recommended to minimize bile pleuritis. If medical management fails, surgical exploration is recommended. Bilothorax in dogs and cats appears to have a good prognosis, with a combined 100% survival rate of currently reported cases.

Conclusion

Pleural effusion is a common consequence of several underlying pathophysiologic processes in dogs and cats. Historical findings can be acute or chronic and clinical signs are variable, with many dogs and cats presenting with a primary complaint related to lethargy, hyporexia, and/or respiratory distress. A thorough diagnostic approach is often needed to determine the underlying disease and subsequently guide treatment options and overall prognosis.

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Section 5

Critical Care Medicine

35

Approach to the Patient in the Critical Care Setting

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Patients presenting to a veterinary emergency room represent a diverse array of illness and injury, ranging from mild to life threatening. The use of a triage system allows these patients to be systematically evaluated and prioritized based on presenting signs, history, and initial vital parameters. While no triage system is perfect, success is enhanced when staff are well trained. Every facility and emergency team should have a standard triage system, appropriately trained staff to perform triage, and a reliably equipped area to allow for efficient and prompt care of these patients' needs.

A clinician's relationship with a critical patient often begins upon presentation to the hospital or, in the case of a referral center, upon admission to the intensive care unit (ICU). As the direct definition of the word "critical" states, a critical patient is one that is at a stage of disease when an abrupt change for better or worse may be expected, or that has an illness or condition involving danger of death. Due to this unstable position, these patients require intense and continuous assessment and care and may benefit from consultation with a critical care specialist.

Physical Exam

A thorough initial physical exam, as well as frequent sequential exams, should be performed with the goal of promptly identifying current and evolving problems. Advanced diagnostics may become necessary in order to fully illuminate clinical findings but should never be used in place of a physical exam. While each clinician should have a routine by which they approach an exam, it may be required that the order of the exam be varied in critically ill patients, based on each patient's current condition and stability. Care must be taken to ensure that all systems are assessed due to possible variation in exam sequence. The exam may need to be performed in multiple phases to allow for patient comfort and safety.

Due to the critical condition of these patients, initial exam time should be spent on evaluating critical systems, particularly airway and breathing, heart and circulation, and neurologic status. For patients in respiratory distress, brief attempts at an exam may need to be interspersed between periods of rest in an oxygen chamber. Observation of the patient's respirations with attention to chest wall and abdominal movement may also provide information as to the cause of distress. Emphasis should be placed on thoracic auscultation to help discern the cause of distress, noting stridor, air movement or increased/decreased lung sounds. If the patient is not breathing or is ineffectively moving air, intubation and manual ventilation is required.

The heart should be ausculted while peripheral pulses are palpated. If heartbeat and pulses are absent, CPR must be instituted immediately (see Chapter 37). If the heart is beating and pulses are absent or irregular, further investigation and intervention are required to restore effective circulation. During heart auscultation, the heart rate and rhythm should be noted and heart sounds should be evaluated for presence of murmurs or muffled nature.

The patient's neurologic status should be evaluated and continuously monitored for alterations or deterioration. Particularly with trauma, signs of spinal cord injury should be sought and appropriate stabilization initiated prior to further manipulation of the patient. If traumatic brain injury is suspected, efforts to increase cerebral perfusion and decrease intracranial pressure (ICP) should be instituted, including blood pressure support, head elevation, and minimal jugular vein occlusion. Judicious IV fluid therapy is recommended to restore blood pressure to a minimum of a systolic of 90 mmHg or a mean of 60 mmHg.

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Occasionally, emergency interventions are necessary at the time of examination to stabilize the patient so that further examination and diagnostics can be performed and an overall treatment plan composed. If it is possible to complete a comprehensive exam at the time of initial evaluation, it should done.

History

A complete history is required for appropriate care of a critical patient. During triage and emergency presentation, the need for speed and efficiency often prevents the gathering of a thorough history. Once the patient's condition allows, further history to be discovered includes past medical problems, past and recent surgical interventions, origin and travel history, and general wellness and preventive care (vaccines, flea/tick/parasite prevention) schedule. Medications administered by the owner should be determined, with specific questioning about vitamins, supplements, and over-the-counter medications. Efforts should be made to obtain copies of medical records from other veterinary facilities where the patient has been treated recently and in the past. These records should be carefully reviewed to identify areas in the patient's history that the owner may have forgotten or misunderstood.

Assessment

After the history and physical exam have been completed, time should be taken to document the information and to form an active problems list. The initial list may consist of an identified problem without an underlying cause. Initial therapeutic interventions directed at the current problem(s) should be initiated and the problem list and eventual diagnosis list updated as indicated by response to therapy or results of additional diagnostics. While a written problem list is commonly used by beginning clinicians and then discarded as clinicians gain experience, with complicated cases it remains essential to ensure best patient care.

Record Keeping

Not only are formal medical records required by law, they help the clinician keep the case documented and organized and assist in transfer between clinicians and facilities. Medical records also provide information for follow-up care after discharge and in the future. The medical record should consist of the presenting history and physical exam, a problem list, a diagnosis list, and results of laboratory and imaging procedures. For the duration of hospitalization, a minimum of one physical exam should be documented daily as well as an updated problem/diagnosis list and an updated treatment and diagnostic plan. The ideal medical record will also document communications between the treating veterinarian and owner and any consulting veterinarians that have been involved.

Client Communication

The assessment and medical management of a critical patient are complicated and challenging enough. Adding to the difficulty is the need for the clinician to communicate effectively and compassionately with the owner. As the case evolves, the client needs to be informed of the working diagnosis, financial costs, and short- and long-term prognosis for the current condition. Apprising the owner of the risks and benefits of each proposed treatment or therapy is necessary in order for them to make an informed decision. As many of these patients are unstable, a CPR resuscitation code is a required topic of conversation to ensure that the owner's wishes are followed in the event of an arrest. Detailed written client communications should be kept as part of the formal medical record. These notes help all clinicians involved with a case to know what has been discussed and when. They are also invaluable should a case go to litigation.

Referral

When treating a critically ill patient, a large consideration is whether the current facility can offer the patient and client the level of care that they need and want. While many facilities may be able to meet the minimum standard of care, it is always best to inform the owner of the option of referral, making sure to communicate the pros and cons of transfer as well as the expected financial cost of treatment at another facility. While some owners may opt to not pursue referral, many will elect to transfer to a hospital that has 24-hour doctor care or other advanced capabilities. For many general practitioners, referral to a 24-hour facility for any patient requiring overnight IV fluids or observation is common. Cases may also need referral for advanced diagnostics including imaging (ultrasound, computed tomography, magnetic resonance imaging), advanced surgical procedures (soft tissue and orthopedic), or for advanced therapeutics (long-term ventilation, transfusion, dialysis).

Prior to referral of critically ill patients, the treating clinician should call the intended receiving facility and speak to the specialist who will be taking control of the case to ensure the transfer is made as safe and efficient as possible. All available medical records should be copied and should accompany the pet in a hard copy format.

The "Rule of 20"

In addition to serial physical exams and frequent reevaluation of the active problem list, there are a multitude of critical parameters that need to be evaluated at least daily in the critical patient. Developed by Rebecca Kirby, a founding Diplomate of the American College of Veterinary Emergency and Critical Care, the "Rule of 20" provides a comprehensive tool to guide the continuous evaluation and integration of a patient's organ systems, laboratory findings and treatment and many critical care specialists find it useful to refer to the "Rule of 20" on a daily basis with critically ill patients. Each element will be discussed below, many of which will be covered in detail in other chapters.

Fluid Balance

Fluid therapy is a common treatment in critical patients with a goal to reestablish and maintain hydration and to ensure circulating volume is maintained. Often dehydration and hypovolemia require rapid fluid replacement in the form of boluses. After initial volume expansion and rehydration, each patient's "maintenance" fluid needs will differ due to underlying conditions, ongoing losses, and variations in metabolism. Each patient will also have a unique ability to tolerate administered fluids. The consequences of overhydration or inappropriate fluid redistribution include pulmonary edema, peripheral edema, and third spacing of fluids within body cavities. Assessment of response to administered fluids requires monitoring of many parameters, including mucous membrane color and moistness, skin turgor, heart rate, and body weight. Each of these parameters should be assessed several times per day. Monitoring of blood pressure and urine output can provide additional information on a patient's needs. Monitoring of central venous pressures and changes in blood gas variables (lactate, base deficit) are used for advanced monitoring of fluid therapy.

Blood Pressure and Perfusion

There are many methods to monitor blood pressure, including direct (via an arterial catheter and pressure transducer) and indirect (Doppler and sphygmomanometer or oscilllometric measurements) options. A good general goal is to maintain a mean arterial blood pressure >60 mmHg and a systolic blood pressure >90 mmHg for optimal organ and tissue perfusion. Hypotension that is nonresponsive to fluid therapy may indicate the presence of an underlying acid–base or electrolyte disorder or the need to begin therapy with a vasoactive agent. Central venous pressure and lactate monitoring can provide additional information on the need for vasopressor therapy. While less commonly encountered clinically, monitoring for and treatment of hypertension are useful to prevent complications including retinal detachment, neurologic impairment, and end-organ injury.

Cardiac Function

Heart function should be evaluated not only by heart rate and rhythm but also ability to effectively pump blood forward through evaluation of peripheral limb temperatures and capillary refill time. Electrocardiographically confirmed arrhythmias should be treated if perfusion is compromised. Echocardiography is helpful in identifying underlying structural heart disease as well as visualizing cardiac filling and contractility. Additional treatments directed at optimizing cardiac function, including IV fluids, inotropic support or afterload reduction, should be introduced as indicated.

Albumin

Albumin is a blood protein produced by the liver that plays an essential role in a multitude of physiologic processes, including fluid balance, drug transport, tissue healing, and coagulation. Synthetic colloids can be used to maintain fluid in the intravascular space but they do not substitute for albumin's other roles in the body and may be associated with acute kidney injury. Albumin levels <2 g/dL have been associated with a poor prognosis in critically ill patients and may indicate the need for replacement with plasma (frozen or fresh frozen) or canine albumin transfusions.

Oncotic Pull

Adequate oncotic pressure is required to maintain appropriate intravascular volume and prevent interstitial fluid loss that can propagate hypovolemia and edema formation. Oncotic pressure changes in direct correlation with albumin concentration and can therefore be augmented with administration of natural colloids.

Oxygenation and Ventilation

Oxygenation can be assessed by arterial blood gas measurement (PaO_2) or pulse oximetry (SpO_2), and allows a clinician to evaluate how well a patient is moving oxygen into the blood. A PaO_2 <80 mmHg or a SpO_2 <96% indicates the need for supplemental oxygen which can be provided by flow-by oxygen, nasal oxygen cannula, an oxygen chamber or endotracheal intubation with 100% oxygen. Ventilation is evaluated by assessing the arterial $PaCO_2$ or indirectly by using end-tidal CO_2 concentration. End-tidal CO_2 monitoring can be used on intubated as well as nonintubated patients using a tight-fitting facemask or a nasal cannula. In situations of hypoventilation, hypercarbia ($PaCO_2$ >60 mmHg) should be treated with supplemental oxygen and mechanical ventilation if needed. Repeated measurements are required to monitor response to therapy.

Glucose

Ideally, glucose should be maintained in the normal range (75–120 mg/dL). Hypoglycemia can manifest as peripheral weakness, altered neurologic function (obtundation, stupor or seizures), and hypotension. Severe infection, synthetic liver failure, neoplasia, and hypoadrenocrticism are common causes of hypoglycemia in critical patients. Young and undernourished animals are predisposed to developing hypoglycemia. Administration of supplemental dextrose in IV fluids is indicated if normoglycemia cannot be maintained via enteral nutrition. Hyperglycemia due to diabetes requires exogenous insulin administration to prevent ketoacidosis, hyperosmolarity, and dehydration due to osmotic diuresis. Hyperglycemia associated with trauma is associated with a worsening prognosis. Although well described in the human medical literature, the benefits of tight glycemic control for hyperglycemia in veterinary medicine are unproven and should only be attempted at a 24-hour critical care facility.

Electrolyte and Acid–Base Balance

Critically ill patients often have significant acid–base and electrolyte disorders that contribute to their overall clinical condition. Important electrolytes to be monitored include sodium, potassium, ionized calcium, chloride, magnesium, and phosphorus. Many disease states are associated with particular electrolyte arrangements and care should be taken to customize monitoring to an individual patient's signs and diagnosis. Critical patients should have electrolytes monitored at least once daily while on IV fluid therapy. Acid–base derangements can be the result of metabolic or respiratory conditions, or a combination of the two. In addition to pH, PCO_2 and HCO_3^-, lactate levels should be evaluated to assist in identifying the origin of an acid–base disorder. Most hyperlactatemia is the result of impaired oxygen delivery and rapid resolution is generally associated with better patient outcome.

Mentation and Intracranial Pressure

Close monitoring and documentation of a patient's mentation is necessary to allow prompt detection of any changes that may indicate progression of intracranial disease or a hemodynamic or metabolic disease with neurologic consequences. Elevated ICP is common in patients with head trauma and inflammatory encephalitides. It should be remembered that not all mentation changes are due to structural changes or ICP alterations. Hypotension and hypoglycemia can manifest as altered mentation. Hepatic diseases resulting in encephalopathy can lead to neurologic signs that may indicate progression of a disease process.

Coagulation

Impaired coagulation in the critical patient due to thrombocytopenia or clotting factor deficiency is easy to identify. It is more difficult to evaluate patients for hypercoagulability, which can result in thromboembolic sequela and secondary complications. Hypercoagulability can be due to systemic inflammation from trauma, infection or neoplasia as well as a multitude of underlying metabolic and endocrine disorders. Advanced diagnostics, including thromboelastography, are required to fully evaluate a patient for hypercoagulability. As underlying conditions predisposing to a hypercoagulable state are identified, clinicians should weigh the benefits versus risks of initiating thromboprophylaxis.

Red Blood Cell and Hemoglobin Concentration

Adequate oxygen delivery is important for all patients, but is especially crucial for critical patients whose systems are already taxed by underlying conditions. Hemoglobin is necessary for oxygen transport and delivery and red blood cell transfusions should be administered in response to clinical signs associated with anemia, including tachycardia, increased respiratory rate, hypotension, and weakness. While there is no standard transfusion "trigger" point, each patient should be individually assessed for the need for a transfusion based on clinical signs, underlying disease processes, and anticipated losses. Evaluation of venous oxygen saturation may allow early identification of inadequate oxygen delivery.

Utilizing a goal-directed approach, red blood cell transfusion to maintain a hematocrit >30% is recommended if central venous oxygen saturation ($S_{cv}O_2$) >70% is not maintained despite supplemental oxygen and normalization of intravascular volume and systemic blood pressure.

Renal Function and Urine Output

Kidney function should be frequently evaluated in critically ill patients as hypotension, thrombosis, and nephrotoxic medications can cause temporary or permanent injury resulting in renal insufficiency. Urine output should be at least 1 mL/kg/h but oliguria should be evaluated in light of fluid input for an individual patient. An indwelling urinary catheter, and recording fluid in and fluid out, assists in evaluating a patient's overall fluid status. In addition to urine output, insensible losses, losses from surgical drains, chest tubes or wounds should also be accounted for. Commonly accepted insensible loss rates are 10–20 mL/kg/day. Fluid input includes IV fluids (crystalloids and colloids) as well as nutritional support in the form of parenteral or enteral nutrition. In patients with possible renal impairment, close monitoring of fluid ins/outs may assist in maintaining fluid balance. Daily monitoring of serum BUN and creatinine is recommended to detect potential renal injury early. Especially in patients with normal renal values at the time of presentation, even mild changes in BUN or creatinine (even within the reference range) can be a harbinger of renal injury or multiorgan failure. Early detection and aggressive treatment can have a dramatic impact on patient outcome. Analyzing urine for casts, glucose, and protein is also used to identify renal injury and dysfunction.

Immune Status and Antibiotic Coverage

Critically ill patients are often battling infections and may have overextended or overwhelmed immune systems. Empirical antibiotic therapy is recommended for patients with suspected infections and antibiotic selection should be based on presumed site of infection, likely organism involved, and hospital surveillance profiles. When empirical antibiotics are used, initial broad-spectrum coverage is recommended with deescalation based on results of culture and sensitivity panels. In addition to bacterial infections, clinicians should be aware of the concern for rickettsial, protozoal, fungal, and parasitic infections that may require additional antimicrobial therapies. In all critical patients, care should be taken to practice aseptic techniques when examining and treating them. Clinicians and nurses should practice good hygiene with frequent hand washing. Exam gloves should be worn at all times when handling any patient and the use of isolation gowns should be considered if the patient is severely immunocompromised.

Gastrointestinal (GI) Motility and Integrity

Many underlying conditions can result in gastric and intestinal ileus and compromise of the GI mucosal barrier. Decreased intestinal motility results in stasis of intestinal contents and overgrowth of normal bacterial flora. An altered mucosal barrier results in an increased risk for bacterial translocation and subsequent sepsis. Gastric and small intestinal stasis may result in vomiting, while large intestinal derangements may lead to diarrhea, which can create and/or exacerbate hypovolemia. Medical intervention (promotility medications, physical activity) to increase GI motility and protect the mucosal barrier is recommended. If possible, enteral nutrition is recommended to maintain enterocyte health, decrease villous atrophy, increase GI motility, and improve mucosal integrity.

Drug Metabolism and Dosage

Medication doses and routes should be reviewed daily for accuracy, safety (side-effects, metabolism, and drug interactions) and continued necessity. In the face of altered renal or hepatic function, it may be prudent to reduce the dose or increase the interval of medications to decrease the risk of toxicity and side-effects. Highly protein-bound drugs should be used with caution in hypoalbuminemic patients due to the potential for higher than expected plasma levels.

Nutrition

All attempts should be made to provide appropriate nutritional support to critical patients in order to avoid a negative energy balance contributing to organ dysfunction, delayed healing, immunocompromise, and GI dysfunction. Enteral nutrition is ideal and can be accomplished by voluntary patient eating or feeding tubes (e.g., nasogastric, esophageal, gastrostomy or jejunostomy tubes). Total or partial parenteral nutrition is an option for providing nutritional support to patients with a contraindication to enteral nutrition (severe ileus, intractable vomiting, malabsorptive conditions).

Analgesia

Appropriate pain management is necessary to improve patient comfort and decrease the secondary effects of pain. Common signs of pain include increased heart rate, agitation, and discomfort upon palpation of wounds. Multiple pain scoring systems have been validated for

use in veterinary medicine and provide a systemic and repeatable approach to evaluating pain and a patient's response to pain medications.

Nursing Care and Patient Mobility

While focusing on the medical care of a critically ill patient, it is easy to overlook patient comfort and husbandry. In patients that require extensive nursing care, these measures may be skipped due to the time and staffing they require, especially in larger patients that may require multiple people to move and support them. Many of these patients are nonambulatory and physical therapy should be provided several times a day. Passive range of motion of limbs keeps muscles and joints flexible and can improve circulation. For patients with peripheral limb edema, tissue massage from distal to proximal can assist in resolution. Deep bedding and frequent repositioning are necessary to prevent pressure sores, lung atelectasis, and edema formation. Standing sessions are useful and allow patients to attempt supported ambulation. If possible, underwater treadmill therapy is an option for assisted mobility to increase flexibility, strength, and circulation. Efforts should be made to frequently take nonambulatory patients out of their cages and, if feasible, outside for a "visual vacation." For patients with lung consolidation from pneumonia or other conditions, positional coupage based on afflicted region can be useful in resolving consolidation. In patients with surgical incisions or traumatic tissue injury, cold laser therapy can be considered to improve tissue blood supply and increase healing. Patients should be diligently cleaned to prevent skin irritation and burns from urine and feces soiling.

Bandage and Wound Care

All IV catheters should be routinely changed and catheter insertion sites evaluated for infection and inflammation. Each facility should establish a protocol for the placement and maintenance of peripheral IV catheters and advanced catheters such as central IV catheters and arterial catheters. At a minimum, daily bandage changes should be required but other considerations include acceptable indwelling duration, flushing/locking procedures, level of sterility during placement and handling, and a protocol for investigation and treatment of suspected catheter site infections. Indwelling urinary catheters also require set protocols for placement and maintenance including prepuce/vulva flushing, collection system handling/changing, acceptable indwelling duration, and a protocol for investigation of suspected infections due to catheterization. Bandages placed on wounds require frequent changing to evaluate for changes in underlying wounds. During critical illness, peripheral edema can rapidly develop and cause wraps or bandages to become tight and constricting. Soiled or wet bandages should be immediately changed as they provide an excellent source of infection. Wounds and incisions should be closely monitored for healing and any changes that occur, including bruising, odor, swelling, and discharge, should be immediately investigated.

Tender Loving Care

Amongst all the medications, procedures, and treatments, time should be taken to simply sit with a patient to provide comfort and affection. Once again, this is an area that is easy to omit when a patient has intense medical treatments and support staff is spread thin. Patients that require many treatments are often mislabeled as being "difficult cases" rather than appreciated for the multiple levels of complex care they require to support their severe disease states. Many times patients will only eat when being petted. Owner visits should be encouraged and efforts made to allow visits to occur outside the hospitalization area to allow patients stress-free periods during which they may eat or rest. In 24-hour care facilities, efforts should be made to allow the patients to have treatment-free periods during which uninterrupted rest can occur. Clinicians should attempt to arrange treatments in groupings to establish greater intervals of time when the patient is not being handled or interacted with. Especially during evening hours, further emphasis should be placed on treatment-free periods. During these evening times, lights should be dimmed and attempts made to decrease ambient noise. There may be benefit to playing relaxing music such as soft classical or nature sounds.

Euthanasia

For many critical patients, compassionate euthanasia may be the most humane treatment available. As a case progresses, lines of communication regarding euthanasia should remain open between owners and the medical staff. Despite being common in veterinary medicine, some owners may not know it is an option for their pets. Broaching the subject of euthanasia can be difficult and needs to be handled with special attention. Even in cases with a grave or guarded prognosis, owners may not consider euthanasia due to religious or ethical beliefs.

Conclusion

Each critical patient will require a unique and customized approach to every element of their care. While the

care for these cases is more complicated, with it comes a greater feeling of success when a patient is discharged to its family. Many critically ill patients will not have a positive outcome and often the deciding factor in outcome is determined by the attention provided to the patient and owner. It is easy to influence a client to terminate care for a patient with a guarded prognosis, but experience and clinical knowledge should be used to assist clients in making the best decision for them and their pet.

The care of critical patients can be exhausting for the entire medical team. Clinicians should take the time to frequently discuss the details of these cases with support staff to ensure that they understand the importance and motivation behind medical treatments and owners' decisions.

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36

Fluid Therapy

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Intravenous fluids are a commonly used treatment in small animal medicine. A full understanding of the indications and potential fluid choices allows clinicians to reap the maximum benefit from fluid therapy while minimizing possible complications.

Vascular Access

Catheter Types

Fluid therapy can be administered via a number of different routes, including intravenous, subcutaneous, and intraosseous. In order to administer fluids intravenously, venous access must first be established. Most commonly, this involves the placement of a catheter within a peripheral vein or within the jugular vein. There are a variety of catheter types currently available, including winged needle (butterfly catheters), over the needle, through the needle and catheters that are placed using a guide wire. When placing an intravenous catheter, a number of questions should be considered to ensure the most appropriate catheter is selected.

Butterfly-type catheters are rigid needles with a plastic "butterfly" at the needle hub to make handling easier. The needles are then attached to a length of tubing that can be connected to a syringe for bolus drug delivery or blood sample collection. This type of catheter is useful for instances where the catheter does not need to be maintained within the vein. An example would be an IV bolus injection of medication or a single episode of venipuncture to collect blood samples.

If a catheter needs to be maintained within a peripheral vein for any duration of time then an over-the-needle type catheter is most commonly used. Theses catheters are relatively easy to place and can be maintained within a vessel for a number of days with diligent nursing care. If placed in the critically ill, emergent or surgical patient, the short length of the catheter coupled with a reasonable diameter allows for rapid bolusing of fluids. This type of catheter is usually secured in place with medical tape.

Through-the-needle catheters are also widely available. This type of catheter tends to be greater in length and is used when central venous access is desired for repeated blood sampling or the administration of a hyperosmolar solution such as total parenteral nutrition. Catheters placed using a guide wire can be single lumen or multilumen and are placed into a central vein. This type of catheter allows for blood sampling, fluid administration, including the concurrent administration of noncompatible fluids through separate lumens, as well as the administration of hyperosmolar solutions that would cause significant phlebitis if administered peripherally. Placement of a central venous catheter also allows for monitoring of central venous pressure in patients to guide fluid therapy.

Intravenous catheters may be made of a number of different materials, including polyurethane, Teflon®, and silicon elastomer (silastic). Polyurethane and Teflon catheters are most commonly used, as they are cost-effective and relatively easy to insert. Silicon elastomer (Silastic®) catheters are very flexible and less likely to result in catheter-related thrombophlebitis but they are more expensive and technically challenging to place. Silastic catheters are used for long-term catheterization, while Teflon or polyurethane catheters are reasonable choices for shorter term catheterization.

The placement of intravenous catheters is common in small animal veterinary medicine. Peripheral catheters are most commonly placed in the cephalic, medial or lateral saphenous or femoral vein. In some animals, the veins of the ear can also be used for catheterization. Central catheters are placed within the jugular vein or threaded from a peripheral vein into the vena cava. In order to preserve the integrity of the catheter and minimize discomfort and inflammation, catheters should not cross a joint. Common sense would also dictate that the

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patient's disease process might make one catheterization site preferred over another. An example is the parvoviral enteritis patient with voluminous diarrhea; a hind leg catheter should not be the first choice, as it would probably become soiled in short order.

The area selected for placement should be clipped and aseptically prepared, taking care not to abrade the skin, as this can increase the rate of catheter-related complications. In addition to preparing the patient, staff members should also wash their hands and wear gloves. Once the catheter is seated within the vein, it is flushed with sterile saline. There has been no proven benefit to using heparinized saline in lieu of sterile saline as a catheter flush. Peripheral catheters are secured to the limb with medical tape. It is common to suture central lines in place and then to protect them further with a bandage. Catheter sites should be kept clean and dry and inspected at least daily for evidence of inflammation.

Catheter-Related Complications

Catheter-related complications are common but can be minimized with relative ease. Any material used for an intravenous catheter will cause some inflammation within a vessel so it is important to diligently assess catheter sites for indication of not only infection but also thrombophlebitis. Catheter sites should be inspected daily for swelling, pain, or induration of the vessel. An indurated vessel will feel firm and ropey when palpated. It is also important to monitor patient response when infusing medications. As catheter integrity degrades, the animal may object when drugs are infused.

The possibility of infection or thrombophlebitis should be suspected in any patient who has an intravenous catheter and develops signs of infection or exhibits a reaction to injections that were previously well tolerated. A patient who develops a low-grade fever in hospital without another potential nidus of infection or inflammation should have all catheter sites promptly inspected. While in the past it has been recommended that catheters be removed after 72 hours to prevent infection, multiple studies have shown that the rate of infection does not increase if catheters are allowed to remain in place for longer periods of time and that it is more important to keep the area clean and the catheter dressing unsoiled.

Infiltration occurs when a catheter moves out of a vein into the surrounding tissue. Any fluids or drugs administered through the catheter are therefore infiltrated into that area instead of being delivered to the vein. Most commonly, infiltration is identified by swelling and tenderness at the catheter site. If vesicant medications are administered perivascularly, the term used is *extravasation*. The sequelae of extravasation can be more severe and may include heat, pain, redness, swelling, and induration. Sloughing of the skin and the perivascular tissue can then follow. If the catheter is a central line, it may not be immediately evident that the position of the catheter has changed. Infiltration of fluid in this instance can result in mediastinal or pleural fluid accumulation that can be severe enough to cause dyspnea.

The key to preventing catheter-related complications is vigilance. Place catheters away from joints and avoid using rigid materials, like a butterfly catheter, for prolonged infusion. Inspect the catheter site frequently. Before infusing drugs, aspirate the catheter for blood (a "flash") and then flush with saline to ensure proper placement and patency of the catheter.

Catheter foreign bodies occur when a portion of the catheter becomes free within a vessel and lodges (most commonly) in the heart or a pulmonary artery. Catheter foreign bodies may occur when catheters are accidently cut during removal or when a through-the-needle catheter is cut off by the introducer needle. It can also occur when an over-the-needle catheter is partially advanced and then replaced on the needle while seated within a vein. Infrequently, the shaft of a catheter can become disconnected from the catheter hub. These types of mishaps can be associated with serious complications, including cardiac perforation, endocarditis, pulmonary embolism, sepsis, and arrhythmias. Options for management of catheter foreign bodies include surgical retrieval, endovascular retrieval, or leaving the catheter *in situ*. In human medicine, attempted retrieval of the foreign body is preferred. Successful retrieval of intravascular foreign bodies using endovascular techniques has been reported in five dogs, a goat, and a horse.

Air emboli occur when air is introduced into the vascular system through a catheter. This can be seen when a central line is advanced into the thoracic cavity and the change in pressure draws air into the system. More commonly, air can be introduced through incorrectly prepared IV lines or when air is injected into rigid fluid containers to speed an infusion. Small emboli are usually clinically silent. Large air emboli can result in a dramatic increase in pulmonary vascular resistance followed by pulmonary edema formation and dyspnea. If a large enough bolus of air is delivered, the right ventricular outflow tract can be obstructed. If a central line is in place when an air emboli occurs, aspirating the air out of the heart is the best choice for treatment.

Body Fluid Compartments

Body Water Distribution

Approximately 60% of body weight is water. This percentage can change based on age, gender or body

composition. Both humans and dogs have been shown to have a decrease in total body water with age. Body composition also plays a role and it is useful to base fluid therapy recommendations on lean body mass as opposed to body weight. In the normally fleshed animal, the lean body mass is approximately 80% of total body weight. In obese patients, fat (which has a lower water composition than other tissues) is abundant, so lean body mass can be estimated as 70% of body weight. By contrast, in the underconditioned animal, measured body weight is equivalent to the lean body weight.

Total body water is further divided into body fluid compartments. The largest portion of total body water is found within the cells, with the intracellular fluid (ICF) compartment accounting for roughly two-thirds of total body water. The remaining one-third is found in the extracellular fluid (ECF) compartment. The ECF compartment is further divided into the interstitial space, which contains roughly 75% of the water of the ECF, and the vascular space, which contains the remaining 25% as plasma volume. While it is useful to describe total body water based on its location, it is important to remember that fluid balance is dynamic and movement between fluid compartments is occurring constantly.

Body fluids contain varying concentrations of solutes in addition to water. The ECF and ICF have vastly different solute concentrations but the total numbers of cations and anions in all body fluids must be equal to maintain electroneutrality. In the ECF, sodium is the major cation and chloride and bicarbonate are the most common anions. By contrast, within the cell, the most common cations are potassium and magnesium and the most common anions are phosphates and proteins. Body fluid compartments are dynamic and the relative volume within the fluid compartments is dependent on the number of osmotically active particles present within the space. The normal plasma osmolality (tonicity) is 300 mOsm/kg in the dog and 310 mOsm/kg in the cat. Approximately 95% of total serum osmolality in the normal animal results from the presence of sodium, potassium, chloride, bicarbonate, urea, and glucose while large molecules such as albumin have little effect on osmolality.

The body must balance daily fluid losses with intake. In addition to pathologic fluid losses, all animals have insensible fluid losses via the urinary tract, gastrointestinal tract, and respiratory system. When fluid and solutes are lost from the body, the relative effect on the different body compartments is dependent on the tonicity of the fluid lost. Lost fluid can be hypertonic to plasma, isotonic, or hypotonic. Usually fluid is lost from the ECF. When hypotonic fluid is lost from the ECF, the ECF becomes hypertonic relative to the ICF. Because the solutes (sodium, potassium, and chloride) are effective osmoles, the majority of equilibration will occur by the movement of water from the ICF to the ECF. This results in a decrease of the ICF volume but a bolstering of the ECF. An example of hypotonic fluid loss would be polyuria seen with renal disease. When isotonic fluid is lost, there is no change in the tonicity between the ECF and ICF. For this reason, there is no net fluid movement between fluid compartments and the volume lost results in an absolute decrease in the volume of the ECF. An example of isotonic fluid loss would be acute hemorrhage. Finally, in the case of hypertonic fluid loss from the ECF, the ECF becomes hypotonic relative to the ICF and water moves from the ECF into the ICF, which further exacerbates the volume loss. It is important to recognize that an animal can have hypovolemia without dehydration but dehydration cannot occur without some degree of hypovolemia.

Water Movement

Movement of fluid between body fluid spaces is governed by Starling's law.

$$\text{Fluid flux} = k_f\left[\left(P_c - P_i\right) - \left(\pi_c - \pi_i\right)\right]$$

In this equation, k_f is a filtration coefficient unique to each tissue bed that reflects the relative permeability of the capillary wall within that tissue bed, P_c refers to the hydrostatic pressure within the capillary and P_i refers to the hydrostatic pressure within the interstitium. Similarly, π_c and π_i refer to the oncotic pressure in the capillary and interstitium respectively. Recall that oncotic pressure differs from osmolality/osmolarity and refers to the force exerted by large, impermeant molecules to hold water within either the capillary or interstitial space. Clinically, oncotic pressure is referred to as colloid osmotic or colloid oncotic pressure (COP). The balance between these opposing forces determines the direction and degree of net fluid movement.

When fluids are administered too aggressively, the intravascular space is overexpanded. This results in an increase in hydrostatic pressure within the capillaries that exceeds the oncotic pressure in the vessels and favors the movement of fluid into the interstitium, which is composed of a meshwork of collagen and glycosaminoglycans as well as proteins and electrolytes in solution. There are three mechanisms, known as tissue safety factors, that prevent fluid accumulation within the interstitium and their relative importance varies between tissue types. As fluid moves in, the hydrostatic pressure rises rapidly due to the nondistensible nature of the interstitium and opposes further fluid accumulation. Opposition to the movement of fluid into the interstitium also occurs as interstitial oncotic pressure drops due

to dilution. Finally, as the hydrostatic pressure increases in the interstitium, lymphatic drainage is increased. If increased capillary hydrostatic pressure persists, however, these safety factors can be overwhelmed and the meshwork within the interstitium can be disrupted. When this occurs, the resistance to further fluid accumulation becomes minimal and manifests clinically as pitting edema, chemosis, and, in rare circumstances, pulmonary edema.

Fluid dynamics in pulmonary tissue have unique characteristics. The pulmonary capillary pressure is usually lower than in other tissues and the interstitial pressure is more negative (some tissues actually have a negative interstitial pressure) while the COP is higher than other tissues. The fact that the pulmonary capillaries are relatively permeable to protein contributes to this higher COP. In addition, the alveolar epithelial cells actively transport sodium into the interstitial space, promoting movement of fluid out of the alveolar space and into the interstitium. The net result of these characteristics is that fluid movement from the alveoli into the interstitium and then to the lymphatics is favored. This tendency is overcome when the pulmonary capillary pressure exceeds 25 mmHg, at which point fluid will accumulate within the alveoli. If the animal also has an increase in pulmonary capillary permeability such as occurs in sepsis or systemic inflammatory response syndrome (SIRS), or if the animal is hypoalbuminemic, pulmonary edema will occur at lower hydrostatic pressures.

Intravenous Fluid Types

In order to make logical choices with fluid therapy, it is important to understand the components and behavior of the different classes of intravenous fluids available in clinical practice.

Crystalloid Fluids

Crystalloid fluids are the most common type of fluids used in veterinary medicine. Crystalloids are defined as fluids containing electrolyte and nonelectrolyte solutes that are capable of entering all the body fluid compartments. They can further be described as "balanced" or "unbalanced." A balanced crystalloid has a composition similar to that of the ECF. An example would be lactated Ringer's solution (LRS) or Normosol-R®. An unbalanced crystalloid's composition does not mimic that of the ECF. An example would be 0.9% NaCl.

Crystalloids can also be described by their osmolarity. An isotonic crystalloid has an osmolarity similar to normal plasma osmolarity (300–310 mOsm/L) while the osmolarity of a hypotonic solution is less than that of normal plasma and a hypertonic solution is greater than normal plasma. An example of this can be seen with the different sodium chloride-based crystalloids: 0.9%NaCl is an isotonic crystalloid solution (308 mOsm/L), 0.45% NaCl is a hypotonic crystalloid (154 mOsm/L), and 7.2% NaCl is a hypertonic crystalloid (2464 mOsm/L).

Finally, crystalloids can be described as replacement fluids or maintenance fluids. The composition of these two categories is quite different and warrants a brief explanation. When a crystalloid fluid is administered intravenously, the majority of the volume given will move out of the vascular space and into the interstitium. When a 1 L bolus of an isotonic crystalloid is given, it can be anticipated that after one hour only 25% of the delivered volume remains within the vascular space. The majority of the delivered volume has moved into the interstitium and for this reason, a replacement fluid is designed to approximate the fluid composition of the ECF. By contrast, a maintenance fluid is designed to meet the ongoing insensible losses of the patient and has a lower sodium concentration and usually a higher potassium concentration. A unique crystalloid fluid that does not fall within the replacement versus maintenance classification scheme is 5% dextrose in water (D5W) that is composed entirely of dextrose and water. When given, D5W is effectively equivalent to administering pure water, as the dextrose is rapidly metabolized to CO_2 and water.

Specific clinical presentations may respond most effectively to specific crystalloid choices but in the majority of instances, a balanced, isotonic crystalloid is appropriate for initial fluid therapy. Some of the clinical presentations where one fluid may be preferred over another include hypochloridemic metabolic alkalosis and Addisonian crisis (0.9% NaCl) and urethral obstruction (LRS or Normosol-R), among others.

Additives such as 50% dextrose, potassium chloride, magnesium sulfate, and calcium gluconate can be incorporated into crystalloid fluids to meet specific patient needs; however, not all fluid additives are compatible with all isotonic crystalloids. Investigation into compatibility is required before fluid supplementation is undertaken. Certain crystalloids such as 0.9% NaCl and D5W are often used as carriers for a variety of drugs, including anesthetics, inotropes, vasopressors, and insulin, but compatibility should always be verified before administration.

Hypertonic saline is available in a variety of concentrations ranging from 3.0% to 7.5% and is a potent expander of the vascular volume. With an osmolarity of 2567 mOsm/L, 7.5% NaCl will effectively increase the extracellular fluid volume by five times the administered volume due to the movement of water from the intracellular and interstitial spaces into the intravascular space

in response to the profound osmotic gradient created. However, like other crystalloid solutions, the intravascular volume expansion will not remain for long if administered alone. For this reason, hypertonic saline is often combined with a synthetic colloid to extend the duration of effect. Because the action of hypertonic saline is dependent on movement of volume from the interstitial space to the intravascular space, it is relatively contraindicated in dehydrated patients. Hypertonic saline is a popular choice for small-volume resuscitation and is the preferred choice for the resuscitation of the hypotensive head trauma patient. In addition, it may also be used in patients with intracranial hypertension with, or in lieu of, mannitol.

Synthetic Colloids

Colloids are molecules of high molecular weight, which exert osmotic activity and thus promote the movement of fluid from the interstitium into the vascular space. Colloids can first be described as natural or synthetic. An example of a natural colloid is the albumin molecule. Synthetic colloids can further be divided into three classes: gelatins, dextrans, and hydroxyethyl starches (HES). The most commonly used class of synthetic colloid is the hydroxyethyl starches, which are plant-derived proteins that have undergone modification to prevent rapid degradation.

When describing hydroxyethyl starches, a number of parameters are used. First is the molecular weight, which affects the degree of "oncotic pull" exerted by the solution, with lower molecular weight solutions generally exerting a greater effect. Molecules in HES formulations tend to be polydisperse and can range in size from a few thousand to a few million kilodaltons. The distribution within a solution follows a bell-shaped curve. By convention, the molecular weight used to describe the solution is the average molecular weight.

The second parameter used in description of HES solutions is the degree of substitution, determined by measuring the number of substituted glucose molecules and dividing by the total number of glucose molecules. HES solutions with a higher rate of substitution resist hydrolysis more effectively than molecules with lower substitution rates and thus persist in the body for a longer period of time, extending duration of action. The rate of substitution is used to describe the fluid and while it is common in veterinary medicine to refer to all hydroxyethyl starches as "hetastarch," this is a misnomer; in fact, a substitution rate of 0.6 is termed a hetastarch, 0.5 is a pentastarch, and 0.4 is a tetrastarch.

The final parameter that can be considered when evaluating HES solutions is the carrier solution. Classically, the majority of HES solutions are provided in 0.9% NaCl. Some solutions are also available in balanced crystalloid solutions such as LRS.

The use of synthetic colloids is somewhat controversial. Studies in both the human and veterinary literature have shown impaired coagulation and decreased platelet clump strength as determined by thromboelastography. The higher the rate of substitution, the greater effect on coagulation. For this reason, HES solutions with a lower rate of substitution such as the tetrastarches are considered theoretically safer as their effect on coagulation is less.

Overzealous administration of any of the HES solutions can still result in a dilutional coagulopathy. In addition to effect on coagulation, synthetic colloids can impact serum total protein and urine specific gravity (USG) measurements. The administration of HES (670/0.75) has been previously shown to elevate the urine specific gravity. In one study, the largest increase in USG occurred 150 minutes following administration with a mean USG of 1.070 +/– 0.021.

Both hydroxyethyl starch and dextran 70 have been shown to affect total solids measured by refractometry. When evaluated using a refractometer, HES will yield a reading of 4.5 g/dL, therefore when administered *in vivo*, the refractometric measurement of total solids will trend to 4.5 g/dL. For this reason, total solids should be interpreted with caution in patients receiving synthetic colloids. In addition, serum amylase may be elevated 200–250% due to binding with hydroxyethyl starch molecules, leading to a decrease in clearance.

Ideally, the efficacy of synthetic colloids is monitored through serial measurement of the COP using a membrane osmometer. In practice, this technology is not widely available and the response to therapy is used instead to guide treatment.

Finally, in human medicine, in particular in the subset of patients with refractory sepsis, concerns have been raised about HES administration and renal injury based on an increase in the need for renal replacement therapy in patients receiving hydroxyethyl starches. At this time, this concern appears to be related to the cumulative dose of HES administered. There have been some studies examining the issue in small animal medicine but the topic remains controversial.

Dextrans are neutral glucopolysaccharides based on glucose monomers. Dextrans are described based on their average mean molecular weight as well as the tonicity of the fluid. Examples of dextrans include products such as dextran 40, dextran 60, and dextran 70. In humans, dextran administration has been associated with anaphylactoid reactions as well as being implicated in the development of renal failure in critically ill patients. This has not been documented in veterinary patients.

The last class of synthetic colloid is the gelatins – polydisperse molecules derived from bovine collagen. These solutions have a mean molecular weight of 35 000 daltons and are rapidly excreted upon infusion. As a result, they are far less effective than the hydroxyethyl starches or dextrans for sustained volume expansion. In addition, the gelatins are associated with the highest rate of anaphylactoid reactions among the synthetic colloids. As a class, gelatins are not available in the United States.

Albumin

Physiologically speaking, albumin is an extremely important protein. It contributes roughly 80% of the COP within the vascular space. In addition to its osmotic activity, albumin has many other roles in the body and functions as a carrier for a variety of substances, including bilirubin, as well as many different drugs. Albumin also plays a role in platelet function and in the scavenging of free radicals. The ability of albumin to create colloid osmotic pressure is enhanced by its negative charge as well as the Gibbs–Donnan effect that describes how charged molecules may not be equally dispersed across a semipermeable membrane due to the relative permeability of the membrane.

Indications for Fluid Therapy

Rapid Volume Expansion

The rapid administration of IV fluids is indicated for the treatment of hypoperfusion. Rapid volume expansion is not appropriate if hypotension is the result of forward cardiac failure for any reason other than cardiac tamponade. The goal of rapid volume expansion is to restore the effective circulating volume (ECV) to levels that permit adequate perfusion and thus tissue oxygenation. Serial monitoring of perfusion parameters is used to guide therapy during rapid volume expansion. Parameters that are commonly monitored include physical examination parameters such as heart rate, pulse rate, pulse quality, mucous membrane color, and capillary refill time (CRT). In addition, monitoring may also include toe-web to core body temperature gradient, urine output, central venous pressure, and blood lactate measurements. A full discussion of end-points of resuscitation can be found in Chapter 37.

The dosing of IV fluids for the treatment of shock varies with the type of fluid chosen for resuscitation as well as the patient's response to therapy. The most common fluid types used for rapid volume expansion are isotonic crystalloids. Classically, a full "shock" bolus is considered to be 90 mL/kg in the dog and 45–60 mL/kg in the cat. These amounts approximate one blood volume. Boluses can be administered over a specific amount of time (for example, a 250 mL bolus of 0.9%NaCl over 10 minutes), or in profoundly compromised patients as rapidly as possible. Frequently, one-quarter of the calculated shock bolus is administered as a starting point for resuscitation. After the bolus is complete, the animal is reassessed. If their perfusion parameters have not responded adequately, additional fluid therapy is indicated. It should be remembered that when using an isotonic crystalloid for rapid volume expansion, that crystalloid should be devoid of fluid additives such as supplemental dextrose, potassium chloride or magnesium sulfate.

Synthetic colloids such as Hespan® or Vetstarch® can also be used for rapid volume expansion. Because synthetic colloids are osmotically active, they promote the movement of water from the interstitium into the vascular space. This movement of fluid between body fluid compartments as well as the volume of colloid administered collectively results in the expansion of the ECV. An initial shock bolus of synthetic colloid would be 5 mL/kg administered over 10–15 minutes.The total shock dose is equal to the recommended total daily dose of 20 mL/kg in the dog. In the cat, the total daily dose is somewhat lower at 10 mL/kg. Rapid administration of hydroxyethyl starch has been associated with nausea and vomiting in the cat. Again, reassessment of the patient following completion of the bolus will guide further fluid therapy. If the response to therapy has not been adequate, additional fluids should be administered until the animal has been stabilized. If the animal is unstable but is deemed to be volume replete, other therapies such as inotropes or vasopressors may be needed. It should be remembered that synthetic colloids are potent osmotic agents so overzealous administration can result in volume overload as well as dilutional coagulopathy.

Hypertonic saline can also be used for rapid volume expansion. Hypertonic saline is commonly supplied as a 7–7.5% NaCl solution. The initial shock bolus is 4–6 mL/kg over 10–15 minutes. Hypertonic saline should not be administered at a rate exceeding 1 mL/kg/min as vagally mediated bradycardia, hypotension, and bronchoconstriction may be seen with too rapid administration. If needed, this initial bolus can be repeated once; further administration of hypertonic saline can result in serious complications such as hypernatremia and hyperchloridemia. Hypertonic saline administered alone will not expand the vascular space for much time, and is usually combined with a synthetic colloid to prolong its volume-expanding effects. Hypotonic crystalloids such as 0.45% NaCl are *not* appropriate for rapid volume expansion.

In certain situations, fluid resuscitation with whole blood or blood component therapy may be indicated. This fluid choice not only provides volume expansion but, in the case of whole blood or packed red blood cells,

it also provides oxygen-carrying capacity that may be crucial in the anemic, hypoperfused patient.

One concern that has been visited many times over the years is the risk of aggressive volume resuscitation in patients that are actively bleeding. Concern centers on the disruption of immature clots and the worsening of bleeding. The classic example of this in veterinary medicine is the patient that presents with a hemoabdomen due to splenic trauma. The animal is aggressively resuscitated which results in a short-term improvement in hemodynamic stability (i.e., blood pressure) followed by a decline as the clots forming on the traumatized spleen are disrupted and active bleeding worsens.

"Delayed resuscitation" refers to the practice of not administering fluid support to correct hemodynamic instability until definitive control of hemorrhage has been achieved. "Hypotensive resuscitation" is the practice of administering rapid volume expansion to the hemodynamically unstable patient but only resuscitating to a mean arterial pressure of around 60 mmHg. Here, the goal is to strike a compromise between the need to perfuse vital organs and the desire to avoid supraphysiologic resuscitation that may worsen injuries such as pulmonary contusions and abdominal bleeding. Any of the fluids appropriate for rapid volume expansion can be used for hypotensive resuscitation. When considering the use of either hypotensive or delayed resuscitation, it is important to keep in mind that these techniques were designed for human trauma patients with penetrating injuries, where the time from presentation to definitive treatment rarely exceeds one hour. There has been limited research in veterinary medicine to examine their efficacy in small animal patients. If definitive treatment is not possible or will not be pursued then delayed or hypotensive resuscitation should not be attempted.

"Small-volume resuscitation," which is also known as limited-volume resuscitation, uses resuscitative fluids in small volumes to achieve moderate increases in hemodynamic stability. In this type of resuscitation, synthetic colloids and hypertonic saline take center stage as they allow for expansion of the effective circulating volume in excess of the administered fluid volume. Again, the goal here is to minimize the deleterious effects seen with overaggressive crystalloid resuscitations. Endpoints with this style of resuscitation include a mean arterial pressure of 70 mmHg, a systolic pressure of 90 mmHg, and clinical improvement of perfusion parameters.

Dehydration

The assessment and correction of dehydration remains one of the more challenging parts of fluid therapy. The challenge lies in the poor sensitivity of physical and laboratory parameters to quantify dehydration. It is important to grasp just how limited these parameters really are. It has been shown that an animal can range from 5% to 16% dehydrated based on body weight and yet have a normal skin turgor. This flies in the face of commonly accepted guidelines where the percentage of dehydration is estimated based on the presence or absence of certain physical parameters. In reality, all of these parameters are flawed to a greater or lesser degree.

As skin turgor essentially assesses the interstitium, it can be altered not only by the water balance within the interstitium but also by alterations in the other components of the interstitium. For example, in the geriatric or cachectic patient, changes in collagen content may alter the skin turgor so that the animal appears more profoundly dehydrated than it truly is. By contrast, the obese patient may have dehydration but a normal skin turgor. Skin turgor is also affected by the location at which it is assessed, the posture of the animal (standing versus supine), age, and body condition.

Although the use of percentage dehydration based on physical parameters is crude, it does still provide a starting point for selecting an initial fluid rate. Usually changes in skin turgor with normal hemodynamic parameters are consistent with mild dehydration of about 5–7% body weight. As dehydration becomes more severe and approaches 10–12% dehydration, hypovolemia may also be evident when perfusion parameters are evaluated. This is evidenced by tachycardia, poor pulse quality, prolonged capillary refill time, and cool extremities. Another indicator of profound dehydration is the presence of sunken eyeballs (enophthalmos).

If hypoperfusion is present, rapid volume expansion to stabilize the patient is indicated prior to attempting correction of interstitial or intracellular fluid deficits. When the tissue safety factors of the interstitium are understood, it is clear that rapid volume expansion is not effective for correcting interstitial deficits. This type of deficit must be corrected slowly over at least 12–24 hours. When fluids are administered at an aggressive rate in the hope of shortening the time needed for correction, the results are unrewarding. This is due to the characteristics of the interstitium which oppose rapid expansion. Aggressive fluid administration will result in rapid increases in interstitial hydrostatic pressure as well as decreases in interstitial oncotic pressure. This in turn will increase lymphatic driving pressure and promote lymphatic flow. The end-result is the clearance of volume via the kidneys instead of a more rapid rehydration of the interstitial space.

Commonly assessed laboratory parameters should provide more insight into fluid balance, but they, too, are limited. Alterations in hematocrit and total solids have

not correlated reliably with alterations in fluid balance based on weight. This may be due to a variety of reasons and is most probably a result of the patient's underlying disease process.

Serum sodium can be used as an indicator of free water balance in most situations. It should be kept in mind that serum sodium does not reflect total body sodium but instead is a reflection of the water balance within the body. Serum sodium is of no value in determining the presence of hypovolemia or the need for rapid volume expansion. The most common types of volume lost are isotonic or hypotonic fluid loss. In the case of hypotonic fluid loss, free water is lost in excess of sodium. As a result, serum sodium concentration elevates. To correct free water deficit, a solution providing free water such as 0.45% NaCl or D5W is used. Interstitial fluid deficits should be corrected before free water deficits are addressed. In addition, when correcting free water deficits, it is imperative to consider the duration of the free water deficit. When free water deficits are long-standing, the brain will synthesize idiogenic osmoles. These are osmotically active particles that oppose the movement of fluid out of the brain in response to hypertonicity. Idiogenic osmoles require several days to be metabolized so it is best to correct long-standing free water deficits slowly over a number of days. Overzealous correction of long-standing hypernatremia can result in cerebral edema. If hypernatremia is acute then it can be corrected more rapidly.

To replace the free water deficit, the volume of the deficit can be calculated using the following equation:

$$\text{Free water deficit} = \text{Weight}(\text{kg}) \times \left[\left(\text{Na}_{\text{present}} / \text{Na}_{\text{normal}}\right) - 1\right]$$

Example : A 10 kg dog with serum sodium concentration of 180 mEq / L

$$\text{Water deficit}(\text{L}) = 10 \times \left[(180/145) - 1\right] = 2.4$$

In this example, the patient had a free water deficit of 2.4 L. This volume will need to be replaced after the interstitium is replete and additional fluids are indicated to meet insensible losses as well as ongoing losses that may be quantifiable.

Maintenance Fluids

Maintenance fluids are designed to meet sensible and insensible losses. In a normal animal, these needs are met through the intake of food and water. In the patient where this is not possible, or intake is inadequate to meet fluid requirements, a maintenance fluid may be used.

As mentioned earlier, the composition of maintenance fluids is different from that of replacement fluids. In general, maintenance fluids have a lower sodium concentration and a higher potassium concentration than replacement fluid. Maintenance fluid requirements will vary with the size, age, and metabolic needs of the patient, taking physiologic derangements into consideration. Smaller and younger patients tend to have higher maintenance fluid requirements. These requirements may also be increased with pyrexia and panting. Diet composition may also affect daily fluid requirements due to the amount of water provided by the food source as well as the relative nutrient composition of the diet. In critically ill or sedentary animals, maintenance fluid requirements may be decreased.

The calculation of maintenance fluid requirements can be done in several ways. One commonly used shortcut is 40–60 mL/kg/day. When using this formula, it should be remembered that larger dogs will usually have maintenance needs near the lower end of the dose range while small dogs will likely have requirements toward the higher end of the range. Another way to consider maintenance requirement is to link it to daily energy requirements. With this approach, the maintenance requirement is roughly 1 mL of water per 1 kilocalorie (kcal) of energy expended. Maintenance energy requirements can be calculated using the following formula:

$$140\,\text{kcal} \times \text{body weight}(\text{kg})^{0.73}$$

Alternatively, the basal energy requirements can be calculated and then multiplied by a factor of 2 to approximate maintenance energy requirements. In critical patients, water requirements may be decreased and therefore the use of maintenance energy requirement calculation may overestimate what is required. In this instance, basal energy requirements may be more reflective of true water requirements. Basal energy requirements (BER) can be calculated using the following formula in the dog:

$$97 \times \text{body weight}(\text{kg})^{0.655}$$

In the cat, BER is roughly 50–60 kcal/kg/day.

Once the degree of dehydration has been estimated and the maintenance fluid requirement and free water deficit calculated, consideration must also be given to ongoing losses. This may be due to loss of volume from the GI tract, urinary tract or third space losses. Also remember to take into consideration the possibility of iatrogenic loss of volume. An example of this would be when residual gastric volumes are discarded following aspiration of a gastric tube. The volume of estimated ongoing losses is then added in to the fluid prescription.

Albumin Replacement

In critically ill veterinary patients, it may become necessary to address albumin deficiency due to ongoing albumin loss (e.g., protein-losing nephropathy, septic peritonitis) or decreased albumin production (e.g., acute phase response, liver failure). The majority of total body albumin actually resides within the interstitial space so correction of an albumin deficit can be difficult to achieve using albumin-containing products such as fresh frozen plasma. Existing interstitial albumin deficits must be replaced before improvement of plasma albumin concentrations will be seen.

Albumin concentrate is administered as either a 5% solution or a 25% solution. The 5% solution of human serum albumin (HSA) has a COP of about 20 mmHg and an albumin concentration approximately equal to plasma while the 25% solution has a much higher COP of about 70 mmHg and an albumin concentration five times that of plasma. In veterinary medicine, both 5% and 25% HSA have been administered for albumin replacement in both dogs and cats. Studies have shown both acute and delayed hypersensitivity reactions in dogs. The incidence of these reactions appears lower in critically ill patients but the studies that have investigated the use of these solutions have been limited. In patients with significant albumin deficits, the volume of plasma that would need to be administered to effect change in serum albumin often precludes its use as an effective therapy. For this reason, concentrated albumin products such as 25% HSA or canine lyophilized albumin (a canine albumin product has been introduced to the US market but little has yet been published regarding its use) are more effective in correcting albumin deficits. When correcting albumin, the following equation can be employed:

$$\text{Albumin deficit}\,(\text{grams}) = 10 \times [\text{desired albumin}\,(\text{g/dL}) - \text{patient albumin}\,(\text{g/dL})] \times \text{body weight}\,(\text{kg}) \times 0.3$$

As an example, to increase the albumin in a 10 kg dog from 1.5 to 2.0 g/dL:

$$\text{Albumin deficit} = 10 \times [2.0 - 1.5] \times 10 \times 0.3 = 15\ \text{grams}$$

Assuming an albumin concentration of 5 g/dL of canine plasma, this patient would require approximately 300 mL of plasma (identical volume to 5% HSA). By contrast, this patient would require 60 mL of 25% HSA. Given the current costs of HSA versus canine plasma, this could result in a significant saving to the client. The recommended dose for the lyophilized canine albumin product has been reported to be 800–884 mg/kg IV.

Constant Rate Infusions

In addition to their uses in volume expansion and the correction of dehydration, intravenous fluids are often used as carriers for drugs that are best administered by constant rate infusion (CRI). Examples include vasopressors, some inotropes, and some vasodilators. Also, CRIs for the administration of anesthetics and analgesics are commonplace. Before starting a CRI, the compatibility of the drug and carrier fluid must be determined. In most instances, 0.9% NaCl or 5% dextrose in water are acceptable choices.

Constant rate infusions are dosed based on both weight and time. For example, a CRI of dopamine might be started at a dose of 5 µg/kg/min. This dose of drug is then administered in a specific volume of fluid. The volume of fluid administered is determined based on the patient's body weight and fluid status, and the concentration of drug that requires delivery. To calculate a CRI, the following information must be known.

- Patient weight (kg).
- Drug dose (5 µg/kg/min, for example).
- Starting rate of fluid administration (5 mL/h, for example).
- Concentration of the drug administered.
- Total volume of carrier fluid to be supplemented.

To be precise, when formulating a CRI, an equivalent volume of carrier fluid should be removed and replaced by the drug being delivered. For examples of CRI formulation, the reader is referred to supplemental materials available online.

Monitoring of Fluid Therapy

One of the great challenges of fluid therapy is to meet the patient's ongoing requirements and replace deficits without overloading the body's ability to cope with the volume. An understanding of the behavior of fluids within the body as well as body fluid compartment dynamics helps to avoid complications. When attempting to assess the adequacy of fluid therapy, various parameters can be monitored.

Perfusion parameters such as heart rate, respiratory rate, capillary refill time, and pulse quality are valuable in determining the need for rapid volume expansion but they do not provide information regarding the correction of dehydration. Perfusion parameters can be normal in the dehydrated animal, although the profoundly dehydrated animal will exhibit signs of hypovolemia.

Patients should be weighed at least once daily to track alterations in fluid balance, keeping in mind that 1 L of water is effectively equivalent to 1 kg of weight. The

importance of body weight monitoring is especially true in the patient in which the potential for third space loss is a concern.

Quantification of urine output allows assessment of adequacy of urine output, especially if oligoanuria from renal injury or polyuria from underlying disease processes is of concern. In addition, serial measurements of USG may provide insight into fluid balance. For example, consider the patient on crystalloid fluid therapy who has a decrease in urine output. Once technical complications such as catheter patency and placement have been considered and it has been determined that perfusion is adequate, USG will help to differentiate between physiologic and pathophysiologic oliguria. Recall that the use of hydroxyethyl starches will invalidate the use of specific gravity measurement in the urine.

The venous side of the circulation is a capacitance system. As such, it has a relatively low pressure until fully replete and distended. Once the venous side of the circulation has no further ability to distend, pressure within the vasculature will rise. This can be correlated to the volumes and pressures within the heart. Based on Starling's law, it is known that initial expansion of ventricular volume will increase cardiac output and cardiac contractility. Overdistension of the ventricles proves maladaptive and results in decreased cardiac contractility as well as increased intravascular pressures. Central venous pressure is generally reflective of venous volume status and can be a useful invasive monitoring technique to guide fluid therapy. When measuring central venous pressure (CVP), a catheter is placed in the jugular vein in close proximity to but not within the right atrium of the heart. When measured in the absence of pulmonic obstruction or pulmonary hypertension, CVP approximates right atrial pressure. CVP can be measured manually using a water manometer or continuously using a pressure transducer. Normal CVP is considered to be 0–10 cmH_20 (1 mmHg is roughly 1.36 cmH_2O). CVP should ideally be measured at the end of expiration in the spontaneously breathing or mechanically ventilated patient but the use of positive end-expiratory pressure (PEEP) will increase CVP measurements.

Although serum lactate is used commonly as an indicator of hypoperfusion, its usefulness as an indicator of dehydration is limited since dehydration must be severe enough to result in decreased oxygen delivery to result in hyperlactatemia. Elevations in serum lactate can also occur due to severe liver dysfunction and spurious elevations in lactate can be seen when difficulty is encountered with sample acquisition.

Conclusion

Fluid therapy is an integral part of small animal practice. Approaching a patient's fluid needs in a logical fashion where the needs for rapid volume expansion versus correction of dehydration or electrolyte abnormalities are identified and then targeted will maximize the benefits of fluid therapy. Each patient is unique. Each of the commonly available fluid types has properties that can be leveraged to the advantage of our patients. This chapter illustrates how perfusion, hydration, and water and electrolyte balance affect not only the type of fluid therapy that is indicated but also the rate and route of fluid administration. By understanding the physiology of fluid balance in the body, clinicians can tailor their fluid prescription to address interstitial dehydration, correct free water and albumin deficits, and manage electrolyte abnormalities safely. This knowledge also allows fluid choices to be altered during rapid volume expansion to meet the special challenges of each case.

The decision to use a specific fluid should be based on the goals of therapy and how effectively that fluid choice will achieve that goal, instead of a knee-jerk response. Veterinary patients are dynamic and the unique needs of each patient vary. The need to identify our patients' fluid needs and to address them appropriately, even if their clinical presentation is unusual, cannot be overestimated.

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37

Cardiopulmonary Resuscitation

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Approximately 330,000 people die of acute cardiac arrest in the United States annually. The incidence of unexpected cardiopulmonary arrest (CPA) in veterinary patients is currently unknown. What is known is that survival rates for dogs and cats that receive cardiopulmonary resuscitation (CPR) range from 2.6% to 25%. The reported survival rates for people experiencing CPR are equally dismal, with overall survival rates following in-hospital arrest ranging from 3% to 27%. The reason for the wide range in outcomes is due in part to the variance in the nature or cause of cardiopulmonary arrest. What the literature generally agrees on is that the chance of a patient surviving to discharge after CPA is small. The likelihood of survival increases if CPA was due to an anesthetic event rather than the culmination of a chronic or traumatic disease process. While the survival statistics are dismal, the long-term neurologic outcomes of patients surviving CPA are generally good to excellent, making CPR a worthy endeavor.

In 2010, veterinary-specific CPR guidelines were developed using an evidence-based approach modeled on the American Heart Association's CPR guidelines. The result of this effort was the publication of the Reassessment Campaign on Veterinary Resuscitation (RECOVER) in 2011. The RECOVER initiative (http://onlinelibrary.wiley.com/doi/10.1111/vec.2012.22.issue-s1/issuetoc) has provided veterinarians for the first time with evidence-based clinical guidelines for performance of CPR.

The progression from severe illness to cardiopulmonary arrest in the veterinary patient is complex. Diseases that can lead to CPA in veterinary medicine include but are not limited to sepsis, pulmonary failure, neoplasia, polytrauma, head trauma, and cardiac failure. Although not all animals progressing toward CPA follow the same clinical course, some physical exam findings that may indicate impending CPA include decreasing level of consciousness, hypothermia, bradycardia, hypotension, and changes in respiratory patterns. Once CPA occurs, all patients will exhibit loss of consciousness, absence of spontaneous ventilation, absence of heart sounds during auscultation, and absence of palpable pulses.

The importance of recognizing CPA quickly is underscored when the hemodynamic impact is considered. Following the onset of CPA, the aortic blood pressure drops precipitously, with intrathoracic aortic pressure dropping from a normal of approximately 120 mmHg to 20 mmHg within 30 seconds. Additionally, carotid blood flow decreases from an average of 190 mL/min to 15 mL/min within 15 seconds and to 0 mL/min within four minutes. Coronary perfusion pressure likewise drops from 60 mmHg to 15 mmHg within 15 seconds and to 0 mmHg within four minutes.

Although the underlying cause of CPA may not be immediately apparent to the clinician, the nature or cause of the arrest can have an impact on the expected outcome and should be ascertained as soon as possible. If a patient is known to have suffered respiratory arrest prior to cardiac arrest, the likelihood of resuscitation may be diminished due to the continued depletion of oxygen from circulating blood resulting in severe hypoxemia at the onset of cardiac failure and institution of CPR. Conversely, if an animal suffers sudden cardiac arrest, the blood oxygen content would be expected to be high at the onset of CPA and subsequent CPR, possibly making successful resuscitation more likely than in the previous instance.

Principles of CPR

Cardiopulmonary resuscitation is intended to provide blood flow to the heart and brain, preserving them until return of spontaneous circulation (ROSC) is achieved. Subsequently, the quality of chest compressions is of the utmost importance, since this is the mechanism by which circulation is generated. Whatever the technique,

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the provision of chest compressions is an inefficient way to move blood out of the heart and into systemic circulation. Even ideal chest compressions are only capable of generating 25–30% of normal cardiac output (CO). However, to maximize the efficiency of chest compressions, the provider should attempt to achieve 30–50% compression of the thoracic diameter. Good–quality chest compressions consist of a 50% duty cycle, meaning 50% of the entire compression cycle is spent with the chest wall being compressed and 50% is spent allowing the chest wall to recoil. Failure to allow complete recoil of the thoracic wall can result in severe impairment to cardiac filling during the noncompression phase. It is often helpful to lift the heel of the hand off the chest wall to ensure that complete recoil has been accomplished.

Hand position during CPR in veterinary patients is not standardized and is left to the individual providing compressions to find what works best for them. In small dogs and cats, a one-handed technique can be employed by placing the sternum in the palm of the hand with the thumb and fingers centered over the heart on opposite sides of the chest. The heart is then compressed between the thumb and fingers in a rhythmic pattern. For larger dogs, it may be necessary to use one or two hands to achieve the desired amount of chest wall compression. In small dogs (<15 kg) and cats, the compressions should be located directly over the heart in an effort to take advantage of direct compression of the ventricles forcing blood forward through the semilunar valves. This is termed the cardiac pump theory. In larger dogs (>15 kg), the compressions should be located at the widest part of the thorax, realizing that this may be at the caudalmost portion of the costal arch. In this case, the clinician is reliant on the intrathoracic pressure generated during chest compressions to compress the vascular structures in the thorax forcing blood forward. This is called the thoracic pump theory.

An oft-overlooked facet of chest compressions is patient positioning relative to the compression provider. It is important that the position of the provider is comfortable and will allow for the best-quality compressions with the least amount of fatigue. Therefore, having the patient at approximately waist level or lower is ideal. If the patient's position is fixed then the provider should stand on a step stool to achieve the desired amount of leverage. If compressions are provided on a table, the tabletop should be rigid and would ideally be incapable of conducting electricity. Wet tables should be avoided. Larger dogs can often be more comfortably resuscitated on the floor with the compression provider kneeling next to the patient. An adjustable height hydraulic table should be considered if CPR is performed on a regular basis.

Diagnosing Cardiopulmonary Arrest

Prompt recognition of cardiopulmonary arrest is paramount to the success of CPR. Therefore any nonresponsive, apneic patient should be immediately evaluated for CPA and resuscitative measures should be started. The clinician should spend no more than 10 seconds attempting pulse detection and cardiac auscultation before beginning chest compressions. The risk of causing serious injury to a patient by providing unnecessary chest compressions is quite small. In a study of human patients receiving unnecessary chest compressions, the injury rate was less than 2% with no life-threatening injuries present, leading to the conclusion that the provision of CPR is not harmful, while inaction may prove fatal.

If the patient is found to be only in respiratory arrest following the brief pulse evaluation then the clinician should proceed with securing an airway with an endotracheal tube or tracheostomy tube. After the airway is secure, the patient should be manually ventilated with 100% oxygen. If not already obtained, attempts at venous access should be made at this time and the patient should be monitored for progression to cardiac arrest. If, on the other hand, the patient is found to be in cardiac arrest at the time of the pulse check then basic life support (BLS) should be instituted immediately.

Basic Life Support

Chest Compressions

While the definitive order in which BLS measures are implemented is not established, it is reasonable to continue using the Airway, Breathing, Circulation approach in which ventilation precedes compressions. Practically, however, instituting compressions does not require any equipment and can often be started earlier than an airway can be secured. Therefore, BLS begins with high-quality chest compressions performed at a rate of 100–120 beats per minute, making every effort to avoid interruptions. During the first cycle (two minutes) of chest compressions, the patient should be instrumented with an electrocardiograph (ECG) and capnography if available. Attempts can also be made to achieve intravenous access if this has not already been done. Intubating or securing an airway can be attempted during this first round of compressions while minimizing interruptions. It is often easier to perform the first cycle of compressions while other members of the arrest team obtain proper sized endotracheal or tracheostomy tubes and laryngoscope and mobilize the crash cart to the location of the arrest.

Following the first round of compressions, the first ECG rhythm check will be performed and a definitive attempt will be made to secure an airway. The purpose of the rhythm check is to determine if a cardiac rhythm may be amenable to electrical conversion. If no such rhythm is identified then chest compressions are immediately resumed. Ideally, the chest compression provider is changed at this time. This two-minute cycle is repeated as needed, alternating the compression provider at each planned rhythm check (i.e., every two minutes) or sooner if fatigue occurs.

There are four arrest rhythms, two of which are responsive to electrical defibrillation: pulseless electrical activity (PEA), asystole, ventricular fibrillation, and pulseless ventricular tachycardia. The most common arrest rhythms in veterinary medicine are asystole, which accounts for 72% of arrest rhythms, and pulseless electrical activity, neither of which is responsive to defibrillation.

Interruptions in chest compressions must be minimized during CPR. Following each interruption in chest compressions, it takes approximately 60–90 seconds to return CO to the preinterruption level. Eliminating hands-off time is therefore a major focus in improving both veterinary and human CPR. Minimizing interruptions during CPR must be balanced with the need to prevent compression provider fatigue. Many studies in human CPR providers document a tendency to lean during the provision of chest compressions. This tendency increases as the duration of compressions increases. The effect of leaning on a patient during CPR decreases cardiac filling and the overall efficiency of CPR by at least 25%. CPR is hard work and two minutes of high-quality chest compressions on even a small to medium-sized dog should be exhausting.

Airway

Orotracheal intubation of dogs and cats is relatively easy, making rapid intubation possible in most circumstances. In the majority of patients that experience cardiopulmonary arrest, an airway can be secured via routine orotracheal intubation. Occasionally, the glottis is obscured by vomit, fluid or saliva. If suction is available, it can be helpful in clearing the oropharynx of excess fluid. If suction is unavailable a gauze 4 × 4 or paper towel can be used to swab the area free of fluid or debris. Care should be taken to avoid excessive manipulation of the epiglottis as this can induce a vagal response. A laryngoscope should be used to facilitate intubation.

If the glottis cannot be visualized, the orotracheal route may still be considered for intubation if the epiglottis can be palpated. A blind intubation is performed by palpating and depressing the tip of the epiglottis and directing the endotracheal tube through the glottis dorsally. Successful intubation can be confirmed by direct visualization of the endotracheal tube between the arytenoid cartilages or visualization of normal chest rise during positive pressure ventilation. Capnography may be useful but should not be used as the sole means of confirming correct placement of an endotracheal tube during CPA since end-tidal CO_2 in CPA patients may be 0 due to lack of pulmonary blood flow.

Once an endotracheal tube is placed and correct positioning is confirmed, the tube should be secured to the patient with tape, gauze tie or rubber band to prevent tube dislodgment. The cuff on the endotracheal tube should be inflated to ensure an airtight seal. This will allow the patient to be effectively ventilated with positive pressure during chest compressions. In some cases, orotracheal intubation may not be possible due to severe swelling, inability to open the mouth or severe facial trauma necessitating emergency tracheostomy.

Ventilation

Positive pressure ventilation with 100% oxygen is begun once an airway is secured. Breaths can be provided by a number of means, including rescue bag, anesthesia machine or mechanical ventilator. Hyperventilation is common in the clinical CPR scenario and can be caused by an excessive respiratory rate, tidal volume or inspiratory time. Regardless of the cause, hyperventilation is detrimental to outcome. During positive pressure ventilation, venous return occurs during the expiratory phase and if insufficient expiratory time is allowed (due to either excessive rate or inspiratory time), cardiac filling will be reduced. Hyperventilation can also lead to decreased cerebral carbon dioxide levels and subsequent cerebral vasoconstriction, further impairing blood flow to the brain during the critical time of resuscitation.

No clear association has been made regarding the timing of rescue breathing with compressions and it is not recommended to attempt to synchronize breaths with compressions. Current recommendations for ventilation are a rate of 8–10 breaths per minute with a tidal volume of approximately 10 mL/kg and an inspiratory time of one second. Assigning the role of rescue breathing to a single team member and providing them with clear instructions on ventilation rates is the best way to prevent hyperventilation.

Advanced Life Support

Advanced life support (ALS) consists of all resuscitative measures that are not included in the BLS algorithm, including vasopressor therapy, vagolytic therapy, fluid and electrolyte therapy, and electrical defibrillation.

The rationale for the use of vasopressor therapy is grounded in the fact that cardiac output during CPR is a fraction of that during spontaneous circulation, making it imperative that the limited cardiac output is directed to the organs that need it most. Therefore, the provision of vasopressors is intended to increase peripheral vascular resistance, forcing more blood into the central circulation and subsequently improving the perfusion of vital structures (i.e., brain and heart).

Stimulation of the alpha-1 receptor results in peripheral vasoconstriction whereas stimulation of the beta-1 receptor increases both inotropy and chronotropy. While epinephrine is a balanced alpha- and beta-adrenergic agonist, its utility during CPR comes primarily from its action at the alpha-1 receptor. In fact, the effects of beta-1 stimulation may be detrimental as they can lead to increased myocardial oxygen consumption and predispose to arrhythmias if ROSC is achieved. The best dose for epinephrine use during CPR has been a topic of debate for many years, with mixed evidence. High-dose epinephrine (0.1 mg/kg IV) has been shown to result in slightly higher rates of ROSC but has not been shown to confer a survival benefit. Based on the lack of documented improved survival, the use of low-dose epinephrine (0.01 mg/kg) is currently recommended early in CPR efforts, with high-dose epinephrine being reserved for cases of prolonged CPR. Epinephrine should be administered following the first cycle of BLS and then following every other cycle.

Adrenergic receptors have been demonstrated to be less responsive in acidotic conditions, such as those found during CPA, making an alternative drug that is not dependent on catecholamine receptors an appealing option. Vasopressin acts on the V1 receptors of vascular smooth muscle cells independent of the alpha-1 receptor. In addition, it maintains its efficacy in the face of acidosis. Due to the lack of adrenergic effects, vasopressin does not cause increases in inotropy or chronotropy, minimizing its impact on myocardial oxygen consumption. The human literature regarding the usefulness of vasopressin in CPR is mixed, with promising results in small trials but failure to demonstrate any clear advantage over epinephrine in larger metaanalyses. The successful use of vasopressin in CPR has been reported in the veterinary literature. Administration of vasopressin (0.8 U/kg IV) in place of or in conjunction with epinephrine may be considered, with subsequent doses administered following every other cycle of BLS.

The use of atropine in ALS is somewhat unique in that atropine is a parasympatholytic drug intended to ameliorate high vagal tone during cardiac arrest rather than directly stimulating catecholamine receptors. The use of atropine should be considered in animals that have asphyxia-induced cardiac arrest or other co-morbid conditions that would be likely to increase vagal tone. A dose of 0.04 mg/kg IV is recommended as higher doses are more likely to result in severe tachycardia and subsequently, increased myocardial oxygen consumption if ROSC is achieved. Repeated dosing of atropine is unlikely to be of benefit (assuming actions directed at the underlying cause have been taken) and should be considered carefully due to the potential for severe tachycardia if resuscitation is successful.

Corticosteroids currently have no place in the CPR algorithm and their use is not recommended. Given the lack of documented improvement in outcome and the known deleterious side-effects, especially in patients with perfusion impairment, this is unlikely to change.

The administration of ALS drugs by intravenous or intraosseous routes (interchangeable in the context of CPR) is always preferred to the intratracheal route. If IV or IO access is not available or not possible then intratracheal administration of drugs can be considered while efforts to attain venous or intraosseous access are continued. If this route is utilized, a long catheter should be advanced through the endotracheal or tracheostomy tube to the level of the carina or beyond. Drugs should be diluted with saline or sterile water. The optimal dosing of drugs for intratracheal administration is not established but doses up to 10 times the normal dose have been recommended. Once established, the IV or IO route should be used for all subsequent drug administrations.

The need for rapid volume expansion with IV crystalloid or colloid solutions during CPR is dependent on the underlying cause of CPA. Animals suffering CPA from severe hemorrhage or hypovolemia should be aggressively resuscitated with IV fluids to reestablish normal circulating volume. Since coronary perfusion pressure is determined by the difference between diastolic aortic blood pressure and right atrial pressure, care should be taken to prevent overresuscitation. IV fluids accumulate in the venous compartment, increasing the central venous and right atrial pressure and consequently reducing coronary perfusion pressure. In general, animals that were euvolemic or hypervolemic (congestive heart failure) do not require volume expansion during CPR and routine use of IV fluids during CPR on these patients is not recommended.

Electrolyte and acid–base disturbances are common during CPA. Severe acidemia occurs frequently during CPA, especially later in the course of resuscitation, and can result in vasodilation, predisposition to arrhythmias, and impaired neurologic function. The administration of 1 mEq/kg sodium bicarbonate can be considered in prolonged instances of CPA lasting 10–15 minutes. The most common electrolyte disturbances during CPA include hyperkalemia and hypocalcemia. Because of the lack of documented improvement in outcomes and the

potential complications associated with over- or under-correction, the management of electrolyte derangements during CPA should be reserved for animals with confirmed rather than assumed disturbances.

Recently, the use of an impedance threshold device (ITD) intended to increase cardiac output during CPR has been described in canine patients and results appear promising. Unfortunately, the use of an ITD is limited to patients greater than 10 kg.

Defibrillation

The purpose of defibrillation is to depolarize as many cardiac myocytes as possible, making them temporarily refractory, allowing the native pace-making cells to resume organized electrical conduction. Electrical defibrillation should only be attempted on rhythms that are potentially responsive to it. Of the four arrest rhythms, only two are responsive to electrical defibrillation: ventricular fibrillation (most significant in veterinary medicine) and pulseless ventricular tachycardia. Any attempts at converting nonresponsive rhythms will not result in return of spontaneous circulation and will only needlessly expose team members to accidental defibrillation and increase time spent without compressions.

There are two types of defibrillators commonly used in veterinary medicine. Monophasic defibrillators function by passing a single electrical current from one electrode through the heart to a receiving electrode. Biphasic defibrillators pass a current from one electrode to the other; the current then reverses direction and is passed back to the original electrode. This technology allows effective defibrillation to be performed using less energy than monophasic defibrillation, resulting in less myocardial injury. If available, biphasic defibrillation is preferred. Being familiar with the type of defibrillator in the practice is important due to the difference in energy selection, with monophasic defibrillator doses beginning at 4–6 J/kg and biphasic defibrillator doses beginning at 2–4 J/kg. If defibrillation is not successful following the first attempt, the dose delivered can be increased by 50% for subsequent defibrillation attempts.

Historically, it was recommended to administer three stacked defibrillation attempts (discharges in rapid succession) prior to resuming chest compressions. The advent of biphasic defibrillators and the recognition that delays in resumption of chest compressions can have a negative effect on outcome have made this recommendation obsolete. It should be remembered that successful defibrillation means that fibrillation has been stopped, not that ROSC has been achieved. Successful defibrillation therefore can result in asystole or an electrocardiographically normal rhythm. However, resumption of normal electrical function does not necessarily correlate with return of normal mechanical function of the heart (i.e., PEA). It is therefore recommended that a single defibrillation attempt be made followed by immediate resumption of chest compressions for a full two-minute cycle prior to ECG evaluation. This improves coronary blood flow to the myocardium, making successful defibrillation with resumption of mechanical activity more likely.

Performing defibrillation begins with selecting appropriately sized paddles. Most defibrillators come equipped with standard-sized adult paddles, which are suitable for most patients larger than 15 kg. Smaller pediatric paddles are usually available as a clip-on attachment and should be used for smaller dogs and cats to ensure focused delivery of the shock through the heart. Defibrillator paste or contact gel is generously applied to the paddles. The animal is typically placed in dorsal recumbency and the defibrillator paddles are placed on either side of the thorax at the level of the costochondral junction with the heart centered between the paddles. The patient is firmly grasped between the paddles and is maintained in dorsal recumbency by the person delivering the defibrillation. Once the patient is positioned, depressing the charge button on the paddles or on the base unit charges the defibrillator. To maintain safety, the patient should be positioned prior to charging the paddles to lessen the likelihood of accidental discharge. Once the defibrillator is charged, the provider should ensure that no one is in contact with the patient or metal tabletop. Verbal commands to "CLEAR" the patient are effective. Once all rescue providers are clear of the patient, the shock is delivered by depressing the shock delivery buttons on the paddles or defibrillator base unit. Animals with thick undercoats that inhibit paddle contact should be rapidly clipped at the intended paddle locations prior to defibrillation attempts. The use of alcohol to improve paddle contact should be strictly avoided due to the risk of fire.

Alternative defibrillation techniques involve the use of defibrillation pads attached directly to the patient and left in place while connected to the defibrillator base unit. The pads are placed on the chest in the same location as the paddles. If pads are used then clipping of the hair is mandatory to ensure good contact between the pads and the patient. The advantage to the use of pads is that no rescue providers have to be in contact with the patient and patient positioning is minimally interrupted. The disadvantage is the necessity of clipping the hair that results in longer time without chest compressions. The use of a posterior paddle assembly, a flat paddle replacement resembling a spatula, may be the best method for delivering defibrillation in veterinary patients. The paddle assembly is coated with paste or gel, as a normal

paddle would be. The assembly is then placed under the patient in lateral recumbency using the normal paddle positioning recommendations. A standard paddle is then used on the upward-facing thoracic wall. This technique allows the patient to remain in lateral recumbency while eliminating the need to clip the area as for defibrillator pads.

Nonelectrical methods of cardiac defibrillation include both chemical and mechanical means. Historically, chemical defibrillation with magnesium or antiarrhythmic drugs has been considered acceptable. Based on the current understanding of CPA in both human and veterinary patients, the use of antiarrhythmic agents is no longer routinely recommended. Among the possible agents available, only amiodarone has been found to be routinely effective. Magnesium salts have only proven to be useful for the treatment of torsades de pointes and electrical defibrillation should always be considered as the best option for ventricular fibrillation or pulseless ventricular tachycardia. The use of a precordial thump has been described as a method for providing mechanical defibrillation. Given the superiority of electrical defibrillation, a precordial thump should only be considered if a defibrillator is not available.

Monitoring During CPR

Monitoring during CPR can be difficult due to lack of normal physiologic responses. The two modalities most useful during CPR are ECG and capnography. Electrocardiography is monitored to determine if an arrest rhythm is amenable to defibrillation while $ETCO_2$ can be utilized as a measure of the effectiveness of chest compressions, as an adjunct to verify placement of the endotracheal tube, and to determine when ROSC occurs.

Traditionally, patients with CPA would be subjected to pulse detection attempts before and during CPR. Unfortunately, pulse detection takes time, is technically difficult in some cases and can lead to increased "hands-off" time, with the patient receiving fewer chest compressions. Capnography has allowed CPR providers a method to monitor not only the effectiveness of chest compressions but also whether or not ROSC has occurred. Following CPA, blood flow through the pulmonary circulation decreases rapidly and $ETCO_2$ levels drop to near 0 since carbon dioxide is not being returned to the alveoli for exhalation. During CPR, pulmonary blood flow is generated by chest compressions. Therefore, any change in $ETCO_2$ levels can be attributed to the cardiac output achieved by the chest compressions, provided the minute ventilation is held constant. $ETCO_2$ is also useful for the detection of ROSC, with a rapid and sustained rise in $ETCO_2$ indicating ROSC due to the much more efficient delivery of blood to the pulmonary circulation by spontaneous cardiac contraction than that achieved during manual chest compressions.

Following the initiation of chest compressions and attainment of an airway, the patient should be instrumented with $ETCO_2$ monitoring if available. Patients with higher $ETCO_2$ levels (15 mmHg dogs, 20 mmHg cats) are more likely to have ROSC than those with lower levels. During CPR, if $ETCO_2$ is less than 15 mmHg, efforts should be made to improve the quality of chest compressions. If compression providers have not been rotated and $ETCO_2$ is found to be low or is decreasing, a rotation should be considered.

Blood gas monitoring during CPR is challenging but is the only way to identify the severe electrolyte and acid–base derangements that are common during CPA. Ideally, a blood sample (venous or arterial) is obtained shortly after the onset of CPA and is evaluated for any abnormalities. Interventions should be directed at severely abnormal results, understanding that complete resolution is not likely and may not be necessary. If sampling is possible, blood gas analysis should be performed every 5–10 minutes during CPR as long as collection of samples does not interfere with the actual provision of rescue efforts. Information regarding acid–base and electrolyte status during CPA and outcome is lacking and should not be used to predict the likelihood of ROSC.

Open Cardiac Massage

Open chest cardiac massage is capable of generating better cardiac output during CPR than closed chest compressions. However, the procedure is invasive and requires significant resources both during and after resuscitation. Therefore, its use is reserved for patients with a clear indication including significant intrathoracic disease (tension pneumothorax, severe pleural effusion), major chest wall defect (flail chest) or pericardial effusion.

To perform open chest CPR, the patient is placed in right lateral recumbency. The fur is rapidly clipped over the 4th–6th intercostal spaces and the skin is quickly wiped with alcohol. The skin is incised at the 5th–6th intercostal space with a scalpel blade. The intercostal muscles are incised with Mayo scissors and the incision is extended from the costochondral junction to the proximal one-third of the rib. Care should be taken to avoid laceration of the lung tissue during this process. Respiration can be temporarily held during this time to further reduce the risk of iatrogenic trauma to the lung. The ribs are then spread with manual retraction or a Finecchetto retractor. The pericardial sac is incised at the

apex of the heart to avoid the phrenic nerve and the sac is then reflected dorsally to the base of the heart. The heart should be compressed from the apex to the base at a rate of 100–120 compressions per minute. This can be done with one or two hands, depending on patient size. In some patients, the descending aorta can be briefly (10–15 minutes) cross-clamped to help direct blood flow to the cerebral and coronary circulation.

If ROSC is achieved, the patient should be maintained in an anesthetized state while a thoracostomy tube is placed and the thoracotomy site is closed. Volatile gas anesthetics have profound vasodilator effects and may be detrimental to a recently resuscitated patient. All efforts should be made to avoid hypotension and total IV anesthesia may be the best option during this time. Prophylactic antibiotics should be considered for patients that have undergone open chest CPR due to the likelihood of contamination.

Postresuscitation Care

Despite initial reported ROSC rates of 35–45% in veterinary medicine, survival to discharge rates range from 2% to 10%. This highlights the need for continued aggressive critical care following ROSC. Initial postcardiac arrest (PCA) care should focus on preventing rearrest, specifically targeting hemodynamic stability and pulmonary/respiratory function. Specific goals of hemodynamic stabilization should include normalization of central venous oxygen saturation, central venous pressure, cardiac output, arterial blood pressure, and arterial oxygen content. IV fluid therapy should be judicious and efforts should be made to prevent overresuscitation. Ventilatory function may be altered in PCA patients with resultant hyper- or hypoventilation. Ventilation should be assessed and positive pressure ventilation should be provided as needed to maintain normocapnia ($PaCO_2$ 35–45 mmHg). Supplemental oxygen or mechanical ventilation is used as needed to maintain normoxemia (PaO_2 90–100 mmHg).

As the PCA period increases, focus should be directed at preventing or minimizing secondary organ damage and neuroprotection. The routine use of corticosteroids, hyperosmotic fluids, and anticonvulsants is not recommended. If evidence of increased intracranial pressure is present then treatment with mannitol or hypertonic saline is warranted. Should generalized seizures develop then appropriate treatment with an anticonvulsant should be started. Prophylactic treatment with anticonvulsant medications may be considered in animals demonstrating global cerebral signs (coma, compulsion) in the postarrest period. The use of corticosteroids has not been documented to improve outcome and their use should be restricted to animals with a clear indication due to the potential for severe adverse effects.

Induction of mild therapeutic hypothermia is rapidly becoming the standard of care in human PCA management. Its use has been described in the veterinary literature but is not widespread at this time. Due to the risks associated and the technical difficulty of safely inducing and maintaining appropriate hypothermia, it is not currently recommended. If, however, mild hypothermia develops spontaneously, the patient should not be aggressively warmed; rather, the return to normothermia should be gradual (0.25–0.5 °C/h).

Discontinuing CPR

The decision to terminate CPR generally lies with the clinician. When making the decision to withhold or terminate CPR, several factors should be considered including the inciting cause of the arrest, interval from onset of arrest to initiation of CPR, duration of CPR, and long-term prognosis associated with the underlying disease process. Although no definitive guidelines exist, continuing efforts for 15–20 minutes is reasonable, after which time the likelihood of a good neurologic outcome is exceedingly small and CPR can be discontinued.

Further Reading

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38

Respiratory Monitoring in Critical Care

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Purpose

The purpose and goals of respiratory monitoring in critical care typically include the following:

- identification of patients in respiratory distress and those experiencing dyspnea
- determination of response to specific or empiric therapies
- assessment of the adequacy of alveolar ventilation
- assessment of the adequacy of oxygenation
- evaluation of gas exchange efficiency
- evaluation of pulmonary mechanics in order to categorize disease states, explain other related clinical findings, or monitor response to therapy.

Identifying Respiratory Distress and Dyspnea

Respiratory distress is a state in which breathing efforts are excessive or inadequate relative to the healthy state or the patient's current requirements. While many definitions rely on inadequate oxygenation or ventilation, such approaches fail to account for patients in whom adequate gas exchange is obtained only with excessive effort. Tachypnea (increased respiratory rate) and hyperpnea (increased respiratory effort and/or chest excursions) are often considered the hallmarks of respiratory distress; however, a smaller subset of patients may present with hyponea (decreased respiratory effort and/or chest excursions), bradypnea (decreased respiratory rate), or both. This second type of patient is also in respiratory distress.

Dyspnea is a term often used synonymously with respiratory distress in veterinary practice, although it has been suggested that this convention is not ideal. In human medicine, dyspnea refers to the unpleasant sensations of feeling unable to catch one's breath or being consciously aware of one's breathing effort. The three subcategories of dyspnea sensations identified in humans are air hunger, increased work/effort, and asthmatic chest tightness. Experimental evidence exists to suggest that vertebrates other than humans are able to experience the first two of these. To date, no experimental approaches have been developed to determine if animals are likely to experience asthmatic chest tightness. Ideally, the term *dyspnea* would be reserved for consideration of the sensory experience (akin to pain) and respiratory distress would be used to describe what clinicians might observe (akin to nociceptive responses). Serial monitoring of patients for signs of respiratory distress or dyspnea is the cornerstone of respiratory monitoring. Respiratory monitoring may include many other tools, but these are always best evaluated in light of current patient status and clinical context.

Clinical Signs of Respiratory Distress

Box 38.1 provides an outline of broad categories of clinical signs that may be present in a patient with respiratory dysfunction or distress. Two categories of sounds may herald respiratory distress: those heard with the ear and those heard with the stethoscope. Stertor and stridor are sounds that typically do not require a stethoscope to be audible. Stertor is the presence of snoring-like noises during respiration. It is the result of abrupt displacement of upper airway soft tissue structures and altered gas flows. It is typically low-pitched, discontinuous, and nonmusical in character. It may be evident on inspiration, exhalation, or both. Stridor is a high-pitched, musical respiratory sound generated by altered gas flows in the large airway. It is more typically heard on inspiration. Either stertor or stridor can indicate an abnormality of the proximal upper airways (i.e., cranial to the thoracic inlet).

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Box 38.1 Categories of signs associated with respiratory distress in dogs and cats

- Abnormal sounds
  - Heard without a stethoscope
    - – Stertor
    - – Stridor
  - Heard with a stethoscope
    - – Diminished breath sounds
      - Regional
      - Focal
    - – Adventitious sounds
      - Crackles
      - Wheezes
      - Rhonchi
    - – Borborygmus
- Changes in position/posture/orientation
  - Orthopnea
  - Trepopnea
  - Neck extension
  - Upright stance (flexed pelvic limbs, extended thoracic limbs)
    - – Sternal recumbency (Sphinx pose)
  - Abducted elbows
- Reflex compensatory changes due to hypoxemia and hypercapnia
  - Tachypnea
  - Tachycardia
  - Hyperpnea
- Signs associated with reduced/altered gas flow velocities
  - Phase prolongation
    - – Inspiration
    - – Exhalation
    - – Both
  - Inability to vocalize
- Adaptive responses which reduce respiratory system resistance
  - Open-mouth breathing
    - – Retracted commissures of the lips
  - Nares flaring
  - Neck extension
- Signs secondary to marked hypoxemia
  - Cyanosis
  - Obtundation
- Abnormal or excessive abdominal motion
  - Passive abdominal motion due to hyperpnea
  - Active expiratory abdominal muscle contraction
  - Paradoxical motion
- Signs of the sensation of dyspnea
  - Obtundation
  - "Anxious" expression
  - Dilated pupils
  - Poorly tolerant of restraint/fractious
  - Not eating, drinking, sleeping, and/or grooming

Altered breath sounds can also herald respiratory distress in small animal patients and may also aid in the determination of the underlying cause. Breath sounds may be altered in their distribution, their volume (i.e., loudness), and their character. Diminished breath sounds in the nondependent lung fields may indicate accumulation of gas in the pleural space, whereas the same finding in the dependent lung regions suggests pleural fluid accumulation or nonventilated lung (or both). Focal absence of breath sounds may indicate that one or more lung lobes are obstructed, consolidated, collapsed, torsed, infiltrated, or compressed by an intrathoracic mass lesion. In addition, adventitious sounds (crackles, wheezes, rhonchi) may indicate lower airway and pulmonary parenchymal pathology. Crackles are explosive, discontinuous, nonmusical sounds generated by small airways abruptly opening. They may be fine or harsh in character. While often heard on inspiration (opening during expansion), they may also be present during exhalation in some settings. Wheezes are higher pitched, musical, and of longer duration than crackles. They are often the result of diffuse lower airway narrowing. Rhonchi are similar to wheezes but substantially lower in pitch. Abnormal sounds that might be ausculted over the thorax also include borborygmus, which may indicate a compromise of the diaphragm with displacement of intestinal viscera into the thoracic cavity.

Changes in body position/posture, orientation of the head and limbs, respiratory rate, and the magnitude of inspiratory excursions all may indicate respiratory system compromise. Patients in respiratory distress often assume an upright posture with the pelvic limbs flexed and the thoracic limbs extended. This posture allows the weight of the abdominal contents to rest on the pelvis rather than the diaphragm and reduces the work of breathing. In cats, a more typical posture is to sit propped in sternal recumbency (sphinx pose). Patients that exhibit greater respiratory distress when in recumbency are termed orthopneic and this may manifest as a reluctance to lie down or be restrained. The head is often held in dorsoflexion with the neck extended. This position reduces the work of breathing by straightening the trachea and minimizes narrowing. Moreover, by fixing the head position in this way, accessory respiratory muscles (e.g., serratus ventralis muscle) can be utilized to promote expansion of the cranial thorax. Elbow abduction and fixing the position of the forelimbs allows for the recruitment of other accessory respiratory muscles and reduces the impact of the weight of these limbs on chest expansion. Respiratory compromise that is more severe in one lateral recumbency than the opposite is termed trepopnea and often is due to asymmetric pulmonary parenchymal disease.

Increases in respiratory rate are often the earliest sign of respiratory system compromise. Tachypnea at rest may frequently precede more overt signs in patients with

chronic cardiac or respiratory disease. Tachypnea and hyperpnea with exertion are also considered early signs in this same setting. Both tachypnea and hyperpnea are adaptive responses in most settings, but not all. These responses represent the clinically apparent consequences of attempts to maximize alveolar ventilation. However, they may be triggered by pain, hypotension, and other factors. In patients with upper airway disease, these responses are generally maladaptive as they increase the work of breathing and may promote further airway narrowing via the Venturi effect.

Tachypnea must be distinguished from panting which occurs in hyperthermic (not febrile) animals with the mouth open. Febrile animals have a reset thermoregulatory set-point and thus the elevation in body temperature will only result in occasional panting when body temperature temporarily exceeds this threshold. Tachypnea does not imply open-mouth breathing whereas this is a hallmark of panting. Panting does not alter ventilatory status whereas tachypnea may result in hyperventilation in some settings but not others.

Respiratory monitoring also includes assessing patients for clinical signs relating to reduced respiratory gas flow velocity. Such flow reductions may manifest as prolongations of the inspiratory (upper airway disease) or expiratory (intrathoracic airway disease) phases of respiration. Both phases of respiration may be affected concurrently in some disease states. One example is feline asthma. Bronchoconstriction results in increased resistance to both inspiratory and expiratory flows, although the increase is generally more marked during exhalation. An inability to vocalize indicates a severe reduction in expiratory gas flows and should prompt immediate assessment of upper airway patency.

Several clinical signs that manifest in veterinary patients with respiratory distress represent adaptive responses that serve to reduce airway resistance. Neck extension as discussed above is one example. Flaring of the nares represents recruitment of the dilator naris muscle and is stimulated by hypoxemia and hypercapnia and inhibited by pulmonary stretch receptor activation. Breathing through an open mouth also reduces respiratory system resistance while foregoing the benefits of gas conditioning (humidification, particle trapping) by the nasal passage. Animals in respiratory distress often breathe with their mouths open although other conditions (pain, hyperthermia) can also elicit this same response. Animals in respiratory distress typically do not hang the mouth passively open, but rather actively retract the commissures of the lips and extend the tongue outward. Activity of the genioglossus muscle may be synchronized with the respiratory cycle, resulting in cyclic protrusion of the tongue outwards.

Cyanosis is a severe but unreliable sign of respiratory compromise. When present, it generally indicates severe hypoxemia. However, in anemic patients, the amount of deoxygenated hemoglobin present in the capillary beds may be too low to result in a color change detectable to the clinician.

Abnormal or excessive abdominal motion during respiration may indicate respiratory distress. Passive abdominal motion and increased abdominal effort are not the same thing, although they may look similar from a distance. More pronounced outward motion of the abdomen on inspiration is passive and caused by increased contraction of the diaphragm. Active contraction of the abdominal muscles (e.g., rectus abdominis) represents recruitment of accessory respiratory muscles whereas passive displacement of the abdominal contents during inspiration does not. The clinician may need to palpate the ventral abdominal muscles during exhalation to distinguish between the two conditions. Tensing of the rectus abdominis during exhalation can usually be clearly felt when increased abdominal effort is truly present. Activation of the abdominal muscles during respiration actively aids exhalation and passively assists inspiration. Increasing intraabdominal pressure (and thus passively increasing intrathoracic pressure) raises the pressure driving expiratory gas flows. This increase in abdominal pressure also serves to place the diaphragm in a more cranial position prior to the next inspiratory effort. This diaphragmatic shift places it in a more favorable orientation for contraction and thus abdominal muscle activity can enhance diaphragmatic performance. True increased abdominal effort generally indicates expiratory flow limitation due to intrathoracic airway narrowing or collapse.

Some patients may have atypical abdominal wall motion. Paradoxical motion (abdomen moving inward on inspiration) may be seen with diaphragmatic hernia, fatigue, or paralysis. A more focal inward movement of the abdominal wall adjacent to the costal arch is often seen in patients with pleural effusion. Any significant motion of the soft tissues in the region overlying the thoracic inlet may indicate abnormal or increased respiratory effort.

Clinical Signs of Dyspnea

Small animal patients may also exhibit clinical signs that one might attribute to the unpleasant sensation of dyspnea. Such signs include a blunted response to the environment (obtundation) as the patient focuses solely on the act of breathing. An "anxious" facial expression with dilated pupils bilaterally is common. Such patients are typically not eating, drinking, or sleeping adequately. A patient that has been in respiratory distress and is now devoting energies to these other needs is likely improving. In cats, the absence of grooming behaviors may be associated with sensations of dyspnea. Returning to normal hygiene routines often accompanies a marked

improvement in respiratory status. Patients that are experiencing dyspnea are often excessively fractious and resistant to physical restraint.

Respiratory monitoring in the critically ill veterinary patient should include initial and serial evaluation for the presence of all the above physical exam findings. Serial evaluation often allows the clinician to put quantitative data (see later) into their proper context. The response to specific or empiric therapies is best assessed based on a combination of these physical exam findings, imaging, and quantitative laboratory assay results.

Determination of Response to Specific or Empiric Therapies

Respiratory monitoring plans are frequently designed with the goal of assessing response to therapy. Serial monitoring of respiratory rate is perhaps the most widely used approach in most settings (e.g., monitoring response to diuretics in presumed congestive heart failure patients). Other examples might include the assessment of pulse oximetry, respiratory effort, and breathing pattern in response to oxygen supplementation. Such minimally invasive approaches can be quite useful but in other cases, more invasive procedures such as intubation, positive pressure ventilation, and arterial blood gas sampling are required both to correct the problem and to monitor progression.

Marked improvement in respiratory status following intubation is expected for upper airway obstruction in the absence of other co-morbidities. Likewise, hypoxemia due solely to hypoventilation should resolve with oxygen supplementation in all cases short of apnea or agonal breathing. Failure of hypoxemia to resolve with oxygen supplementation typically indicates significant venous admixture and physiologic or anatomic right-to-left shunting. Hypoxemia that resolves with oxygen supplementation in a patient that simultaneously demonstrates little or no improvement in clinical signs of respiratory distress can be indicative of pulmonary thromboembolism (PTE). Respiratory monitoring plans should be tailored to the individual patient and the pathology believed to be present.

Assessment of the Adequacy of Alveolar Ventilation

The alveolar gas equation or "PCO_2 equation" ($PACO_2 \sim VdotCO_2/V_A$) provides the rationale for all forms of ventilatory status monitoring. The equation states that the partial pressure of carbon dioxide in alveolar gas varies directly with CO_2 production and inversely with alveolar ventilation. The adequacy of alveolar ventilation is defined by the alveolar partial pressure of carbon dioxide. If alveolar ventilation is adequate for the current level of CO_2 production then $PACO_2$ will be within the normal range. If alveolar ventilation is inadequate or excessive, the $PACO_2$ will be increased or decreased, respectively. The rate of production of carbon dioxide ($VdotCO_2$) is largely irrelevant. Ventilatory adequacy is defined relative to current carbon dioxide production *no matter what that current level might be*. In extreme cases such as malignant hyperthermia, carbon dioxide production exceeds the level that *any* healthy respiratory system could remove from the system; however, those patients are still defined as hypoventilating despite having normal (or even exceptional) respiratory function.

Alveolar gas composition is not uniform across all alveoli and is exceedingly difficult to sample. Thus, the partial pressure of carbon dioxide from other sites serves as a surrogate in clinical practice. Clinically useful surrogate samples include arterial blood, venous blood (mixed, central, or peripheral), and end-tidal exhalate. Typical canine blood values for PCO_2 are shown in Table 38.1.

Table 38.1 Blood gas analysis reference intervals

	Arterial (cat)	Arterial (dog)	Mixed venous (dog)	Central venous (dog)	Peripheral venous (dog)
pH	7.39 +/−0.08	7.40 +/−0.03	7.36 +/−0.02	7.35 +/−0.02	7.36 +/−0.02
PCO_2	31 +/−5	37 +/−3	43 +/−4	42 +/−5	43 +/−3
Base deficit	−2 to +8	−4 to 0	−2 to 0	−4 to 0	−2 to 0
Bicarbonate	18 +/−4	21 +/−2	23 +/−2	22 +/−2	23 +/−1
Total CO_2	N.D.	22 +/−2	24 +/−2	23 +/−2	24 +/−2
PO_2	105 +/−10	102 +/−7	53 +/−10	55 +/−10	58 +/−9

Source: Adapted from Ilkiw et al. (1991). Values are presented as mean +/− standard deviation.
N.D., not determined.

The adequacy of each of these sample types is dependent on patient factors as will be discussed later.

Arterial blood is often an ideal surrogate sample for evaluating ventilatory status. Carbon dioxide is highly soluble and diffusible and alveolar partial pressures typically reach equilibrium with those in the bloodstream as venous blood is arterialized. Diseases that result in impaired diffusion of respiratory gases (e.g., emphysema) often result in fatal hypoxemia before becoming sufficiently severe to cause meaningful limitations in carbon dioxide diffusion, although hypercapnia may develop in these patients by other mechanisms. However, extremes of ventilation–perfusion mismatching can result in a dissociation of arterial ($PaCO_2$) and alveolar ($PACO_2$) carbon dioxide tensions. Even with this limitation, $PaCO_2$ remains the preferred surrogate sample for defining the adequacy of alveolar ventilation.

Venous blood PCO_2 can be useful in the assessment of ventilatory status in certain settings. As shown in Table 38.1, the carbon dioxide tensions in venous and arterial blood are not the same; however, in a hemodynamically stable patient the difference between the two is suitably constant (~5–7 mmHg) so as to allow reasonably accurate prediction of what current arterial values are likely to be. Venous values also define the *maximal* value that may be present in arterial samples at that time. For example, if the $PvCO_2$ is 55 mmHg then the $PaCO_2$ is likely to be 49 mmHg and will not be greater than 55 mmHg. Unfortunately, the utility of venous blood samples for defining ventilatory status is strongly dependent on cardiovascular performance. As cardiac output falls, the difference between $PvCO_2$ and $PaCO_2$ becomes progressively larger. In patients in shock or other low-flow states, venous samples are poor surrogate samples for the assessment of the adequacy of alveolar ventilation.

End-tidal CO_2 ($ETCO_2$) is an important means of monitoring ventilation in critically ill animals and encompasses both capnometry (numeric value only) and capnography (waveform representation). Of the various surrogate markers for alveolar CO_2, $ETCO_2$, when it is working well, is the closest to actually measuring $PACO_2$. End-tidal plateau partial pressures of carbon dioxide largely reflect the levels in alveolar gas. End-tidal CO_2 monitoring is the only tool that currently provides continuous, real-time assessment of the adequacy of alveolar ventilation. In addition, respiratory rate can be determined via this methodology as well. Capnography has the added benefit of allowing waveform inspection, which can be used to monitor for rebreathing, airway obstruction/bronchospasm, apnea, dyssynchronous alveolar emptying, valve malfunctions, and many other events.

Capnography and capnometry can also be useful in determining the status of the cardiovascular system. Exhaled carbon dioxide originates in the tissues and requires cardiac pumping activity to generate venous return and CO_2 delivery. Cardiac arrest is associated with an abrupt decline in $ETCO_2$ levels. Conversely, the adequacy of cardiac compressions can be assessed by capnography or capnometry.

Many modern capnography systems (e.g., $NICO_2$®) include a flow disrupter and differential pressure transducers within the same disposable unit that is attached to the patient's breathing circuit. This allows for monitoring of respiratory mechanics as well as single-breath capnography (CO_2 plotted against cumulative exhaled volume instead of over time). Single-breath capnography provides additional data relating to airway dead space, gas distribution, and perfusion that cannot be obtained easily (or at all) with standard time-plotted capnography. The disadvantages of end-tidal capnography are that it can add considerable apparatus dead space volume in small (<2 kg) patients and promote rebreathing and reduced alveolar ventilation. End-tidal capnography also becomes dissociated from arterial carbon dioxide tensions when significant alveolar dead space is present. A larger gap between arterial and end-tidal carbon dioxide tensions develops in the setting of pulmonary thromboembolism or in cardiovascular instability/profound hypotension.

Hypercapnia and hypocapnia represent (and define) inadequate or excessive alveolar ventilation. The absolute values used to define these states will vary with the analyzer used and the species. Typically, normocapnia is defined as PCO_2 of 35–45 mmHg in veterinary species.

Assessment of the Adequacy of Oxygenation

Hypoxemia is the term used to indicate inadequate partial pressure of oxygen in an arterial blood sample (PaO_2). The values at which samples are considered to indicate hypoxemia vary slightly by region/elevation. At sea level, PaO_2 of less than 80 mmHg and 60 mmHg are considered to indicate hypoxemia and severe hypoxemia, respectively. Hypoxemia does not always equate with reduced arterial oxygen content, however. Polycythemic patients may have near-normal arterial oxygen content (~20 mL O_2/dL of blood) despite mild-to-moderate hypoxemia. The increased hemoglobin concentration can allow for the preservation of total content even when partial pressure of oxygen is reduced.

Determination of the adequacy of oxygenation is relatively straightforward. An arterial blood sample is obtained and the determination of whether hypoxemia is present is made. Alternatively, a surrogate can be used in the form of pulse oximetry. With pulse oximetry, the

partial pressure of oxygen can be inferred from the saturation due to the known relationship between the two (the oxyhemoglobin equilibrium curve). If pulse oximetry were to be employed for this purpose then the cutoffs for hypoxemia and severe hypoxemia become 95% and 92%, respectively.

Hypoxemia may be due to hypoventilation, low inspired partial pressure of oxygen (PiO_2), or venous admixture. Hypoventilation typically only results in hypoxemia when the patient is breathing room air. Supplemental oxygen is sufficient to overcome hypoxemia due to increased alveolar carbon dioxide tension in all cases (except apnea). Low inspired partial pressure of oxygen (PiO_2; often incorrectly interpreted as FiO_2) can commonly be due to decreased total inspired gas pressure (low barometric pressure at elevation) or on very rare occasion to a decreased fraction of inspired oxygen (e.g., rebreathing circuit with inadequate oxygen inflow rates; asphyxiation).

Venous admixture is a term to describe all the means by which venous blood may fail to properly equilibrate with alveolar oxygen tensions during pulmonary perfusion. The principal means by which venous admixture occurs are as follows: (1) right-to-left anatomic shunting (congenital defects predominantly, although acquired shunting may occur if pulmonary hypertension develops), (2) ventilation–perfusion mismatch (most common cause), and (3) diffusion impairment (rarely a sole cause, but contributes to a degree any time alveolar surface area is lost due to collapse or flooding). Ventilation–perfusion mismatching may be severe enough to result in physiologic shunting when perfusion is maintained to alveoli that are receiving no fresh gas via ventilation. The other extreme (ventilation of nonperfused alveoli) results in increased dead space ventilation and does not *directly* lead to hypoxemia.

Both PaO_2 and SpO_2 tell one very little by themselves about the adequacy of oxygen delivery. In an anemic patient, the PaO_2 and SpO_2 may be normal while total arterial oxygen content is completely inadequate. It serves little purpose to assess PaO_2 or SpO_2 in isolation from other factors. If one is seeking to determine the adequacy of oxygen delivery to the tissues then venous partial pressures (PvO_2) and saturations (SvO_2) are more informative in this setting. PvO_2 cannot be used to evaluate pulmonary oxygenating performance as the blood has already been modified by cellular oxygen extraction. Properly handled samples can inform the clinician of the lowest value that PaO_2 could be (i.e., if PvO_2 is 64 mmHg then the patient cannot be *severely* hypoxemic as PaO_2 must be at least 64 mmHg).

PvO_2 serves as a reasonable marker of tissue hypoxia. The partial pressure in the venous blood will be a reflection of the partial pressure present in the end-capillary blood. Mixed and central venous samples are preferable as they represent a larger pooled sample than those obtained from a peripheral vein. Values for PvO_2 below 30 mmHg should prompt the clinician to assess global or regional perfusion and oxygen delivery. Values below 20 mmHg should prompt immediate patient assessment and intervention. Recently published work has suggested that central venous hemoglobin saturations greater than 68% are associated with improved outcomes in critically ill small animal patients. This value was obtained on an instrument not validated for canine blood and may only be directly relevant when that instrument is used; however, the value reported is intriguingly similar to that reported for critically ill humans and titrating therapy to maintain $ScvO_2$ in the high 60s is likely to be associated with improved outcomes in populations, if not necessarily in each individual patient.

Analysis of venous blood gases reinforces an important point: adequate partial pressure *and* adequate total oxygen content are *both* required for optimal oxygen delivery. Total content is essential to ensure that sufficient oxygen is available to be extracted due to oxygen's poor solubility in plasma. Partial pressure must also be high enough to drive diffusion from capillary beds to mitochondria. Neither inadequate carrying capacity (hemoglobin concentration) nor inadequate partial pressure (PaO_2) will allow for optimal cellular utilization of oxygen. Adequate partial pressure maintenance is particularly important when the diffusion distance is increased by tissue edema. The combination of hypoxemia and anemia represents a major challenge to homeostasis and oxygen supplementation is advisable while blood products are being obtained.

Evaluation of Gas Exchange Efficiency

As mentioned earlier, PaO_2 and SpO_2 evaluation taken in isolation may tell one very little about the adequacy of oxygen delivery. They also poorly define lung function when the clinical context is not considered. When one evaluates either parameter, the following factors must be considered at the time the reading was obtained: (1) the nature of the gas the patient is currently breathing and (2) the patient's current ventilatory status. A low PaO_2 on room air may be a result of poor lung function and venous admixture or it may be simply due to hypoventilation. An SpO_2 reading of 96% on room air may be acceptable, whereas it is cause for significant concern on 100% oxygen. These other factors cannot be ignored if any PaO_2 and SpO_2 readings are to be correctly interpreted. One approach to incorporating these factors into

a more holistic approach to interpreting oxygenation parameters is to consider *gas exchange efficiency*.

Gas exchange efficiency measures are a means of taking a given PaO_2 and SpO_2 value and asking, "What *alveolar* partial pressure of oxygen was required to achieve that value?" These tools are primarily a means of assessing how efficient the lung is at bringing pulmonary capillary and alveolar partial pressures of oxygen into equilibrium. When patients are breathing room air, the most widely used tool for this purpose is the alveolar-arterial PO_2 gradient (A-a gradient). This approach is based on the ideal alveolar gas equation (equation 1), which provides a means by which alveolar PO_2 may be approximated.

$$[PAO_2 = FiO_2 * (P_B - P_{H2O}) - PaCO_2 / RQ] \quad \text{(Eq. 1)}$$

In order to perform the calculation, one must know the following factors which are assumed or obtained from an arterial blood gas analysis: (1) FiO_2, the fraction of inspired oxygen (0.21 on room air), (2) P_B, barometric pressure (760 mmHg at sea level), (3) P_{H2O}, water vapor pressure (varies with body temperature, but usually taken as 50 mmHg), (4) $PACO_2$, alveolar carbon dioxide tension (arterial value is usually substituted), and (5) RQ, respiratory quotient (which varies with metabolic substrate used as a fuel source, 0.8–0.9 typically used). A simplified version (equation 2) is often used clinically.

$$PAO_2 = FiO_2(P_B - 50) - 1.2(PaCO_2) \quad \text{(Eq. 2)}$$

Once one has calculated PAO_2, the measured value of PaO_2 is subtracted from it to obtain the difference between the two (A-a gradient). Lower values indicate more efficient pulmonary gas exchange, with values less than 15 considered normal and greater than 20 abnormal.

The normal range for the A-a gradient is affected by the inspired oxygen concentration. One rule of thumb is that a normal animal may have a gradient of 1 mmHg for each percent oxygen they are inspiring (e.g., up to a 20 mmHg gradient is normal on room air and up to a 100 mmHg gradient is normal on 100% oxygen). These values are rough approximations only, however, and serial comparisons are best made on room air whenever possible. A-a gradients greater than 20 mmHg indicate that venous admixture is present and contributing to hypoxemia. This does not rule out hypoventilation as a secondary contributor (both may be present). Conversely, hypoxemia with concurrent hypoventilation and a normal (<20 mmHg on room air) A-a gradient suggests that hypoventilation is the sole cause of hypoxemia.

The "Rule of 120" is a nonquantitative shortcut for assessing whether venous admixture is present. If one takes any physiologically plausible value for $PACO_2$ and calculates what the resultant PAO_2 (using equation 1 above) would be on room air then subtracts 20 mmHg from that value, one obtains the lowest value for PaO_2 that could be present with that level of ventilation and no venous admixture. One finds that the $PACO_2$ and PaO_2 obtained this way always add up to greater than 120 mmHg. Thus, for an arterial blood gas result obtained on room air, the finding that the $PaCO_2$ and PaO_2 add up to more than 120 mmHg suggests that venous admixture is unlikely to be the cause of hypoxemia (if present). This is essentially a rapid, nonquantitative means of determining whether the A-a gradient is greater or less than 20–mmHg using an arterial blood gas obtained on room air. It is the author's understanding that this clever shortcut was developed by Dr Steve Haskins at UC Davis. It has proven to be an effective and efficient screening tool for venous admixture in critically ill dogs and cats.

The A-a gradient performs more poorly when patients are receiving supplemental oxygen because of the wide range of gradients that can be obtained from normal, healthy animals under these conditions. In this setting, the ratio of PaO_2 to FiO_2 (or P:F ratio) is more typically employed. Healthy animals have P:F ratios approximating 500 (unitless). For example, a healthy dog with a PaO_2 of 105 mmHg on room air (21% or 0.21 oxygen) would have a P:F ratio of 500 (i.e., 105/0.21 = 500). Humans and animals with acute lung injury (ALI) typically have P:F ratios of less than 300. This equates to a P_aO_2 of less than 63 mmHg on room air. Humans and animals with P/F ratios of less than 200 are considered to have lung function comparable to patients with acute respiratory distress syndrome (ARDS). The P:F ratio is of no use on room air. All that would represent is a transformation (x/0.21) of the PaO_2, which would provide no additional information. Moreover, since the P:F ratio does not take ventilation into account, abnormal values obtained from patients breathing room air could suggest that lung injury/venous admixture is present when in fact hypoventilation is the sole cause of hypoxemia.

The P:F ratio is best used to compare gas exchange efficiency using values obtained from the same patient while receiving supplemental oxygen or on mechanical ventilation (or both). However, the P:F ratio is highly labile and prognostication and lung recovery assessment are best performed with many serial measurements rather than just two.

Recently, it has been suggested that the ratio of SpO_2 to FiO_2 might serve as a noninvasive alternative to the P:F ratio. This approach has been validated in human patients with ARDS, but as of this writing no such validation has been published in the veterinary literature. One small pilot study tends to support the utility of this approach.

Use of Pulmonary Mechanics to Categorize Disease

In the critically ill veterinary patient, the evaluation of pulmonary mechanics is perhaps most often performed via inspection of ventilator waveforms. A discussion of the topic of ventilator waveform analysis herein is prevented by time and space restrictions. Instead, the reader is referred to the recommended readings, which cover the topic in great depth.

Conclusion

The physical exam is arguably the most valuable tool in respiratory monitoring. Blood gas analysis and capnography can provide useful diagnostic and prognostic information that complements exam findings. Ventilation, oxygenation, the adequacy of oxygen delivery, and gas exchange efficiency can all be assessed to a degree with arterial and venous blood samples. Each of these parameters can be assessed separately, but greater diagnostic value is obtained when they are taken as a whole.

Further Reading

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39

Acute Respiratory Failure

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Etiology/Pathophysiology

Acute respiratory failure occurs when an insult to the respiratory system that is sudden in onset or short in duration results in levels of alveolar ventilation or pulmonary oxygen transfer (or both) that are insufficient to maintain vital metabolic processes and homeostasis. This term does not imply that chronic respiratory compromise is not present concurrently. In a subset of cases, the acute exacerbation of a chronic process or the sudden development of a secondary complication (e.g., respiratory tract infection) may lead to signs of acute deterioration in clinical status. Similarly, chronic pulmonary compromise may lead to fairly abrupt fatigue of the muscles of respiration and provoke an acute crisis. The proximate cause of the acute crisis in such a case is the suddenly inadequate ventilatory capacity; however, the ultimate underlying cause may be an unsustainable workload due to a chronic disease process (e.g., progressive dynamic airway collapse, parenchymal fibrosis, etc.).

Categorization schemes for acute respiratory failure are typically multitiered in their organization. The first level of differentiation is often based on the predominant arterial blood gas alteration. With this approach, one often finds acute respiratory failure initially divided into three main subcategories: (1) hypercapneic respiratory failure, (2) hypoxemic respiratory failure, and (3) mixed respiratory failure.

Hypercapneic Respiratory Failure

Hypercapneic respiratory failure includes those conditions that result in a severe, sustained reduction in alveolar ventilation. By definition, a respiratory acidosis is present. Acidemia, or a reduction in blood pH, may or may not be present concurrently, depending on a host of other factors such as the current capacity of the extracellular hydrogen ion buffering systems. Generally, in acute hypercapneic respiratory failure, inadequate time has passed to allow for generation of maximal compensatory responses and acidemia is present more often than not.

The cut-off value for CO_2 at which hypercapneic respiratory failure is deemed to be present varies, but is typically in the 50–60 mmHg range when arterial or end-tidal exhalate sampling is utilized. A $PaCO_2$ of greater than 60 mmHg is often listed among the indications for mechanical ventilation in the veterinary literature, which can thus serve as *de facto* evidence of respiratory failure in many instances.

Hypercapneic respiratory failure (and hypercapnia in general) is the result of one or more of the following circumstances: (1) inadequate or inappropriate ventilatory drive, (2) insufficient ventilatory capacity, or (3) an excessive mechanical or chemical load imposed on the respiratory system. Inadequate or inappropriate ventilatory drive results from intracranial disease, medications/anesthetics/sedatives, or extracranial encephalopathies. The respiratory centers reside in the medulla with inputs from both the pons and cerebrum. Diseases resulting in compromise of these pontine and medullary centers may lead to marked alterations in respiratory pattern (e.g., Cheyne–Stokes breathing, apneusis, etc.) or alternatively a reduction in respiratory rate and/or tidal volume with little alteration in pattern of breathing. In the setting of hypercapneic respiratory failure due to intracranial disease, hypercapnia may be both a result and a cause of elevated intracranial pressure and imminent herniation. Inadequate or inappropriate respiratory drive is typically identified in the laboratory setting by determining the relationship between minute ventilation and $PaCO_2$ or PaO_2. This relationship is rarely defined quantitatively in the clinical setting, however. Qualitatively, a clinician may note that a hypoxemic patient has failed to hyperventilate as would be expected. Such a finding would suggest altered ventilatory drive or inadequate ventilatory capacity.

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Insufficient ventilatory capacity is the second general mechanism for hypercapneic respiratory failure and is typically the result of compromise of the respiratory muscles or the neural input to them. Respiratory drive may be sufficient (although it is difficult to assess in this setting), while the transmission or end-effector systems are dysfunctional. The problem may lie anywhere along the myoneural axis. High cervical myelopathies (cranial to the C5 spinal segment) can disrupt transmission at a level cranial to the formation of the phrenic nerve roots. Low cervical myelopathies may impair the intercostal nerves while sparing phrenic nerve transmission (which is usually sufficient on its own to maintain ventilatory status). The nerve roots may be impacted by disease as is seen in polyradiculoneuritis (coon hound paralysis). Similar forms of ascending paralysis (tick paralysis, botulism, some snake envenomations) may result in hypercapneic respiratory failure that appears quite similar in nature although occurring via different mechanisms. The phrenic nerve itself may become compromised (phrenic neuropathy) due to trauma (surgical or external), demyelinating diseases, disruption by tumor growth, or idiopathic causes. Unilateral phrenic neuropathy is often well tolerated, while bilateral dysfunction can require mechanical ventilatory support.

Disorders of the neuromuscular junction can lead to hypercapneic respiratory failure. Junctionopathies may be subclassified as presynaptic, synaptic, or postsynaptic in nature. Presynaptic disorders include those that increase (e.g., low serum magnesium and some envenomations such as black widow spider bites) as well as decrease (e.g., hypocalcemia, botulism, tick paralysis, aminoglycoside antibiotics) acetylcholine release into synaptic clefts. Synaptic cleft disorders include diseases that alter the removal of acetylcholine from this site (e.g., cholinesterase inhibitors, organophosphates). Postsynaptic disorders can include forms of myasthenia gravis as well as administration of depolarizing and nondepolarizing muscle relaxants (e.g., succinylcholine).

Myopathies are a potential cause of reduced ventilatory capacity as well. Specific myopathies of the respiratory muscles are rarely diagnosed in veterinary patients except for traumatic myopathies. Traumatic diaphragmatic herniation or avulsion is perhaps the most frequently recognized myopathic process leading to hypercapnia and respiratory failure. Another uncommon but well-recognized myopathy of small animals that may profoundly reduce ventilatory capacity is potassium depletion polymyopathy of cats. While hypokalemic myopathies are more fully characterized in cats than dogs, it should be noted that profound hypokalemia also may result in hypoventilation in dogs. Other causes of diaphragmatic myopathies reported in humans are rarely reported in veterinary species, seldom associated with respiratory failure, or limited to select lines of highly inbred animals (e.g., Duchenne muscular dystrophy, thyrotoxicosis, myxedema, hyperadrenocorticism, systemic lupus erythematosus). Severe abnormalities of the sternum or chest wall may compromise diaphragmatic function by placing it at an unfavorable orientation or resting length.

An excessive mechanical or chemical load imposed on the respiratory system is the third general mechanism of acute hypercapneic respiratory failure. In this case, the respiratory system may be functioning at a high level but has been required to perform its duties in the face of a mechanical or chemical load that would exceed the capacity of any healthy respiratory system. Mechanical loads that are excessive may be the result of reductions in compliance of the chest wall or pulmonary parenchyma, increases in respiratory system resistance, or both. Reductions in compliance can result from alterations in the biomechanical properties of the structural elements themselves or alterations in surface tension forces. In the former instance, such alterations are typically the result of chronic disease processes and excessive fibrosis. However, acute changes can be superimposed iatrogenically in the form of tight wraps on the trunk at either the thoracic or abdominal level (e.g., spica splints, etc.). Elevated intraabdominal pressure (intraabdominal hypertension, abdominal compartment syndrome) can secondarily result in reduced respiratory system compliance and can develop acutely in the setting of hemoabdomen or other forms of rapid peritoneal fluid accumulation. Likewise, pleural filling disorders can compromise the tidal volume achieved with a given degree of respiratory muscular effort. A given volume of air may reduce tidal volume to a larger degree than an identical volume of fluid in the pleural space. Unlike fluid, air can expand and such expansion during inspiration can compromise tidal volume beyond the effect that results from disruption of pleural contact forces alone.

Acute reductions in the compliance of the pulmonary parenchyma and interstitium are often seen concurrently with disruption of surface tension forces in inflammatory and edematous lung diseases. Pulmonary edema, pulmonary hemorrhage, near-drowning, pneumonitis, and pneumonia all may lead to reduced pulmonary compliance both via tissue edema formation and increased surface tension due to surfactant dilution and alveolar collapse. While these effects are important, each of the diseases mentioned in this context is far more likely to cause hypoxemic respiratory failure than the hypercapneic form. Acute hypoventilation often occurs only when respiratory muscle fatigue develops or the airway becomes occluded with exudate, fluid, or foam.

Increased airway resistance is another important cause of hypercapneic respiratory failure due to an excessive

mechanical load. Many commonly diagnosed diseases in small animal practice can lead to excessive airway resistance, which is the resistance to the flow of gases during inhalation and exhalation. Airway resistance can impact both total gas flow into the system as well as intrapulmonary redistribution of gas after bulk flow has ceased (pendelluft). Many common diseases in small animal practice can cause life-threatening increases in airway resistance at the level of the extrathoracic (e.g., laryngeal paralysis, brachycephalic syndrome) or intrathoracic (e.g., feline asthma, tracheobronchial malacia) airways. These conditions are often chronically active with sudden deterioration resulting from additional factors such as increased environmental temperatures, inhaled particulates and antigens, respiratory tract infections, or atypical activity/exertion. Alternatively, disease progression may lead to a new manifestation that represents an intolerable burden (e.g., the onset of new, or higher grade, laryngeal or pharyngeal collapse).

Focal/localized intrathoracic airway narrowing or collapse typically needs to be quite proximal to significantly impair ventilation (e.g., tracheal or lobar bronchial collapse). Diffuse collapse or narrowing of large intrathoracic airways can severely impair ventilation and limit expiratory flow substantially. Narrowing or collapse of smaller intrathoracic airways generally needs to be diffuse in nature to significantly impair ventilation. Feline asthma and bronchiolitis in dogs (e.g., secondary to canine adenovirus infection) serve as examples of diseases encountered in small animal practice that result in diffuse small airway narrowing.

Increased alveolar dead space ventilation also represents a form of excessive mechanical load. In this setting, an atypically high proportion of respiratory muscular work is being devoted to ventilating alveolar units that are not participating in gas exchange. The effective alveolar ventilation is reduced although total minute ventilation may be normal (or more likely increased). This reduction in alveolar ventilation is identified (and defined) by the accompanying rise in alveolar and arterial carbon dioxide tensions. However, end-tidal concentrations become dissociated and reduced. This increase in the gradient between arterial and alveolar carbon dioxide tensions is due to the simultaneous emptying of those alveolar units that did and those that did not participate in gas exchange. Thus dead space gases dilute the carbon dioxide in the exhalate from perfused alveoli. Increased alveolar dead space may result from pulmonary vascular occlusion (e.g., pulmonary thromboembolism) or from decreased pulmonary capillary hydrostatic pressures in hypovolemia and other forms of severe cardiovascular impairment when intraluminal pressures are below alveolar pressures (i.e., extraluminal pressures exceed intraluminal pressures).

An excessive chemical load on the respiratory system can also manifest as hypercapneic respiratory failure. In this context, the high chemical load is in the form of excessive carbon dioxide and this CO_2 burden exceeds that which any healthy respiratory system might be able to eliminate. An excessive CO_2 load can be the result of an abrupt and marked increase in carbon dioxide production ($VdotCO_2$) as is seen in malignant hyperthermia or status epilepticus. Alternatively, the excessive CO_2 load can be the result of rebreathing exhaled carbon dioxide. Rebreathing may occur in several clinically relevant settings such as a maintaining a patient in a poorly ventilated, confined space (e.g., anesthetic induction box), excessive apparatus dead space (e.g., end-tidal monitoring and other devices attached to orotracheal tubes in very small patients), or exhausted soda lime in a rebreathing anesthetic circuit. The greater density of carbon dioxide relative to oxygen and nitrogen has raised concerns that a gradient may develop over time when animals are delivered supplemental oxygen via an improvised oxygen hood or nonpurpose-built oxygen cage (i.e., Elizabethan collar with plastic wrap cover). Convention is often to place the venting site upwards (12 o'clock) so that heat may readily escape; however, periodic shifting of the vent site to a downward location (6 o'clock) may be useful to reduce carbon dioxide accumulation. Typically, patient movement is sufficient to periodically shift the vent orientation without clinician intervention, but active repositioning may be required in moribund patients.

Hypoxemic Respiratory Failure

Respiratory failure that is categorized as hypoxemic largely results from venous admixture in various forms. Venous admixture is a term for the co-mingling of deoxygenated venous blood with arterialized blood during flow from the right heart to the left heart. Some authors prefer to use the term *true venous admixture* to describe right-to-left shunting through an abnormal anatomic conduit (e.g., right-to-left patent ductus arteriosus). In such frameworks, the mixing of deoxygenated venous blood with arterialized blood that occurs in the pulmonary veins in conditions such as increased ventilation–perfusion mismatching is termed *venous admixture-like* in nature. Such distinctions offer little advantage in the author's opinion. A more clinically relevant approach might be to define venous admixture as those conditions which produce hypoxemia with an accompanying increase in alveolar-to-arterial PO_2 gradient (A-a gradient). The predominant mechanisms resulting in hypoxemia are listed in Box 39.1.

Hypoventilation results in hypoxemia by reducing alveolar oxygen tensions. The retention of carbon dioxide within the alveolar spaces reduces the partial pressure

Box 39.1 Mechanisms of hypoxemia

Associated with a *normal* A-a gradient (no venous admixture)

- Hypoventilation
- Decreased PiO_2

Associated with an *increased* A-a gradient (venous admixture)

- Right-to-left shunting (anatomic shunting)
- Perfusion of nonventilated alveoli (no V–Q; physiologic shunting)
- Ventilation–perfusion mismatching (low V–Q)
- Diffusion impairment

of oxygen via dilution to a degree, but it is ultimately the failure to provide adequate inflow of oxygen to replace what has been taken up that reduces PAO_2. For this reason, hypoxemia due to hypoventilation may be readily corrected by restoring appropriate levels of alveolar ventilation, by increasing the proportion of inspired gas that is oxygen (i.e., FiO_2), or both. Hypoventilation is thus best considered as a form of hypercapneic respiratory failure rather than a truly hypoxemic form. Hypoventilation is an implausible mechanism of hypoxemia in patients receiving supplemental oxygen if one excludes complete apnea from the discussion.

Decreased PiO_2 is an often incorrectly or incompletely categorized cause of hypoxemia. Many authors will list decreased FiO_2 instead of PiO_2 as the mechanism. A truly decreased fraction of inspired oxygen is quite rare as the proximate cause of hypoxemia and would generally only be encountered if a patient were on a rebreathing circuit with inadequate fresh gas inflow. One would hope that this is a rare occurrence. Low PiO_2 in contrast is quite common and occurs any time an animal is taken significantly above sea level unless they are maintained in a suitably pressurized environment such as an aircraft. The hypoxemia that develops at elevation is the result of a decrease in PiO_2 with a normal FiO_2 (i.e., the atmosphere is still 21% oxygen, but total pressures and thus all partial pressures are decreased). For a patient breathing room air at sea level, decreased PiO_2 is not a reasonable differential diagnosis for hypoxemia. In the case of both hypoventilation and decreased PiO_2, the hypoxemia that is observed is due to a decrease in PAO_2. This decrease is accompanied by a proportional decrease in PaO_2 and thus the A-a gradient remains within the normal range.

As mentioned above, causes of hypoxemia that are associated with an increased A-a gradient are those that fall under the overarching category of venous admixture. Venous admixture includes all mechanisms by which blood passing from the right heart to the left heart fails to be properly oxygenated despite an adequate alveolar partial pressure of oxygen (PAO_2). Calculation of the A-a gradient is covered in Chapter 38.

Right-to-left shunting (anatomic shunting) is a relatively uncommon cause of hypoxemia in veterinary practice relative to other forms of venous admixture. Tetralogy of Fallot is perhaps the most common congenital defect in which right-to-left shunting occurs routinely. In many other conditions, a potential shunting conduit may be present but right-to-left shunting does not occur unless cardiac pressures on the right side exceed those on the left (e.g., septal defects). Similarly, pathology involving the great vessels such as patent ductus arteriosus would not be expected to result in right-to-left shunting unless significant pulmonary hypertension, profound systemic hypotension, or both were present. In such cases, differential cyanosis may alert the clinician to the presence of this pathology. When significant anatomic right-to-left shunting is present, hypoxemia may become refractory to correction with supplemental oxygen. When shunt flow reaches 30% of cardiac output, hypoxemia is largely unresponsive to supplemental oxygen, with no improvement expected at all when shunt flow approaches 50% of total blood flow. The shunt equation is slightly cumbersome and a clinically useful shortcut is to estimate 5% extra shunting (5% is normal so this is *additional* shunting added to the 5% baseline value) for every 100 mmHg that the PaO_2 is below the expected value for that FiO2. For example, if a patient has a PaO_2 of 200 mmHg on 100% oxygen then one would estimate the shunt fraction to be 20% (expected PaO_2 is 500 mmHg on 100% oxygen).

Physiologic shunting occurs when perfusion is maintained to nonventilated alveoli. This situation could be considered a failure of hypoxic pulmonary vasoconstriction. Inflammatory mediators and drug agents can compromise the function of both the sensing and effector arms of this response system. As alveolar oxygen tensions drop, the expected response is that the local vascular resistance to those alveoli will increase, thus diverting flow to better-ventilated alveoli. In the case of zero alveolar ventilation, the optimal response would be to reduce perfusion to that region as well. Failure to do so results in physiologic shunting. The effect is the same as if the lung were not there at all and the blood was passing through an anatomic shunt. This mechanism explains why obstruction of ventilation to a lung lobe during lung lobectomy (e.g., during one-lung ventilation for thoracoscopic lung lobectomy) results in hypoxemia, but the subsequent lung lobectomy itself does not. Removal of an excessive amount of lung tissue (e.g., all the lung lobes on the right side) can result in hypoxemia, but this is due to ventilation–perfusion mismatching (excessive perfusion relative to ventilation) in the remaining lung lobes rather than physiologic shunting. Much as is observed

with anatomic shunting, physiologic shunting, when excessive, can result in hypoxemia that is unresponsive to oxygen supplementation. In this setting, the clinical priority is to restore ventilation to the nonventilated alveoli, which often mandates mechanical ventilation with positive end-expiratory pressure (PEEP).

Ventilation–perfusion (V–Q) mismatch is perhaps the most common cause of hypoxemic respiratory failure in small animal practice. Aspiration pneumonia, cardiogenic edema, and noncardiogenic edema are commonly encountered causes of hypoxemia in small animal patients and can each result in respiratory failure. Pleural filling disorders can result in V–Q mismatch as well as hypoventilation. Atelectasis and pulmonary thromboembolism each result in V–Q mismatch as well, albeit by vastly different mechanisms. Pulmonary hypertension is increasingly recognized as a major health concern in veterinary species and can result in substantial V–Q abnormalities. Figure 39.1 illustrates the basic concepts of V–Q matching and mismatching.

In the ideal lung, ventilation and blood flow would be delivered proportionally to alveoli. An increase in ventilation relative to blood flow (high V:Q ratio) is akin to dead space ventilation and does not directly cause hypoxemia since blood flowing to such alveoli encounters alveolar oxygen tensions that are normal or slightly above typical values. Perfect one-to-one matching likewise produces conditions that are favorable for pulmonary capillary and alveolar oxygen tensions to reach equilibrium, assuming blood flow rates are not excessive (and they rarely are except in extreme circumstances). It is in those alveolar units where perfusion is disproportionately high relative to ventilation that hypoxemia develops. In this setting, blood encounters atypically low alveolar oxygen tensions and saturation is submaximal. The mixing of this poorly arterialized blood with the blood draining high and normal V–Q regions results in systemic hypoxemia. The shape of the oxyhemoglobin equilibrium curve precludes the high V–Q regions from "compensating" for the low V–Q regions. The flat portion observed at high PO_2 values prevents an increase comparable to the decrease observed at lower PO_2 values (the steep portion). Moreover, the low V–Q regions may be of that nature because of high flow (not just low ventilation) and are thus contributing a disproportionately high volume to the final mixture. Likewise, the high V–Q regions may represent areas with normal ventilation but lower perfusion and are thus contributing relatively less volume to the final mixture.

As with physiologic shunting, V–Q mismatch may be considered a failure of hypoxic pulmonary vasoconstrictive responses in many settings. Whether the problem arose due to a reduction in ventilation or an increase in perfusion, adaptive compensatory adjustments would be expected in any otherwise healthy animal. In other circumstances, inadequate hypoxic pulmonary vasoconstriction may not be primarily responsible for the V–Q inequality. In massive pulmonary thromboembolism (PTE), the portion of the lung to which blood flow is compromised is now a high V–Q region. It has become physiologic dead space and is not directly responsible for hypoxemia (high V–Q regions provide well-oxygenated blood). In this setting, if cardiac output does not fall substantially then the remaining lung is now overperfused and represents a large region of low V–Q alveolar units. In this way, hypoxemia can result indirectly.

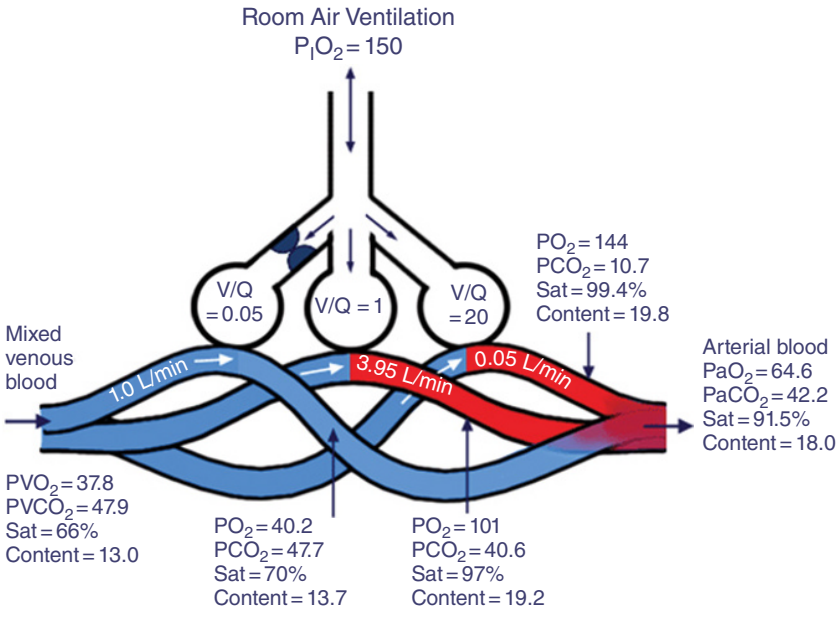


Figure 39.1 Ventilation–perfusion mismatching. Partial pressure values are in units of mmHg. Flow to normal and high V–Q regions produces appropriately arterialized blood. The blood perfusing the region with reduced alveolar ventilation (far left alveolus) produces hypoxemic blood. The final mixture is hypoxemic due to the disproportionate decrease in saturation in the blood (70% vs 97%) from the low V–Q regions and the minimal increase (99.4% vs 97%) in saturation in the blood from the high V–Q regions. Moreover, the low V–Q region has disproportionately high flows relative to the high V–Q regions (1.0 L/min vs 0.05 L/min).

This explanation seems insufficient to explain clinical experiences with this disease process, however. Surgically removing a similarly sized region of lung would presumably produce the same level of overperfusion, but does not typically result in hypoxemia. The missing portion of the mechanism for hypoxemia in this setting is likely to be altered bronchomotor tone. It was first demonstrated in 1942 that pulmonary thromboembolism (or external mechanical occlusion of a pulmonary artery) results in bronchospasm in the dog. The hypoxemia seen in PTE, but not following lung lobectomy, is likely the result of overperfusion combined with regional decreases in ventilation. Relief in sensations of dyspnea in humans is reported following theophylline administration. This may be due to a reduction in bronchospasm or reduced activation of pulmonary C-fibers via adenosine receptor antagonism.

Diffusion impairment is a common contributor to hypoxemia in small animal patients, but rarely a sole or primary cause of such. Fick's law of diffusion details the major contributing factors to gas or solute flux via diffusion: (1) concentration or partial pressure difference, (2) length of the diffusion pathway, and (3) surface area available for diffusion. With these factors in mind, both hypoventilation and low PiO2 represent a reversible form of diffusion impairment. Many of the diseases listed above under V–Q mismatch result in alveolar flooding or collapse which represents a loss of surface area for diffusion. In a similar manner, PTE results in the formation of excessive alveolar dead space, which also represents a loss of surface area for diffusion. Among the diseases common to small animal practice, chronic congestive heart failure likely represents the best example of increased diffusion distance. Remodeling of the alveolar epithelial–capillary endothelial interface in chronic congestive heart failure can result in thickening of this barrier and an increased diffusion distance.

Despite these many examples of means by which common disease processes can compromise the process, diffusion limitation is considered to be a primary cause of hypoxemia on only rare occasion. In human medicine, emphysema can result in a massive sustained loss of surface area and diffusion limitation is considered a more significant cause of hypoxemia in that species. The limited role of diffusion impairment in producing hypoxemia in small animal species is perhaps best illustrated in the setting of chronic congestive heart failure. In this syndrome, some degree of diffusion limitation is likely chronically present yet hypoxemia is rarely noted in the absence of pulmonary edema with alveolar flooding and V–Q mismatch. Pioneering work by Norman Staub has previously demonstrated in acute models of canine congestive heart failure that interstitial pulmonary edema is insufficient to produce hypoxemia in the absence of alveolar flooding in this species. Many clinicians have reported the experience of managing congestive heart failure patients in which clinical signs of respiratory distress have resolved yet thoracic radiographs still demonstrate persistent interstitial edema. Such experiences may reflect resolution of hypoxemia prior to clearance of excessive fluid accumulation in the pulmonary interstitium.

Diffusion impairment may be overcome by increasing the partial pressure gradient by raising PAO_2 or instead by recruiting additional surface area (or both). The recruitment of additional surface area can involve both recruitment maneuvers (breath hold) and the application of PEEP during mechanical ventilation.

Epidemiology

The epidemiology of respiratory failure in small animal patients is largely unknown. The epidemiology of respiratory failure in human medicine is also poorly understood. Most definitions of respiratory failure are based on arterial blood gas values. In human pediatrics, noninvasive tools are widely employed for the assessment of pulmonary function (e.g., pulse oximetry, cutaneous gas monitoring systems, etc.). Conservative estimates suggest that as many as 35% of respiratory failure patients in pediatrics are excluded because noninvasive monitoring methods were employed. Similar concerns are raised in studies of the epidemiology of respiratory failure in adult humans to a lesser degree. Between 2001 and 2009, hospitalizations for acute respiratory failure rose from 1 million cases to 1.9 million cases per year in the United States alone. The associated healthcare costs rose from $30 billion to $54 billion. A decrease in mortality has been observed over this period despite overall rates of mechanical ventilation remaining unchanged.

Attempts could be made to estimate the prevalence or incidence of small animal respiratory failure based on previously published large retrospective studies of mechanical ventilation in small animal patients. However, such data are heavily biased and likely poorly represent small animal patient populations as a whole. Patients in such studies represent only those with the following characteristics: (1) patients that were presented to a secondary or tertiary care center that offers long-term (>24 h) mechanical ventilation, (2) patients in whom respiratory failure was recognized by the attending clinician, (3) cases in which mechanical ventilation was offered, (4) cases in which clients elected to pursue this therapeutic option, and (5) cases which were not excluded from the analysis. Such reports almost certainly document only a small fraction of respiratory failure cases cared for by small animal practitioners.

One recent study examined the distribution of disease type/localization in dogs presenting for respiratory distress (termed *dyspnea* by the authors) [1]. In this study, upper airway disease, lower respiratory tract disease, pleural filling disorders, and cardiac disease represented 32%, 33%, 19%, and 12% of the cases, respectively. If one were to assume that each of these was equally likely to progress to respiratory failure then period prevalence rates might be estimated. However, this is clearly not the case. For example, pleural filling disorders are likely to be managed effectively via drainage methods before overt respiratory failure becomes persistent. Dogs in this study with lower respiratory tract disease were less likely to survive to hospital discharge. It is likely that these patients and patients with upper airway disease are more representative of patients that develop acute respiratory failure. Dogs with upper airway disease and pleural filling disorders were younger on average than dogs with cardiac disease. This finding may impact the epidemiology of respiratory failure if such data were to become available.

While respiratory distress is widely recognized as a common presenting complaint in small animal practice, the epidemiology of respiratory failure in veterinary medicine will remain largely unknown until consensus definitions and routine surveillance measures become commonplace.

Signalment

Acute respiratory failure can result from diverse disease processes and thus the signalment varies widely with the precipitating cause. Certain breeds may be associated with diseases that can predispose them to the development of respiratory failure. Select examples of such diseases for which breed dispositions have been reported include feline asthma, laryngeal paralysis, brachycephalic syndrome, cervical myelopathies, pulmonary fibrosis, tracheal collapse, bronchomalacia, metastatic neoplasia, congenital diaphragmatic hernia, mitral valve insufficiency, dilated cardiomyopathy, and myasthenia gravis. The signalment will thus be heavily dependent on the underlying cause. As mentioned above, dogs with upper airway disease and pleural filling disorders were younger on average than dogs with cardiac disease presenting for respiratory distress. Such associations might also be found in respiratory failure case series, but such has not yet been reported.

History and Clinical Signs

History and clinical signs commonly associated with acute respiratory failure will again vary substantially with the underlying cause. For example, aspiration pneumonia will typically be associated with an historical finding of vomiting, regurgitation, or a recent anesthetic procedure. Alternatively, respiratory failure patients may present with a history of generalized weakness, regurgitation or dysphagia, and megaesophagus if myasthenia gravis is present concurrently. Laryngeal paralysis may be identified more typically in patients with a history of recent voice change, persistent panting, and heat or exercise intolerance. Many other examples could be provided, but space constraints preclude an exhaustive accounting of all the historical and clinical signs that may precede respiratory failure.

What are likely to be uniformly noted among all patients with acute respiratory failure are signs of respiratory distress that precede overt failure. Tachypnea and hyperpnea are commonly, yet not uniformly noted. Patients with hypercapneic ventilatory failure (excluding those with excessive respiratory workload) may present with hypopnea or bradypnea which are often less obvious than other findings in this setting. A more extensive accounting of the signs of respiratory distress and dyspnea may be found in Chapter 38.

Diagnosis

The diagnosis of acute respiratory failure is traditionally based on arterial blood gas analysis. A sustained, repeatable $PaCO_2$ of greater than 60 mmHg is often sufficient to diagnose acute hypercapneic respiratory failure. End-tidal carbon dioxide monitoring may serve as a surrogate for $PaCO_2$ in many patients, but may have reduced sensitivity in patients with cardiovascular compromise and reduced pulmonary blood flows. Venous blood gas measurements serve as poor surrogates for $PaCO_2$ when cardiac output is diminished and should be used cautiously, if at all, to diagnose hypercapneic respiratory failure. Hypoxemic respiratory failure is diagnosed based on PaO_2 levels of less than 60 mmHg in patients breathing room air at sea level. Pulse oximetry may be substituted if arterial blood samples cannot be obtained. Saturation readings obtained by these means of less than 90–92% are consistent with hypoxemic respiratory failure. Venous samples cannot be used to define acute hypoxemic respiratory failure although they may be the more relevant sample for defining alterations in systemic oxygen delivery. Diagnosis of respiratory failure is discussed in more detail in Chapter 38.

Therapy

Therapy will be dependent on the form of acute respiratory failure present. Hypercapneic and hypoxemic respiratory failure will be discussed separately below although the two forms may occur simultaneously.

Hypercapneic Respiratory Failure

In acute hypercapneic respiratory failure, the primary goal is to reestablish adequate levels of alveolar ventilation. If the underlying cause is *reduced respiratory drive*, then therapy should be aimed at increasing central drive by one or more of the following means:

- reversal of agents such as opioids which may be suppressing central drive
- administration of agents that may enhance/increase central drive such as doxapram
- alleviation of elevated intracranial pressure if known or suspected to be present with agents such as mannitol or hypertonic saline
- enhancing elimination of agents suppressing central drive such as toxins or anesthetic agents. This may require fluid diuresis, short-term ventilation, or extracorporeal techniques such as hemodialysis.

If *reduced ventilatory capacity* is the underlying cause of hypercapneic respiratory failure then supportive measures may often play a larger role than specific therapies. Supplemental oxygen and/or mechanical ventilation (see also Chapter 40) may be required until normal ventilatory capacity can be reestablished. In some cases, supportive care may be required for a few days only (e.g., supportive care following removal of the tick in tick paralysis) and in others it may need to be provided for many weeks. Correction of metabolic myopathies and junctionopathies due to hypokalemia or hypomagnesemia should be addressed by rapid correction via parenteral supplementation. Antivenins, when available, may be appropriate for hypercapneic respiratory failure syndromes secondary to envenomations. Reduced ventilatory capacity due to cervical myelopathies may be amenable to surgical treatment in many cases. Stabilization and decompression may speed the restoration of effective transmission of efferent signals to respiratory muscles. Toxic causes of reduced ventilatory capacity may on occasion have specific therapies that may be employed to increase recovery rates. Organophosphate toxicity treated with atropine and pralidoxime (2-PAM) would be just one example. Reducing metabolic rate and carbon dioxide production can help to bring ventilatory capacity and need closer to adequacy. Addressing fever, preventing hyperthermia, and controlling muscle tremors and seizures become even more important goals than usual in this setting.

Lastly, the diaphragm is similar to cardiac muscle in that maximal contractile strength is strongly dependent on adequate perfusion. Typical skeletal muscle is able to maintain contractile strength in the face of reduced perfusion to a larger degree. Diaphragmatic blood flow may be improved by reducing intraabdominal pressures (e.g., removing ascites) or by pharmacologic means (e.g., methylxanthine administration). Maintaining global cardiac output and mean arterial pressures should be a primary goal.

When excessive mechanical loads are the proximate cause of hypercapneic respiratory failure, the primary goal is to restore loads on the respiratory system to more normal values. Intubation and temporary tracheostomy are essential means by which upper airway obstructions can be bypassed and airway patency restored. Having the necessary supplies and personnel immediately on hand is advised in cases where such measures seem likely to be required in the near future. Permanent tracheostomy may be a suitable long-term solution in dogs, but has been associated with poor overall outcomes in cats in one study. Laryngeal paralysis is another example of a cause that may be amenable to surgical therapeutic approaches. While corticosteroids are advocated on occasion for the reduction of upper airway edema, the empirical evidence for beneficial effects of this therapy remains quite limited. Continuous positive airway pressure (CPAP) might be of benefit in many cases of dynamic upper airway narrowing; however, more often than not, this therapy requires general anesthesia in veterinary patients and thus offers less potential benefit over traditional positive pressure ventilation. Heated, humidified, high-flow nasal cannula oxygen therapy (HHHFNC) has comparable effects to nasal mask/pillow CPAP in human pediatrics. The author uses one such device (PrecisionFlow®, Vapotherm) in his practice to provide this form of therapy although direct comparisons have not yet been made to other similar products and no specific recommendations are made here.

Excessive mechanical load due to low tissue compliance may be addressed by reducing parenchymal inflammation and reducing extravascular lung water (edema). Diuretic administration and maintaining a neutral or negative fluid balance are advised in cardiogenic edema states and in some noncardiogenic edema states. However, in patients on mechanical ventilation, the cardiovascular effects of high PEEP may preclude the clinician from keeping the patient as "dry" as one might prefer. Reduced blood volume with high PEEP can often lead to intolerably poor cardiac performance. In some noncardiogenic pulmonary edema states such as the acute respiratory distress syndrome, the use of diuretics remains controversial. In this setting, pulmonary vascular permeability may be increased to the point that diuretic therapy does little to reduce the rate of transcapillary fluid flux and may lead to reductions in cardiac output with no discernible benefit. The pathophysiology of *neurogenic* pulmonary edema is complex

and there is empirical evidence to support both hydrostatic and inflammatory components. Diuretic usage is not considered absolutely contraindicated, but is unlikely to yield the profoundly beneficial responses observed with cardiogenic edema.

Excessive mechanical loads due to chest wall compliance issues (e.g., flail chest, congenital defects, etc.) may be challenging to address unless they are iatrogenic in nature. Iatrogenic alterations in chest wall/diaphragmatic compliance can result from excessively tight thoracic and abdominal wraps, splints, and casts. Incremental loosening of such wraps until chest wall compliance is not excessively low is advised.

Excessive chemical loads are the result of marked increases in carbon dioxide production. Malignant hyperthermia (MH) is perhaps the most common cause and is thankfully a rare occurrence. Active cooling, mechanical ventilation, discontinuance of all volatile inhalational anesthetics (or succinylcholine), and the administration of dantrolene remain the mainstays of MH therapy. In settings other than MH, excessive CO_2 production is addressed by minimizing muscle activity (seizures, tremors) and lowering body temperature when possible. In many instances, active cooling is not required; rather, one needs to only *not* provide active warming therapies. Maintaining adequate hydration to promote effective evaporative heat loss is advised.

Hypoxemic Respiratory Failure

As with hypercapneic respiratory failure, the optimal therapeutic approach to hypoxemic respiratory failure will vary with the underlying cause. In cases of hypoxemic respiratory failure in which a normal A-a gradient is found, therapy should be directed at restoring alveolar ventilation and appropriate inspired gas pressures. This would entail removing the patient from elevations above sea level, providing supplemental oxygen, or the measures described above under hypercapneic respiratory failure.

When venous admixture is the underlying cause of hypoxemic failure, the primary goals are as follows:

- reduce anatomic or physiologic shunting if present
- increase alveolar partial pressure of oxygen
- correct V–Q inequalities
- recruit alveolar surface area available to participate in gas exchange

Achieving a reduction in anatomic shunting often requires an invasive or minimally invasive surgical approach to reducing or ablating flow through the shunt conduit. Reductions in physiologic shunting may be achieved by surgical removal of lung lobes too diseased to be salvaged in some cases. Restoring ventilation to alveolar regions that are atelectatic, obstructed, collapsed, or flooded should improve V:Q ratios. This goal may be achieved by increasing mean airway pressure (mechanical ventilation, typically with PEEP), enhancing alveolar fluid clearance, breath hold recruitment maneuvers, and addressing inflammatory or infectious insults to the lower airways with appropriate drug therapy. Diffuse alveolar hemorrhage syndromes should be addressed with appropriate drug therapies and blood products when they are the result of a coagulopathy. Note that the majority of therapies that aim to reduce physiologic shunting also will generally recruit alveolar surface area and improve overall V–Q matching. The removal of air or fluid accumulations from the pleural space can result in marked improvements in V–Q matching in many cases. Early recognition of pleural filling disorders can lead to improved outcomes.

Ultrasound is the preferred imaging modality if it is available in the emergency room. Many of these patients are not stable enough to tolerate radiographic imaging until after air or fluid has been evacuated from the pleural space. Thoracocentesis should be performed until negative pressure is achieved. If negative pressure cannot be obtained or if pleural filling rapidly recurs then chest tube placement is required.

Increases in the alveolar partial pressure of oxygen may be achieved by several means. First, the restoration of ventilation to alveolar regions with limited fresh gas flows will raise PAO_2 in those areas. More widespread increases in PAO_2 are achieved by providing supplemental oxygen. Mechanical ventilation with PEEP can simultaneously increase alveolar ventilation, recruit underventilated/nonventilated alveolar units, raise mean airway pressures, and provide supplemental oxygen. Intermittent positive pressure ventilation (IPPV) is frequently required in hypoxemic respiratory failure cases and is discussed in Chapter 40. The indication for mechanical ventilation in hypoxemic respiratory failure would be *acute*, persistent severe hypoxemia (PaO_2 <60 mmHg or SpO_2 <90%) that is unresponsive to supplemental oxygen therapy alone. In *chronic* disease states, hypoxemia of this degree of severity may be better tolerated and occasionally requires neither supplemental oxygen nor IPPV.

Supplemental oxygen is generally required in cases of hypoxemic respiratory failure in which the underlying cause cannot be immediately addressed. Supplemental oxygen may be sufficient to address hypoxemia in cases not requiring mechanical ventilation. Delivery may be via nasal or tracheal cannulae, facemask, intubation/tracheostomy with spontaneous respiration, or via an oxygen cage. The lowest FiO_2 required to prevent hypoxemia

Table 39.1 Approximate flow rates of 100% oxygen via nasal cannulae required to achieve an FiO_2 between 30% and 90%. Body weight must be considered and FiO_2 values above 50% may be difficult to achieve in large dogs using this method

	Required flow rate in L/min to achieve an FiO_2 of…		
Body weight (kg)	**0.3–0.5**	**0.5–0.75**	**0.75–0.9**
0–10	0.5–1.0	1.0–3.0	3.0–5.0
10–20	1.0–3.0	3.0–5.0	>5.0
20–40	3.0–5.0	>5.0	ND

ND, not determined.

should be determined on an individual case basis. In many cases, FiO_2 will be known (e.g., 21% or 100%) but at other times it must be estimated. In humans breathing with nasal cannulae in place, the rule of thumb is that one can add 4% for each L/min of oxygen flow. Thus, a person breathing with a 2 L/min flow of oxygen would have an estimated FiO_2 of 28–29% (i.e., 21 + (2 × 4)). This rule works poorly in veterinary patients as their size and tidal volumes vary so much more widely than in humans. Estimates of FiO_2 can be made based on a consideration of both flow rate and patient size (see Table 39.1). Prolonged (>24 h) exposure to greater than 60% oxygen can result in pulmonary oxygen toxicity in most mammals although the toxic range varies with species and age.

However supplemental oxygen is provided, it is important that the gas be properly conditioned. Conditioning in this sense means appropriately warmed and humidified. The inhalation of improperly conditioned gas is associated with several adverse effects in humans, including increased nasal airway resistance, damage to the nasal mucosa (both structural and functional, including epithelial metaplasia and keratinization), increased work of breathing, difficulty in subsequent intubation, patient discomfort, and poor patient compliance. Breathing cold, dry gas from compressed sources can lead to airway dessication (particularly if the nasal passages are bypassed), increases in the tonicity of airway lining fluid, and mast cell degranulation. This airway drying hypothesis is one explanation proposed for exercise-induced asthma.

Prognosis

A specific prognosis for acute respiratory failure cannot be provided in a meaningful way. Clearly, acute respiratory failure is not good news in any context. However, some causes may be easily resolved and carry a good prognosis (fluid overload) whereas others are challenging to address and carry a quite guarded prognosis (ARDS). The prognosis will naturally vary with the underlying cause. Further, prognosis is impacted by whether a specific, effective therapy is available for that disease process or whether one must rely solely on supportive measures. The issue of prognosis is further complicated by the inherent difficulty in reaching a definitive diagnosis in many cases of acute respiratory failure. Patients are often too unstable to undergo the diagnostics required to definitively identify the underlying cause and thus owners are often required to make difficult decisions based on incomplete information.

As mentioned above, retrospective studies of long-term mechanical ventilation in veterinary patients provide some insights into acute respiratory failure, but represent a highly biased sample of such cases. In one such study, veterinary patients with pulmonary parenchymal disease (i.e., hypoxemic respiratory failure) were able to be successfully weaned 36% of the time, with an overall rate of 22% of cases surviving to hospital discharge. Outcomes were better for patients experiencing hypercapneic respiratory failure, with 50% being successfully weaned and 39% surviving to hospital discharge. Patients with mixed respiratory failure (both hypoxemic and hypercapneic) had the poorest outcomes in this study. Overall, cats fared more poorly than canine patients. Whether this is due to the types of diseases that lead to the need for IPPV in cats or whether cats are at greater risk for complications such as ventilator-induced lung injury (VILI) remains undetermined. Cats are a smaller species on average than dogs and smaller species develop VILI more readily than do larger species even when identical inspiratory pressures are applied. No direct comparison of VILI incidence in cats versus 3–7 kg dogs has yet been performed.

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40

Mechanical Ventilation

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A respirator or mechanical ventilator is a therapeutic device that performs some or all of the work of breathing. Ventilators are used in clinical practice to provide short- or long-term support of respiratory function in patients with respiratory disease or failure.

Two primary functions of the lung are oxygenation of the arterial blood and the elimination of carbon dioxide from the venous blood in order to provide metabolic substrate, remove metabolic waste, and maintain homeostasis. The ability of the lung to properly oxygenate the pulmonary capillary blood depends largely on several key factors:

- adequate replenishment of alveolar gases with inspired air
- adequate surface area for gas exchange
- proper matching of ventilation and perfusion
- maintenance of the structural integrity of the gas exchange barrier.

In contrast, elimination of carbon dioxide is primarily dependent on the repeated movement of fresh gas into the alveoli and removal of portions of alveolar gas, a process known as alveolar ventilation. Respiratory failure can result from diverse disease processes that interfere with one or more of the lung's primary functions. Patients with respiratory failure can generally be divided into three groups: those with hypoxemic failure, those with hypercapneic failure, and those with mixed respiratory failure, which shares aspects of both of the other two types.

Indications for Mechanical Ventilation

There are three primary indications for mechanical ventilation. The first is persistent severe hypoxemia (PaO_2 <60 mmHg) despite supplemental oxygen therapy. Severe hypoxemia may also be recognized by the presence of cyanosis or SpO_2 <90% when arterial blood gas analysis is impractical or unavailable. Patients with severe hypoxemia will frequently have significant lung disease such as pneumonia, acute respiratory distress syndrome (ARDS), pulmonary edema, diffuse alveolar hemorrhage, or pulmonary contusions. Pulmonary vascular disorders such as pulmonary thromboembolism (PTE) may also cause severe hypoxemia. Other causes such as anatomic right-to-left shunting are far less commonly encountered in veterinary practice.

The second primary indication for mechanical ventilation is persistent severe hypercapnia (hypoventilation) that is refractory to other therapeutic measures. Severe hypoventilation is marked by a $PACO_2$ >60 mmHg. The $PACO_2$ is determined primarily by alveolar minute ventilation and carbon dioxide production (which is often reasonably constant). Alveolar ventilation is dependent on the total amount of fresh gas that reaches the alveoli over time and is equal to the product of the respiratory rate and effective tidal volume. Effective tidal volume is total tidal volume minus dead space volume. Causes of severe hypoventilation are typically diseases that impair the ability of patients to maintain an adequate respiratory rate and/or tidal volume. Examples include intracranial disease, cranial cervical myelopathies, peripheral neuropathies, junctionopathies, and myopathies.

Severe hypoxemia or severe hypoventilation will not always require mechanical ventilation, but the criteria provided above may help to identify potential candidates for ventilator therapy. The necessity of mechanical ventilation should be made on a case-by-case basis and knowledge of the primary disease process and related patient data should factor heavily into the decision. Ventilator therapy is not entirely benign and a careful weighing of the risks and benefits should be made before the provision of this approach.

The third primary indication for mechanical ventilation is persistent, excessive respiratory effort that may

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potentially lead to respiratory muscle fatigue and exhaustion. Such patients may be able to maintain acceptable blood gas values for a period of time, but uncertainty lies in how long this effort can be sustained. Determination of excessive respiratory effort is largely subjective and based on clinical judgment. Intermittent positive pressure ventilation (IPPV) is indicated in these patients to avoid abrupt exhaustion, asphyxiation, and subsequent arrest. Asphyxiation in experimental canine studies is accompanied by an abrupt drop in heart rate of about 50 beats per minute. Any comparable drop in pulse rate in a dog laboring to breath should prompt immediate patient evaluation and careful consideration of intubation and mechanical ventilation. In these aforementioned canine studies, failure to prevent complete asphyxiation often leads to cardiac arrest in the form of pulseless electrical activity; this is a particularly challenging form of cardiac arrest to reverse and is often refractory to therapy.

Patients with excessive respiratory effort usually have an excessive mechanical or chemical load imposed upon their respiratory system (see also Chapter 39).

Ventilator Settings

Positive pressure ventilators achieve gas flow into the lungs by generating positive airway pressure in a manner similar to that achieved by squeezing the rebreathing bag on an anesthetic machine. Modern therapeutic ventilators have an array of settings that can be altered to change the characteristics of the delivered breath. Despite the complexity of many therapeutic ventilators, there are only a few key settings that are essential to understand in order to provide effective ventilation in most cases. When choosing ventilator settings, the clinician must first select a mode of ventilation and then input initial ventilator settings based on general guidelines (described below) and their own understanding of the nature of the patient's respiratory compromise. Following initiation of mechanical ventilation, the ventilator settings are then adjusted as required to achieve the blood gas, cardiopulmonary performance, and/or oxygen delivery goals desired.

Ventilator Breath Types

There are three main ventilator volume delivery (breath) patterns commonly used in veterinary medicine: assist/control (A/C) ventilation, synchronized intermittent mandatory ventilation (SIMV), and continuous spontaneous ventilation (CSV). Some ventilators only have one breath pattern option, such as a compact volume-control ventilator designed for use in the operating room. Modern therapeutic ventilators typically offer all three formats.

In A/C ventilation, all breaths are completely machine generated. These are termed *mandatory breaths*. In this mode of ventilation, the clinician sets a minimum respiratory rate. If the trigger sensitivity (i.e., pressure or flow alteration required to trigger delivery of a breath that was not prescheduled to be delivered) is set appropriately then the patient can increase the respiratory rate above this minimum value, but all breaths delivered will be full ventilator-delivered (mandatory) breaths. The tidal volume of these ventilator breaths will depend on the machine settings (and any patient–ventilator dyssynchrony if present). Ventilator breaths can either be pressure (PC) or volume controlled (VC). When VC is employed, the clinician presets the desired tidal volume; the resultant peak airway pressure will be dependent on the size of the tidal volume chosen and the compliance of the respiratory system. More compliant lungs will accept a given volume at a lower peak pressure than less compliant lungs. In PC ventilation, the clinician presets the peak airway pressure; in this setting, the tidal volume generated will depend on the level of peak airway pressure chosen and the compliance of the respiratory system. Assist/control ventilation provides maximum support of the respiratory system and is used in patients with severe respiratory disease or those with healthy lungs but reduced respiratory drive or ventilatory capacity.

In SIMV, the operator also sets the number of full ventilator (mandatory) breaths to be delivered. However, between these breaths the patient can breathe spontaneously, depending on their needs. The machine will try to synchronize the ventilator breaths with the patient's own respiratory efforts. This is accomplished by partitioning the periods between mandatory breaths into two periods. The first period immediately follows a mandatory breath. During this period, the patient may breathe spontaneously without triggering a machine-delivered breath. The second period is immediately prior to the next scheduled mandatory breath. Patient effort during this period will trigger early delivery of the next mandatory breath. This latter period is the "synchronized" portion and is what distinguishes SIMV from intermittent mandatory ventilation. As this mode combines full ventilator breaths with spontaneous patient breaths, it is often used for animals that need less than 100% assistance from the ventilator or during the weaning period. Neurologically impaired animals with highly labile respiratory drive or patients with resolving lung dysfunction may not need as much support as A/C provides and SIMV can prove a useful option in these conditions.

There are two widely available options for provision of continuous spontaneous ventilation: continuous positive airway pressure (CPAP) and pressure support ventilation (PSV). In CPAP, the ventilator does not deliver breaths; rather, all breaths are spontaneous breaths and are completely patient generated. The respiratory rate, inspiratory time, and tidal volume are all determined by the patient. CPAP provides a constant level of positive airway pressure (the amount is preset by the operator) throughout the respiratory cycle. Airway pressure is thus maintained at supraatmospheric pressures throughout the respiratory cycle. CPAP has the potential benefits of decreasing respiratory system resistance and increasing pulmonary compliance. These effects as well as the increase in mean airway pressure may serve to improve gas exchange and oxygenation relative to what the patient could achieve without this support. Increased pulmonary compliance effects of CPAP can best be explained by considering the shape of a typical lung pressure–volume relationship (aka compliance curve). Pulmonary compliance curves are typically nonlinear with a flat slope at volumes just above functional residual capacity (FRC). This relatively flat slope indicates that changes in pressure generated by early inspiratory effort are accompanied by only slight changes in lung volume (low compliance). CPAP can reduce the work of breathing by shifting the starting point of breath initiation to a portion of the curve with a steeper slope (higher compliance). Further, maintaining the lung at a higher volume increases mean airway diameter of noncartilaginous airways and reduces airway resistance. With modern ventilator models, the machine will alarm if the animal does not generate adequate breaths or develops apnea. This makes it a useful "monitoring" mode for weaning patients or monitoring intubated patients.

As with CPAP, all PSV breaths are spontaneous breaths; the ventilator does not trigger, deliver, or initiate any breaths. In PSV, the tidal volume is generated by the patient, but also augmented by the machine. The amount of pressure support provided during the inspiratory period depends on what level of PSV support the clinician has prescribed. This mode reduces the effort required to maintain adequate alveolar ventilation and gas exchange in patients with adequate respiratory drive but reduced ventilatory capacity. Pressure support ventilation can be used independently, in conjunction with CPAP, or to augment the spontaneous breaths during SIMV.

Tidal Volume Settings

The normal tidal volume reported for dogs and cats is generally in the range of 10–15 mL/kg although many reports cite a tidal volume for healthy sedated cats of approximately 20 mL/kg. Lower tidal volumes (6–8 mL/kg) may be targeted in animals with severe lung disease to avoid overdistension of the less severely diseased lung tissue. When using volume control ventilation, the clinician presets the desired tidal volume. As overdistension of the lung can lead to significant alveolar injury, it is recommended to start with no more than 10 mL/kg initially. The tidal volume can subsequently be increased if it is determined to be inadequate once an initial steady state is achieved (typically 15 minutes after initiating IPPV or following a settings adjustment). If pressure control ventilation is used then the operator presets a desired peak airway pressure and once the animal is connected to the ventilator, the tidal volume achieved with the preset pressure is evaluated and peak inspiratory pressure adjusted as needed. A tidal volume of around 10 mL/kg would be an acceptable result in most cases.

The clinician must bear in mind that whole-body carbon dioxide stores are enormous relative to the relatively minimal whole-body oxygen stores (excluding pinniped mammals). Step changes in ventilation will result in abrupt, modest changes in $PaCO_2$, but a new steady-state value can take quite a long time to be reached. Only the CO_2 in large, well-perfused organs can truly be considered rapidly exchangeable and this represents a small fraction of whole-body stores. Allowing 15 minutes to pass prior to reassessing steady-state $PaCO_2$ values is a clinically reasonable approach.

Airway Pressure Settings

Patients with healthy lungs such as hypoventilating anesthetized patients, patients with reduced respiratory drive, or those with reduced ventilatory capacity typically only require peak airway pressures in the range of 8–15 cmH_2O. Avoiding peak inspiratory pressures above 20 cmH_2O is preferable whenever feasible. Animals with significant lung disease often have relatively stiff lungs and typically require higher airway pressures to achieve adequate tidal volumes. Peak airway pressures as high as 30–35 cm H_2O may be required in such animals. When using pressure control ventilation, the peak airway pressure target is set by the clinician. Once the animal is connected to the ventilator, the tidal volume achieved with that airway pressure should be determined. Alternatively, in volume control, the tidal volume is preset and the associated airway pressure needs to be monitored. Initially, airway pressures of 10–15 cmH_2O should be targeted; higher airway pressures can be utilized if indicated by unacceptable blood gas values.

Trigger Settings

Most modern ventilators will allow the patient to trigger machine breaths, which allows breath delivery to be

better matched to the patient's intrinsic efforts. The "trigger" or "sensitivity" setting determines what the ventilator will acknowledge as a genuine inspiratory effort by the patient. Appropriate trigger sensitivity is essential to ensure the ventilator recognizes actual respiratory efforts made by the patient while not delivering breaths as a result of minor fluctuations in circuit pressure or flow. Appropriate trigger sensitivity increases patient comfort, reduces dyssynchrony between patient effort and machine delivery, and allows the patient to increase the respiratory rate as required by their needs. The trigger variable can be too sensitive such that nonrespiratory efforts such as patient handling and cardiac contractions may initiate breaths. This situation should be avoided as it leads to patient discomfort, excessive mean airway pressures, breath stacking, auto-PEEP, and greater dyssynchrony. An airway pressure drop of –2 cmH_2O or a gas flow change of 2 L/min are reasonable trigger sensitivity settings to start with. These settings can then be altered as required. Some ventilators (e.g., AutoTrak on the Phillips Esprit line) have proprietary forms of trigger sensing that combine the flow and pressure signals into an integrated variable. Evidence of superiority of this means of sensing patient inspiratory effort is currently lacking in the veterinary literature.

Positive End-Expiratory Pressure Settings

Positive end-expiratory pressure (PEEP) maintains pressure in the breathing circuit above atmospheric pressure during exhalation so that the patient cannot exhale all the way down to functional residual capacity (FRC). This increased expiratory pressure maintains the lung at a higher volume, with less small airway collapse, and improves oxygenating efficiency. PEEP may also help to recruit alveoli collapsed due to atelectasis or increased surface tension forces. Evidence suggests that it may reduce ventilator-induced lung injury by altering cyclic stresses and strains on the alveoli and peripheral airways. Typically, a small amount of PEEP (~2 cmH_2O) is applied in all ventilator modes to reduce atelectasis and to account for the increased work of breathing required simply due to the physical nature of the ventilator circuit (e.g., valves, circuit resistance). In patients with significant lung disease, much higher levels of PEEP may be required to improve oxygenating ability. In continuous spontaneous ventilation, CPAP is functionally equivalent to PEEP although they are often generated by different means (i.e., closure of the expiratory valve at supraatmospheric pressures versus continuous inflow to maintain a given circuit pressure during the expiratory phase).

Inspiratory:Expiratory (I:E) Ratio and Respiratory Rate Settings

An operator-set respiratory rate is available on nearly all ventilators. A respiratory rate of 15–20 breaths per minute with an inspiratory time of approximately one second reflects typical initial ventilator settings in the authors' practice. These settings can then be adjusted as needed to meet the patient's needs. The ratio of the duration of the inspiratory phase relative to the expiratory phase (I:E ratio) may be preset by the clinician or may be a setting that is determined automatically based on rate and inspiratory time settings. Commonly, an I:E ratio of at least 1:2 is utilized to increase the likelihood that patients are able to fully exhale prior to the delivery of the next breath. As respiratory rates are increased, the expiratory time will be reduced in order to accommodate the increased number of breaths. High respiratory rates can lead to a situation known as auto-PEEP or intrinsic PEEP if the patient is not able to fully exhale before the start of the next inspiration. Such an occurrence can easily be detected by inspecting the flow scalar graphic if waveform displays are available. Failure of expiratory flow to return to zero before the next breath is delivered is indicative of the presence of auto-PEEP. To avoid this problem, it is recommended to keep an I:E ratio of 1:1 or higher whenever possible. If a higher respiratory rate is required, a shorter inspiratory time will allow maintenance of an acceptable I:E ratio and is often better tolerated by the patient.

General Guidelines for Initial Ventilator Settings

As discussed above, the optimal ventilator settings for a given patient cannot be predicted reliably. It is likely that animals with hypoxemic respiratory failure will require more aggressive settings than those with hypercapneic respiratory failure. One must choose some initial settings prior to connecting the patient to the ventilator. First the mode of ventilation must be selected; A/C, SIMV or continuous spontaneous ventilation. If A/C or SIMV are selected then it may be necessary to next decide between volume control (VC) or pressure control (PC) ventilation. The more modern and advanced the ventilator, the more options one is likely to have. Ventilator manufacturers are creating new proprietary ventilation modes faster than clinicans can evaluate them. Even the most renowned respiratory therapists in the world admit that they cannot keep up with every mode becoming available. This situation is unlikely to change as equipment manufacturers are often less than forthright about how these novel modes are designed. The settings that need to be selected will vary with the

mode of ventilation chosen. In VC the tidal volume is preset by the operator, once the patient is connected to the machine the operator should note the peak inspiratory pressure associated with this tidal volume and determine whether it is acceptable for this patient. In PC ventilation, the clinician presets the peak airway pressure. Once the patient is connected to the ventilator the operator will need to note the tidal volume and mean airway pressure and determine whether they are acceptable for this patient.

These settings can then be altered as needed once the patient is connected to the ventilator. Whenever possible, it is best to have the ventilator already running and confirmed to be working properly before the patient is connected. When this is not possible, for example initiating mechanical ventilation for patients already on an anesthetic machine, then it is best to start with quite conservative settings and titrate them upwards as required to avoid inadvertent over-distension of the lung. It is imperative to always have a method for performing manual ventilation (e.g. Ambu-bag, Bain's circuit) close at hand during IPPV in case of equipment malfunction, power failure, or operator error.

Mechanical Ventilation for Hypoxemic Respiratory Failure

Patients suffering from hypoxemic respiratory failure often require inspiratory pressure settings that are substantially greater than normal. Pulmonary parenchymal disease often reduces lung compliance and increases airway resistance. The result is that higher pressures will be needed to achieve the same tidal volume. It is now recognized that excessive distension of the lung (or volutrauma) is a major cause of ventilator-induced lung injury. For this reason, it is recommended to deliver smaller tidal volumes when ventilating patients with significant pulmonary parenchymal disease. In very severe lung disease such as ARDS, it may be necessary to deliver tidal volumes as low as 6 mL/kg.

Anesthesia

Unless the patient has significant neuromuscular or intracranial disease, anesthesia will be necessary to allow positive pressure ventilation and maintenance of an airway. Balanced anesthesia incorporating 2–3 drugs is advised to reduce the dose required (and adverse effects) of any single agent. Propofol or alfaxalone infusions are commonly used anesthetic agents in conjunction with a benzodiazepine and/or an opioid and/or a dexmedetomidine infusion. The aim is to keep the patient anesthetized sufficiently such that it will tolerate the endotracheal tube and PPV but to avoid excessive depth of anesthesia in an effort to minimize the adverse effects of the anesthetic drugs. This requires some experience in anesthetic monitoring and constant tinkering with the anesthetic drug infusion rates as drug requirements will change with time.

Typical intravenous anesthetic doses used to maintain patients on mechanical ventilators at the authors' practice include the following.

- Midazolam: loading dose 0.2–0.4 mg/kg IV; constant rate infusion (CRI) 0.1–0.5 mg/kg/h IV.
- Propofol: loading dose 0.5–2.0 mg/kg IV; CRI 0.05–0.4 mg/kg/min IV.
- Fentanyl: loading dose 2–5 µg/kg IV; CRI 1–7 µg/kg/h IV.

The vast majority of patients receiving long-term mechanical ventilatory support in our practice are anesthetized with some combination of these three agents. The occasional patient will also receive a dexmedetomidine infusion (0.1–3.0 µg/kg/h) either as a replacement for one of those three agents or in addition to them. Etomidate is rarely if ever given and has resulted in marked suppression of adrenal function when it was employed. Diazepam may be substituted for midazolam as required. Pentobarbital, once a mainstay in our practice, is rarely used now due to relative expense, reduced availability due to shortages, and prolonged recovery times.

Anesthetic depth should be formally assessed every hour and recorded on the patient's flow sheet/medical record, but caregivers should be continuously assessing anesthetic depth as they work on the patient. It is important to have drug dose charts that correctly convert the mg/kg/h drug doses to mL/h for the drug concentration you are using. In addition, it is recommended to have precalculated some "rescue doses" of drugs in case animals suddenly become light and try to extubate themselves.

Initial Stabilization on the Ventilator

When patients are first connected to the ventilator circuit, an inspired oxygen fraction (FiO_2) of 100% is advised as a safety measure. The FiO_2 can be reduced later once stabilization of the patient has been achieved. When ventilating patients with hypoxemic respiratory failure, it can be beneficial to keep them in sternal recumbency during the initial stabilization period. These animals frequently oxygenate better in sternal recumbency than in other body positions. After connection, the patient's thoracic wall is observed for appropriate movement. When insufficient or excessive thoracic wall motion is observed, the ventilator settings should be adjusted appropriately.

The thorax is next auscultated bilaterally to ensure breath sounds are audible. Next, other monitoring parameters are evaluated (e.g., blood pressure, ECG, pulse oximeter, $ETCO_2$, etc.). Once the patient appears stable, serial arterial blood gas analysis is ideal for accurate titration of ventilator settings. If an arterial blood sample is not available, a venous blood gas can be used to assess PCO_2 if cardiac output is not excessively low. The evaluation of oxygenation by pulse oximetry is the standard of care in some settings (e.g., human neonatology) and may serve as both a noninvasive alternative and a means of reducing iatrogenic blood loss.

Goals of Mechanical Ventilation

The goal of IPPV therapy is to maintain acceptable blood gas values with the lowest level of ventilator support possible. The optimal ventilator settings for each individual patient cannot be predicted and are determined through a careful process of trial and error. The patient should be fully evaluated after every change in ventilator settings, including blood gas analysis whenever possible. It is advisable to make only one change in ventilator settings at a time in order to accurately evaluate what effect each change alone has on gas exchange. Whenever feasible, it is advised to allow 15 minutes to pass before reevaluating $PaCO_2$. Whole-body stores of carbon dioxide are quite large and a quarter of an hour or more may be required for a new steady state to be reached. Common blood gas goals of mechanical ventilation include a PaO_2 of 80–120 mmHg (or SpO_2 >95%) and a $PaCO_2$ of 35–55 mmHg (35–40 mmHg in patients with intracranial hypertension).

In some settings, permissive hypercapnia may be employed. In this approach, $PaCO_2$ is allowed to climb higher to 60–70 mmHg as long as the resultant acidemia does not become too severe (pH <7.1). This approach is often taken when the clinician fears that maintaining carbon dioxide tensions within the normal target range will require injurious ventilator settings. Permissive hypoxemia approaches may also be employed at times. With this approach, the clinician focuses on maintaining central venous hemoglobin saturations ($S_{CV}O_2$) above 65–68%. Hypoxemia (PaO_2 <80 mmHg) is tolerated as long as tissue oxygen delivery appears adequate based on $S_{CV}O_2$ readings. This approach reflects a school of thought in which it is felt that clinicians should focus more on maintaining adequate global oxygen delivery rather than arterial blood gas values.

Adjustments to Improve PaO_2

If the PaO_2 is higher than the desired range (>120–150 mmHg), the first priority should be to decrease the FiO_2 until it is <60%. Once FiO_2 is less than 60%, emphasis shifts to reducing PEEP and peak airway pressure. If the PaO_2 is lower than desired (<80 mmHg), the first option is to increase the FiO_2. If there is an acute and severe drop in PaO_2, placing the animal on 100% oxygen is appropriate until the issue can be resolved and more definitive therapy can be provided. Ultimately, it is hoped that manipulation of ventilator settings will increase the oxygenating efficiency of the lung and allow lowering of the FiO_2 once again. All increases in oxygenation are obtained by raising FiO_2, mean airway pressure, or both. Mean airway pressure may be increased by increasing peak pressure, respiratory rate, PEEP, inspiratory time, or the format of flow delivery (e.g., block versus sine versus descending ramp flow patterns). Acute hypoxemic episodes are life-threatening complications that require immediate intervention.

Adjustments to Improve $PaCO_2$

The $PaCO_2$ is dependent on alveolar minute ventilation, which is the product of the effective tidal volume (excluding dead space volume) and the respiratory rate. If the $PaCO_2$ is higher than the desired range then the respiratory rate, tidal volume, or both should be increased. If the $PaCO_2$ is too low, the respiratory rate and/or tidal volume should be decreased. Excessive gas trapping may lead to carbon dioxide retention. Increasing expiratory time or reducing I:E ratio may increase alveolar ventilation in this circumstance. In patients with lower airway or parenchymal disease, inspiratory times that are too short may lead to minimal ventilation of alveoli with high time constants (product of resistance and compliance). In this instance, prolongation of the inspiratory time may enhance alveolar ventilation.

An abrupt increase in $PaCO_2$ in the ventilator patient may indicate a life-threatening complication. Similarly, an abrupt drop in end-tidal carbon dioxide may reflect a sudden increase in physiologic dead space (e.g., pulmonary thromboembolism) or an abrupt reduction in cardiac output.

Nursing Care for Ventilator Patients

Nursing care of the ventilator patient is one of the most labor-intensive and important aspects of ventilator patient management. Each ventilator patient usually requires a dedicated caregiver and two or more people are needed for many of the patient care procedures. Nursing care includes airway management, oral and eye care, catheter care, and recumbent patient care.

Humidification

Anesthetized patients are not able to cough or clear airway secretions effectively and this can contribute to development of ventilator-associated pneumonia (VAP) and tube occlusion. Airway management is essential in an effort to try to reduce these complications. Gas flow bypasses the nasal passages during mechanical ventilation and is therefore not humidified or filtered. This can lead to a loss of heat and moisture, which can damage the respiratory epithelium. Humidification is also critical in making secretions less viscous and easier to remove.

The breathing circuit should be humidified appropriately without excessive accumulation of liquid in the circuit. There are two basic options for airway humidification: active heated water humidifiers or passive heat moisture exchangers. The heated water humidifiers are very effective, are ideal in patients with substantial airway secretions, and help prevent hypothermia, which can be an issue in small patients. They are expensive and unless they are used in conjunction with heated wire circuits, they are associated with substantial "rain out" in the circuit. This refers to water accumulating in the limbs of the breathing circuit, which in large volumes can interfere with ventilator function. More concerning, it greatly increases the risk of VAP. Heat moisture exchangers (HME) are inexpensive devices that fit on the end of the endotracheal tube and passively take heat and moisture from the exhaled gas and return it to the inhaled gas. They have been found to be equally effective at humidifying the airways as the active humidifiers and may reduce the incidence of VAP by reducing moisture in the circuit. They can occlude and this has the potential to be a life-threatening event. For this reason, the authors advise that they be avoided in patients with excessive airway secretions.

Suctioning

Airway suctioning is another critical aspect of airway management. There are risks associated with this procedure, and proper technique must be followed. The inhaled oxygen concentration should be increased to 100% prior to and during suctioning. The suction catheters should be sterile, soft, and flexible with more than one distal opening and a proximal thumbhole to control the level of suction. Sterile gloves should be worn and sterile technique observed throughout the procedure. Closed suction systems are also available which are helpful in maintaining sterility and preventing issues with disconnection. Suction should be applied while withdrawing the catheter from the airway for no more than five seconds at a time. This procedure can be repeated two or three times as long as the patient's oxygenation remains adequate and the patient does not seem distressed. If suctioning is productive, it can be performed as frequently as every 2–4 hours.

The risks of suction include hypoxemia, patient discomfort, damage to the tracheal mucosa, collapse of small airways and alveoli, and contamination of the lower airways.

If the secretions are too dry to suction well or adequate humidification is not being provided, small aliquots of sterile saline (0.2 mL/kg) may be instilled into the airway prior to suctioning. This practice has been challenged because of the lack of evidence of beneficial effects coupled with the risk of introducing infection.

Tracheal Tube Management

Ventilator patients require an artificial airway, which is most commonly accomplished via endotracheal (ET) intubation and general anesthesia. It is important that ET tubes are sterile and ideally have high-volume/low-pressure cuffs. Tracheal mucosal blood flow can be occluded by pressures over 25–35 mmHg. Ideally, cuff pressure should be maintained between 20 and 25 mmHg and measured regularly with a pressure gauge system. Higher pressures impede mucosal blood flow and may lead to tracheal necrosis. Lower cuff pressures are associated with an increased risk of aspiration. Although frequently used, the pilot balloons do not correlate well with cuff pressure and should not be used as an indicator of appropriate inflation.

Tracheal injury can also be minimized by deflating the cuff and repositioning the ET tube slightly to change the pressure point and then reinflating the cuff every four hours. The mouth and pharynx should be flushed and suctioned prior to deflating the cuff. Endotracheal tubes should be securely tied with IV tubing or another nonporous material, which is less likely than gauze to become saturated with oral secretions and bacteria. The ties should be moved and secured in a different position every four hours to minimize lip trauma.

The endotracheal tube may need to be changed every 24–48 hours, depending on the amount and character of the secretions. It is important to preoxygenate with 100% oxygen prior to changing the tube and to be prepared for a difficult intubation. Tracheostomy tubes should ideally have an inner cannula, which should be cleaned every four hours. If there is no cannula, the tube should be suctioned regularly and changed every 24 hours. The tracheostomy tube should also have a cuff to protect the airway from the migration of oral secretions and to allow PEEP to be used.

Oral Care

Care of the oral cavity is of the utmost importance in these patients. Oral ulceration is a common problem and with poor oral care may occur in 90% or more of patients. Oral ulceration is a primary source of bacterial proliferation and has been reported as a major cause of VAP in human PPV patients. Prevention of oral ulceration with careful positioning of mouth gags, keeping the tongue and mucous membranes moist, and frequent repositioning of the tongue and ET tube are essential. The mouth and oropharynx should be carefully rinsed and suctioned every four hours. A chlorhexidine rinse of the mouth should be performed every eight hours.

Eye Care

Ventilator patients are under anesthesia and require eye care to prevent the development of corneal drying and ulceration. Artificial tear ointment should be applied at least every two hours. If an ulcer is suspected, fluorescein staining should be performed and the patient should be started on an antibiotic ophthalmic ointment. Temporary tarsorrhaphy may be necessary in some cases.

Recumbent Patient Care

Prolonged recumbency can lead to muscle atrophy, pressure sores, peripheral edema, and nerve damage. Patients should be repositioned at least every four hours and should have passive range of motion exercises performed. Ventilator patients should be kept on sufficient padding that is changed immediately if soiled. Frequent changes in body position also help prevent the pooling of secretions in one region of the airways and atelectasis of the dependent lung lobes. Turning may be associated with desaturation in animals with substantial pulmonary pathology; some patients will not tolerate lateral recumbency in which case they may require sternal recumbency with only their hips turned regularly. Oxygenation should be monitored carefully after changes in position. Sternal positioning is generally associated with the best lung function and may be beneficial in hypoxemic patients.

Catheter Care

All indwelling catheters should receive diligent catheter care as ventilator patients are at high risk for secondary infections and catheters provide possible entry sites for microorganisms. Urinary catheters require appropriate cleaning and care every eight hours. Intravascular catheters should be unwrapped and cleaned every 24–48 hours. Other indwelling catheters such as chest tubes should be cared for as appropriate.

Complications of Mechanical Ventilation

Hemodynamic Compromise

Positive pressure ventilation can lead to reductions in cardiac output in some patients. The associated increase in intrathoracic pressure can reduce systemic venous return which in the steady state is equal to cardiac output. Although animals with higher mean airway pressures are at greater risk for developing impaired cardiovascular performance, those with significant pulmonary disease tend to have such poorly compliant lungs that very little of the increased airway pressure is transferred to the cardiovascular system. Hemodynamic compromise secondary to PPV is more of a problem for animals with concurrent hypovolemia or other causes of reduced cardiac filling pressures. Continuous heart rate and blood pressure monitoring is advised for all ventilator patients. Fluid and drug therapy should be given as appropriate if hypovolemia or volume-unresponsive hypotension develops.

Ventilator-Associated Pneumonia

In human medicine, VAP occurs in 10–48% of patients and leads to an increase in mortality. Endotracheal intubation compromises the normal upper airway defenses and bacteria from the oral cavity have greater access to the lower airways. This problem can be compounded by intermittent aspiration of oral secretions or gastroesophageal contents.

Ventilator-associated pneumonia is typically diagnosed when new radiographic evidence of pulmonary infiltrates is detected 48 hours or longer after beginning IPPV. Decreases in oxygenation, a change in the character of airway secretions, new rhonchi or crackles, changes in white blood cell count, and new fevers are also common clinical signs associated with VAP. Prevention of VAP includes maintaining careful oral hygiene standards, including chlorhexidine rinses and the use of sterile technique when handling the circuit or endotracheal or tracheostomy tube. Minimizing circuit disconnections is advised. It is now recommended in some guidelines that ventilator circuits only be replaced every five days (earlier if gross contamination is evident). Many VAP infections have been found to come from the hands of caregivers, so wearing gloves and frequent hand washing are strongly recommended for all those dealing with ventilator patients. Wearing gloves should be considered mandatory when dealing with the oral cavity.

Ventilator-Induced Lung Injury

Ventilator-induced lung injury (VILI) describes pulmonary damage that occurs as a result of stresses and strains placed on lung tissues during PPV. In addition to increasing pulmonary pathology, in human medicine VILI has been found to increase the incidence of multiple organ dysfunction and patient mortality. It is believed that pulmonary inflammation resulting from VILI leads to the elaboration of inflammatory mediators, which amplify the systemic inflammatory response and subsequent organ damage. Indeed, some have suggested that the improved outcomes observed with lung-protective ventilator strategies are not due to improvements in pulmonary performance but rather to reductions in distant organ damage.

There are several mechanisms by which VILI can occur. The two major proposed mechanisms are overdistension of the lung by excessive tidal volumes and repetitive alveolar and peripheral airway collapse. Titration of ventilator settings should always be focused on providing the lowest possible level of ventilator support that still allows the targeted goals to be achieved. When the blood gas value goals cannot be achieved despite the use of high airway pressures and PEEP, a valid alternative approach is to change the blood gas goals for this particular patient. Permissive hypercapnia or permissive hypoxemia-based strategies may be employed in these instances as described previously.

Oxygen Toxicity

Pulmonary oxygen toxicity is discussed elsewhere in this text and the interested reader is referred to the appropriate sections (see also Chapter 39).

Pneumothorax

A pneumothorax can occur in the ventilator patient when alveolar or airway rupture leads to air escaping from the respiratory tract and accumulating in the pleural space. Although pneumothorax is a major concern when high airway pressures are present, studies in human patients have not been able to demonstrate a significant association between airway pressure and the occurrence of pneumothorax. Rather, the incidence of pneumothorax seems to vary with the nature of the lung pathology present. Overdistension of the lung is thought to be the major cause of pneumothorax. Thus, maintaining low tidal volumes, especially in patients with significant lung disease, is currently recommended.

Pneumothorax can be rapidly progressive in patients receiving IPPV and it is imperative that it be recognized early to avoid adverse outcomes. The acute onset of an elevated $PaCO_2$ and a decreased PaO_2 is a common early warning sign. Airway pressure would be expected to be increasing if a pneumothorax occurs in a patient being ventilated with volume control, while tidal volume would decrease if pressure control ventilation is employed. Auscultation may reveal decreased lung sounds, but this finding may be difficult to appreciate in the mechanically ventilated patient. Thoracic radiographs will provide a definitive diagnosis, but are often impractical. Thoracic ultrasound can also be helpful in identifying a pneumothorax if the operator is suitably trained and experienced.

Ultimately, a pneumothorax can be rapidly fatal in the ventilator patient. If there is any doubt that one is present, a diagnostic thoracocentesis should be performed immediately. If a pneumothorax is detected, unilateral or bilateral chest tubes are likely to be required.

Weaning from Mechanical Ventilation

Weaning (or liberation) from the ventilator is generally an ongoing process of gradual reduction in the ventilator settings. Often, as the patient improves, the mode of ventilation may be changed to one that requires the animal to perform an ever-increasing proportion of the work of breathing. SIMV and pressure support modes are often employed for this purpose. If animals have been anesthetized for prolonged periods of time, it may take some time (hours to days) for them to recover adequate ventilatory capacity. Some anesthetic protocols (e.g., barbiturates) employed for IPPV may have very prolonged withdrawal periods. It is important to consider reducing or changing the anesthetic drugs administered when patients begin to improve and weaning becomes a realistic possibility.

Prior to discontinuance of IPPV, the patient should first obtain certain physiologic goals, including the following:

- the original disease process is stable or improving
- a stable and appropriate level of respiratory drive has been demonstrated
- the patient no longer requires significant ventilator support to achieve adequate gas exchange
- adequate gas exchange efficiency has been restored (i.e., PaO_2:FiO_2 ratio consistently above 200; greater than 300 is preferred).

Reasons to suspect that a patient is not ready to be weaned include cardiovascular instability, requirement of high FiO_2 (greater than 60%), high peak inspired airway pressures (>25 cmH_2O), and/or high PEEP levels (>5 cmH_2O).

When a patient has improved sufficiently to consider removing them from the ventilator, it is advised to first determine if they can maintain spontaneous breathing

while still intubated. During such a "spontaneous breathing trial," the patient requires frequent, intensive monitoring. CPAP is often an ideal mode to use during a spontaneous breathing trial as the tidal volume, respiratory rate, and end-tidal carbon dioxide can all still be closely monitored. The development of hypoxemia, hypercapnia, hyperthermia, tachycardia, hypotension, and/or tachypnea are all indications that the trial has failed. Hypertension and the development of a rapid, shallow breathing pattern are common markers used in the authors' practice to identify weaning failure. Positive pressure ventilation should be reinstituted once weaning failure has been identified.

In human medicine, it is frequently recommended to perform spontaneous breathing trials daily once the patient qualifies according to the criteria listed above. When the patient can maintain adequate blood gases without anxiety or fatigue, anesthesia can be discontinued and extubation performed.

Nursing Care

No chapter on mechanical ventilation would be complete without acknowledging the absolute requirement for skilled, highly trained technicians. Patients receiving IPPV require continuous monitoring and care. In the authors' practice, the patient:nurse ratio for ventilator patients is always 1:1. Additional nursing staff needs to be available as required for turning, airway and oral hygiene, circuit changes, and many other nursing procedures. Large numbers of highly skilled veterinary technicians are required to provide mechanical ventilator support and may be the single largest determinant of outcomes in many cases.

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41

Approach to the Patient with Shock

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Shock is a clinical entity that veterinarians come into contact with regularly and is defined as inadequate delivery or usage of oxygen at the cellular and subcellular level. The result of cellular and tissue hypoxia is the central driver of the pathology of shock. Subsequently, resolving this hypoxia must be the clinician's primary focus to effectively treat a patient in shock. Cellular hypoxia results in the failure of energy-dependent mechanisms. When cells lack the necessary energy, dysfunction of the organelles occurs which ultimately results in the death of the cell. When cells die, organs become dysfunctional and compensatory mechanisms meant to be protective instead exacerbate injury and lead to the death of the organism.

Classically, shock has been defined as lack of organ perfusion resulting from the impaired ability of the cardiovascular system to deliver oxygen to the tissues of the body. This can result from many diseases, but the global effects are similar regardless of cause. There are clinical situations in which the delivery of oxygen to the tissues is normal or increased whilst the tissues are unable to use the oxygen presented to them that can lead to shock. This, fortunately, is not recognized often in veterinary medicine so this chapter will focus on the failure of oxygen delivery rather than failure of oxygen utilization.

It is often helpful to classify shock states according to their underlying etiology. This enables formation of a general treatment plan. In general, shock can be classified as hypovolemic, cardiogenic, distributive, or obstructive. Hypovolemic shock occurs when intravascular volume is reduced, resulting in decreased cardiac output. This can include whole-blood loss (hemorrhagic shock) or loss of plasma volume. Cardiogenic shock is a result of poor cardiac function that reduces cardiac output. Distributive shock develops from inappropriate vasodilation and decreased resistance to blood flow lowering blood pressure despite normal or even increased cardiac output. Obstructive shock is a result of physical impedance of diastolic filling of the heart and subsequent decrease in cardiac output. It is possible for patients to fit more than one category and limiting classification to a single category can lead the clinician astray. For instance, patients that are septic may have shock that has characteristics of hypovolemic, cardiogenic, and distributive etiologies.

In addition to categorizing etiology, shock can be characterized by severity as either compensated or decompensated. The sympathetic nervous system attempts to compensate for perceived decreases in intravascular volume and/or blood pressure, generating some of the clinical signs associated with shock. While the etiologies vary, there are commonalities in the clinical signs of shock. The recognition of shock centers on identifying the compensatory mechanisms the patient displays in response to decreased oxygen delivery. If a patient is in the compensated phase of shock, the sympathetic nervous system has been activated and the subsequent increases in chronotropy, inotropy, and systemic vascular resistance (SVR) will all converge to increase oxygen delivery. Patients in compensated shock will often have a normal blood pressure and mentation on presentation, but will likely have other clinical signs suggestive of shock such as tachycardia and tachypnea. If the initiating cause of shock has been removed then patients in compensated shock may not progress further.

If the underlying etiology of shock is severe or persistent, compensatory mechanisms will be unable to restore oxygen delivery and the patient will progress to decompensated shock. These animals will have profound clinical signs including depressed mentation, cold extremities, thready pulses, and hypotension. If left untreated, patients in decompensated shock will generally progress to an irreversible shock state in which compensatory mechanisms cease to function. This is termed *autoregulatory escape* and results from global vasodilation as oxygen-starved tissues finally demand blood flow. Clinical

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signs of autoregulatory escape include venous pooling, bradycardia, and hypotension unresponsive to fluids or vasopressors and eventual death.

There are some specific treatments for each type of shock, but key similarities exist between all categories. The ultimate goal in the treatment of shock is to restore homeostasis by ensuring adequate oxygen delivery to the tissues. For the most part, these treatments do not address the underlying cause of shock; rather, they are nonspecific augmentations of oxygen delivery. The ideal treatment of shock would prevent death, allow the patient time to heal from the initiating insult, and limit ongoing injury as much as possible.

Pathophysiology of Shock and Effect on Organ Systems

Cellular Effects of Hypoxia

Shock occurs due to failure of oxygen delivery to the tissues which results in cellular and mitochondrial hypoxia. The resulting anaerobic metabolism leads to a significant decrease in production of adenosine triphosphate (ATP) with generation of lactate as a byproduct causing acidosis at both local and systemic levels.

The ATP deficiency that occurs during shock has numerous detrimental effects on the cell. ATP-dependent transport proteins cease to function and membrane gradients of electrolytes are lost. This results in cellular swelling, cellular death, and ultimately organ dysfunction if enough cellular death occurs. Cell death resulting from hypoxia is usually necrotic and not apoptotic, and can therefore induce an inflammatory response. This organ failure, if not corrected in time, results in the death of the organism.

Sensors of Cardiovascular Homeostasis

In order to maintain homeostasis, volume, pressure (baroreceptors), and chemical status (chemoreceptors) of the blood must be monitored at all times. This is the job of afferent sensors in various parts of the body capable of sensing a change in one or more of these variables. These sensors send signals primarily to the autonomic nervous system and if an abnormality is detected, cause physiologic responses intended to reestablish homeostasis.

Baroreceptors are mechanoreceptors located within the walls of vessels that are excited with stretch of the vessel wall (pressure) and are important for the beat-to-beat regulation of blood pressure. The information collected by baroreceptors is used to regulate the function of the heart, vascular smooth muscle tone, and endocrine responses aimed at managing intravascular volume.

Chemoreceptors are sensory organs responsible for monitoring the blood for appropriate concentrations of key chemicals, primarily oxygen and carbon dioxide. The carotid bodies, which are located near the carotid bifurcation, sense oxygen tension and the partial pressure of carbon dioxide (CO_2) in arterial blood. The aortic body, located in the aortic root, senses pressure in addition to oxygen and carbon dioxide tension and pH of arterial blood. These chemoreceptors send signals to the medulla oblongata to regulate breathing and blood pressure and are a potent mechanism by which respiratory rate and heart rate are controlled.

Compensatory Mechanisms

During shock, hypoxia is sensed centrally which prompts the firing of the respiratory center efferent nerves, increasing the respiratory rate in an effort to raise the amount of fresh gas presented to the alveoli to ensure oxygen extraction from the atmosphere is maximized.

Control of cardiac output is regulated by the autonomic nervous system. The sympathetic branch of the autonomic nervous system acts on the areas of the heart that have pacemaking capability (i.e., sinoatrial node, atria, atrioventricular node ventricles). Sympathetic stimulation results in an increase in sinoatrial node rate of firing, decrease in atrioventricular node delay, and increase in speed of the spread of an action potential through the specialized myocardial conduction system. Sympathetic stimulation directly increases the strength of contractility through the action of epinephrine stimulating beta-1-adrenergic receptors. Indirectly, sympathetic stimulation increases inotropy by increasing vascular tone through arteriolar vasoconstriction, increasing resistance to blood flow (systemic vascular resistance) and blood pressure. Preferential vasoconstriction shunts blood flow away from peripheral sites and to the brain and heart, increasing preload and causing a reflex increase in inotropy.

The parasympathetic branch of the autonomic nervous system regulates chronotropy (heart rate). Parasympathetic stimulation slows the heartbeat with little effect on the strength of ventricular contractions. In shock, parasympathetic tone is reduced to increase the heart rate. The net result of the increase in sympathetic tone and decrease in parasympathetic tone is increased inotropy and chronotropy. As a consequence, most patients in shock exhibit tachycardia. Patients with hyperkalemia or in the decompensatory phase of shock may demonstrate bradycardia, however.

Other less immediate compensatory mechanisms are also activated during shock. The renin-angiotensin-aldosterone system (RAAS) is activated and a nonosmotic release of antidiuretic hormone in response to hypotension occurs. Both of these responses attempt to

expand intravascular volume by inducing retention of water. This process takes hours to days to occur and is therefore of little use in the immediate compensatory attempt to return homeostasis.

Macro- and Microcirculation

Clinicians often consider shock to be a macrocirculatory phenomenon (i.e., an absolute decrease in blood flow and perfusion in large arteries). It must be remembered, however, that the purpose of the entire circulatory system is to deliver blood through the capillaries (microcirculation) to exchange oxygen and nutrients and remove waste products from individual tissue beds. While arteriolar constriction will increase global pressures and improve macrocirculatory parameters, it can reduce blood flow to the capillary or downstream side of the arterioles.

Under normal conditions, arteriolar tone changes from minute to minute depending on the metabolic demand of the particular tissue bed in which it is located. If a tissue demands more or less oxygen, concentrations of metabolites including adenosine, oxygen, and carbon dioxide will cause vasoconstriction or vasodilation. This is termed *chemical autoregulation* and is key in coupling blood flow to the metabolic needs of the tissue. In shock states, however, sympathetic stimulation causes vasoconstriction and overrides local tissue autoregulatory mechanisms. This often reduces perfusion of the tissues supplied by the constricted arterioles and, if oxygen consumption is higher than oxygen delivery, will result in the onset of anaerobic metabolism.

It is possible, if not common, for a patient in shock to have normal or even increased cardiac output and blood flow to the level of the arterioles yet have poor flow through the capillaries. This alteration in microcirculation is especially significant in septic shock and ischemia/reperfusion injury.

Diagnosis

A key feature of shock is that all organ systems are affected due to a global decrease in oxygen delivery, differentiating shock from local perfusion derangements. Due to the systemic nature of shock, the compensatory mechanisms in place are meant to preferentially perfuse the organ systems most important for immediate survival. This means that the brain and heart are perfused at the expense of the abdominal viscera such as the kidneys, gastrointestinal (GI) tract, and liver. Therefore, the clinical signs of shock represent the compensatory changes that occur in response to, rather than directly from, the cause of shock, meaning the underlying etiology of shock may not be evident on initial physical exam since similar clinical signs are present in all types of shock.

Tachycardia is one of the most consistent clinical signs of shock and although it is a frequent finding, the etiology is often multifactorial. The origin of tachycardia typically belongs in one of three categories: related to pain or anxiety, related to an appropriate physiologic compensatory mechanism, or due to primary cardiac disease. As usual, cats provide a notable exception to this generalization and frequently present bradycardic, as do dogs in the decompensatory or terminal stage of shock. In general, bradycardia in the context of shock should be considered a negative clinical sign and if recognized, should elicit a rapid and diligent search for the underlying reason for shock.

Pale mucous membranes can represent either anemia or vasoconstriction and mucous membrane evaluation provides a very crude assessment of hemoglobin concentration and microcirculation. While it is possible that a patient in shock is anemic, more commonly mucous membrane pallor is due to vasoconstriction. Capillary refill time (CRT) reflects the amount of time it takes for blood to fill the capillaries after they have been forcibly evacuated and provides an estimate of the efficiency of microcirculation. Normal CRT ranges from one to two seconds and prolongation of the CRT would reflect microcirculatory disturbance. Patients with pallor typically have a slow or difficult to evaluate CRT due to anemia preventing appreciable blanching of the mucous membranes. Occasionally, patients will have bright red mucous membranes and faster than normal CRT. This finding suggests the patient has vasodilation in conjunction with normal or high cardiac output and this occurs most frequently in septic shock or in shock associated with heat stroke. It does not imply that these patients have better than normal perfusion. Similarly, patients can have dark or dusky mucous membranes and a prolonged CRT indicating the presence of vasodilation and decreased cardiac output, as is seen in cardiogenic shock. Patients with these findings can have significant perfusion deficiencies and the clinician should seek to treat these patients aggressively.

Weak pulses are inconsistently present in shock. If the animal is in the compensated stage of shock, there is likely sufficient blood pressure to generate a detectable pulse. Some clinicians use the presence of a pulse in different areas of the vascular tree to give an estimate of blood pressure and argue that detection of pulses in the dorsal pedal artery and in the femoral artery represent systolic pressures of 80 mmHg and 60 mmHg respectively. There is limited evidence to support this finding in veterinary medicine and quantitative measurement of

blood pressure should always be used when available. A systolic blood pressure of less than 90 mmHg or a mean arterial pressure (MAP) of less than 60 mmHg should be aggressively pursued.

Numerous factors can confound the interpretation of pulses in clinical cases. Since the pulse that is palpated is the difference between the systolic and diastolic pressures, a small difference will cause the pulse to be weak or thready and a large difference will cause the pulse to be strong or bounding. None of these descriptions reflect the actual pressure within the vessel, and all of these pulse qualities can represent a patient in shock. An obstruction to blood flow can also inhibit the detection of pulses, as is the case in aortic thromboembolism by causing an absolute reduction in blood flow through the artery.

Patients in shock also frequently demonstrate tachypnea as the body attempts to maximize oxygen delivery to the alveoli and subsequently to the arterial blood. Respiratory rates in excess of 40 breaths per minute for a dog and 60 breaths per minute for a cat are consistent with shock. In this instance, tachypnea must be differentiated from true dyspnea or respiratory distress, the presence of which may indicate an underlying etiology but does not lead to a diagnosis of shock. Tachypnea is also a common response to pain, which may confound the use of respiratory rates for evaluation of possible shock. Often, evaluating the respiratory rate after administration of analgesia provides a better representation of the patient's ventilatory status.

Altered mentation is seen in patients in decompensated shock as blood flow and oxygen delivery to the brain are reduced. Since the brain has high demands for energy and little reserve for energy production, cerebral function and consciousness are affected early after decompensation begins. The typical patient in compensated shock will appear bright and alert while the patient in early decompensated shock will be mildly to moderately obtunded. As shock progresses so will mentation change and patients that find themselves in late decompensated shock will appear severely obtunded to stuporous. Pain can also affect a patient's response to its environment and care should be taken to ensure that changes in behavior are in fact due to altered mentation rather than pain. Evaluation of mentation is especially relevant in cases with head trauma when the level of consciousness can be used as a prognostic sign or metric of the severity of injury. In these cases, shock and pain should be addressed before those assessments are made or at the very least, they should be interpreted with these facts in mind.

The GI tract is affected in almost all cases of shock as evidenced by the ubiquity of the term "shock gut." Recall that the GI tract is one of the organ systems that is sacrificed in order to divert the scarce blood flow toward the heart and brain. This decrease in splanchnic blood flow has a significant impact on the mucosal integrity of the GI tract, leading to the vomiting and hemorrhagic diarrhea often seen in shock. As with most of the exam findings associated with shock, GI signs are usually mild to absent in animals in the compensatory stages of shock and can be moderate to severe in animals that have progressed to the later stages of decompensated shock.

The use of biomarkers for detection of shock and comorbidities has become widely accepted as standard of care in human medicine. These measurements (i.e., electrolytes, blood glucose, creatinine) can provide important information regarding the underlying cause of shock in addition to aiding in its recognition and diagnosis. Biochemical abnormalities can be prognostic or diagnostic and can direct the clinician to appropriate therapeutic interventions. All patients in shock should have a blood gas profile with lactate as a part of the initial and ongoing evaluation of the patient whenever possible.

Lactate is an important marker of tissue perfusion and has been the most widely used biomarker of shock in veterinary patients. Lactate is easily measured in clinical practice with a range of options from bench-top blood gas analyzers to handheld monitors that have been validated in veterinary patients. Blood lactate concentrations greater than 2.5 mmol/L are indicative of significant anaerobic metabolism and, in a patient with other signs consistent with shock, should be considered to be diagnostic for failure of oxygen delivery.

The availability and use of ultrasound in veterinary medicine has become very common. While not particularly useful for the diagnosis of shock itself, ultrasound has become especially useful because it allows identification of the etiology faster. The use of focused assessment with sonography for trauma (FAST) protocols for the abdomen (AFAST) and thorax (TFAST) have been very well described in veterinary medicine. These techniques can be performed with minimal training and are quite effective at the identification of fluid in cavities as well as the presence of a poorly contracting heart or pneumothorax. If available, and as long as positioning and restraint will not be detrimental to the patient, ultrasound should be used to evaluate patients in shock to attempt to determine the underlying cause. A description of the FAST procedures is provided in Chapter 46.

Classification of Shock

The following provides a guide to the classification of shock. The categorization of shock can be beneficial for formulating a diagnostic and therapeutic approach to a patient. While clinically useful, it should be reiterated that a patient in shock might often have disease processes

occurring that overlap categories, and it is possible that categorization may change as the underlying pathology progresses. Therefore, a singular approach to each specific shock category is not possible.

Hypovolemic Shock

Hypovolemic shock occurs when there is an absolute or perceived decrease in the intravascular volume. This is the classic example of shock and is arguably the most common cause of shock in veterinary patients. Hypovolemic shock can result from a loss of whole blood, loss of sodium-rich fluid (plasma) or in severe cases lack of adequate water intake. Chronic endocrine diseases can occasionally present as a unique subset of hypovolemic shock. As an example, a patient in a hypoadrenicortical (Addisonian) crisis may be hypovolemic but may not exhibit the typical clinical signs of shock.

Hemorrhagic shock is the classic example of hypovolemic shock. A distinguishing characteristic that sets hemorrhagic shock apart from other causes of hypovolemic shock is the absolute loss of whole blood, which can occur as overt blood loss from the laceration of a vessel or covert blood loss resulting from cavitary bleeding. A complicating component of hemorrhagic shock is the necessary loss of red blood cell mass concurrent with the loss of intravascular fluid. Patients suffering from hemorrhagic shock may only have shock completely ameliorated by the administration of both IV fluids and hemoglobin-containing products.

Cardiogenic Shock

Cardiogenic shock results from an inability of the heart to move blood into the pulmonary or systemic circulation. This is classically imagined to be a result of "forward failure" of the heart due to the heart being unable to maintain forward blood flow. As in the case of congestive heart failure, this may occur in the face of normal or increased preload. Due to the unique etiology and treatment approach to cardiogenic shock, a closer examination will be made in Chapter 42.

Distributive Shock

Distributive shock describes shock that occurs primarily due to loss of systemic vascular resistance (i.e., blood pressure). This is most often a result of inappropriate vasodilation resulting in decreased venous flow and thus decreased preload. Recall that in the absence of significant heart disease, preload is positively correlated with cardiac output. Besides the decrease in cardiac output that occurs in distributive shock, regional perfusion is disrupted with loss of blood pressure.

The classic example of distributive or vasodilatory shock is anaphylaxis whereby massive vasodilation lowers blood pressure to such a degree that capillary blood flow decreases. This reduction in capillary blood flow limits oxygen delivery to the tissues and results in tissue oxygen debt. In addition to vasodilation, an increase in the permeability of the capillaries results in a higher than normal net movement of water from the intravascular space to the interstitial space, further decreasing intravascular volume and worsening hypotension.

Neurogenic shock is an uncommon manifestation of CNS injury specifically in the brain, cervical or thoracic spinal cord and results from a decrease in sympathetic tone leading to significant loss of systemic vascular resistance. The presumed mechanism behind this rapid vasodilation is disruption of the autonomic paths in the spinal cord and is different from "spinal shock," which refers to the temporary loss of function of the spinal cord after spinal cord trauma.

Obstructive Shock

Obstructive shock results from impairment of blood return to the heart. It is typically associated with intraabdominal disease that sequesters blood within the abdomen and decreases preload (e.g., gastric dilation and volvulus [GDV]). Some argue that pericardial effusion with cardiac tamponade is a form of obstructive shock. Similar to GDV, during pericardial tamponade the intrapericardial pressure is higher than the venous pressure and results in decreased preload of the right atrium.

Septic Shock

Septic shock can be considered a form of distributive shock but has enough unique characteristics that it is often classified as a separate entity. As a result of infection and systemic inflammation, fluid is lost to the interstitium, water intake is decreased, systemic vascular resistance decreases, and myocardial performance is impaired. The therapy for septic shock must address each of these in turn as well as the underlying cause of sepsis. Septic shock will be investigated in detail in Chapter 43.

Oxygen Delivery

At its most basic, there are two primary components of oxygen delivery: cardiac output (CO) and arterial oxygen content (CaO_2). Therefore, a useful way to approach the treatment of shock is to separate the components of the cardiovascular system into the individual determinants

of oxygen delivery (DO_2). In fact, only seven parameters can be manipulated to augment oxygen delivery: those associated with cardiac output (heart rate, preload [end-diastolic volume], afterload [MAP], systemic vascular resistance, and ejection fraction), and those associated with arterial oxygen content (hemoglobin concentration and partial pressure of inspired oxygen).

Cardiac Output

Cardiac output is determined by the amount of the blood ejected from the heart with each beat (stroke volume) and the rate at which the heart is beating (heart rate). Stroke volume, in turn, is determined by the amount of blood that returns to the heart (preload), the force that must be overcome to eject blood out of the heart (afterload/systemic vascular resistance), and the physical force that the heart must generate to move blood (contractility or inotropy). Cardiac output is arguably the easiest component of DO_2 to manipulate. Accordingly, increasing preload is the most common initial treatment of shock and is accomplished with the administration of IV fluids and vasoactive medications to augment preload by increasing venous pressure and consequently right ventricular volume.

The heart has the ability to increase or decrease the force of contraction (inotropy) exerted during systole. Intrinsically, the heart pumps more powerfully when there is a larger amount of blood present in the ventricle at the end of diastole (Starling law of the heart). Sympathetic stimulation can also increase the force of contraction and is in fact the primary mechanism by which inotropy can be altered by the clinician through administration of beta-1-adrenergic agonists.

The impediment of flow that must be overcome to eject blood out of the heart is the systemic vascular resistance (afterload). This is the force that the cardiac wall is placed under when it contracts in systole and is usually considered as the mean arterial blood pressure (MAP). Although convenient, this is not always accurate. As an example, MAP and afterload are uncoupled when an anatomic obstruction to flow exists, such as subaortic stenosis. Manipulation of afterload (SVR and MAP) is possible through the administration of agents acting on specific vasoactive receptors (alpha, dopamine, and vasopressin). Most frequently, the goal is to increase both SVR and MAP. Afterload reduction is infrequently a concern in veterinary patients although it is common in humans due to that species' propensity for developing primary hypertension.

Heart rate changes are important for the second-to-second adjustment of cardiac output. During shock, increases in heart rate typically parallel increases in inotropy. Clinically, heart rate measurement is a useful tool for diagnosing a patient in shock. Heart rate can be manipulated pharmacologically with beta-2-adrenergic agonists and anticholinergic drugs. However, the ability of changes in heat rate to improve cardiac output is limited. Diastolic filling time is essential for preload and tachycardia shortens the amount of time spent in diastole during the cardiac cycle. At very high heart rates, this shortened diastolic time can significantly decrease preload and cardiac output. Patients in the decompensatory stage of shock can become absolutely or relatively bradycardic as the heart begins to fail due to poor oxygen delivery to the heart itself.

Arterial Oxygen Content

Oxygen content of the blood is the sum of the oxygen dissolved in the blood (PaO_2) and the amount of oxygen that is bound to hemoglobin. The amount of oxygen bound to hemoglobin is a much more important contributor to total blood oxygen content while PaO_2 is a more important indicator of the lungs' ability to oxygenate the blood.

Interventions directed at improving arterial oxygen content include provision of supplemental oxygen (increasing PaO_2) and transfusion of hemoglobin in the form of red blood cells or hemoglobin-based oxygen carriers (increasing oxygen-carrying capacity). The importance of hemoglobin concentration in oxygen delivery cannot be overstated. Hemoglobin makes the transport of oxygen in the blood and subsequent offloading at the tissue bed much more efficient. Consequently, raising hemoglobin is the best way to improve arterial oxygen content if lung function and ventilation are normal. Supplementation of oxygen to those patients who are normoxic (have a normal PaO_2) will do little to increase the amount of oxygen presented to the tissues (assuming the supplementation is at normal atmospheric pressure) when compared to supplementation of hemoglobin. Consider a dog breathing room air; assuming a hemoglobin concentration of 6 g/dL (HCT 18%), PaO_2 of 90 mmHg, and arterial hemoglobin saturation (SaO_2) of 95%, the calculated CaO_2 would be 8.0 mL O_2/dL. By increasing the fraction of inspired oxygen to 40%, the resultant CaO_2 would increase to 8.55 mL O_2/dL for an 8% increase. Now assume raising the hemoglobin with no oxygen supplementation. By increasing the hemoglobin concentration to 9 g/dL (HCT 28%), a CaO_2 of 12 mL O_2/dL can be achieved for a 54% increase. In order to extract the most benefit from an increase in hemoglobin concentration, it must be maximally saturated with oxygen so oxygen supplementation is always warranted during shock to ensure the highest possible PaO_2 is achieved.

Treatment

If possible, the treatment of shock should be directed at the underlying cause and should be aggressive and comprehensive. Most patients in shock can be initially resuscitated in a similar or identical manner with a few notable exceptions. If the patient has an obvious cause of shock with tachycardia without significant heart disease present or suspected, then fluid therapy is almost always beneficial. In cases of hypovolemic, distributive, or obstructive shock, increasing intravascular volume often results in significant improvement. The exception to fluid administration for shock is cardiogenic etiology.

The type and dose of fluid administered for shock are among the most controversial topics in medicine. In most circumstances, isotonic crystalloids are as effective or better, as safe or safer, and less expensive than any of the other choices for the initial resuscitation of shock. There are subtle nuances, with different resuscitative fluid strategies for specific disease states, but in general replacement crystalloid fluids are suitable choices.

The traditional dose of fluids for patients in shock for dogs and cats respectively is 90 mL/kg and 60 mL/kg of crystalloid fluids. This represents approximately one blood volume that is intended to be administered over a short period of time. Many patients do not require an entire shock dose of fluids to be effectively resuscitated so the most utilized clinical approach is to divide the dose into four equal parts and administer the aliquots until endpoints of resuscitation are reached. Although effective at restoring circulating volume, the duration of effect of replacement crystalloids is short due to rapid redistribution of bolus fluids into the interstitial space. For this reason, it may be necessary to administer subsequent boluses to maintain the desired volume expansion. Unfortunately, overaggressive resuscitation can lead to interstitial edema formation and dilutional coagulopathy. Because of this risk, it is necessary to keep track of the total volume of replacement crystalloid administered to a patient and to consider alternative methods of resuscitation if initial crystalloid boluses do not result in lasting resolution of shock.

Alternatives to replacement crystalloid fluids include hypertonic saline, blood products (i.e., fresh frozen plasma, fresh whole blood or packed red blood cells), synthetic colloid solutions (i.e., hydroxyethyl starches), albumin-based colloid solutions (human serum albumin or lyophilized canine albumin), hemoglobin-based oxygen carriers (HBOC), or combination of any of the above. Of these, hypertonic saline and synthetic colloids are used the most frequently.

Hypertonic saline has the advantage of being relatively inexpensive and having a long shelf-life. Doses of 4–6 mL/kg of 7.5% NaCl can be used in nondehydrated traumatized or hemorrhaging patients and may be particularly useful for resuscitation of animals with head trauma. Hypertonic saline recruits fluid from the intracellular space to rapidly increase the intravascular volume, providing much needed volume expansion while minimizing the risk of overresuscitation and edema formation. Boluses of hypertonic saline can be administered over a shorter period of time than boluses of isotonic crystalloid fluids due to the smaller volume required. Unfortunately, hypertonic saline behaves in a similar manner to replacement crystalloids, with rapid redistribution of fluid into the interstitial space, and because of the high osmolarity of hypertonic saline and the absolute solute load, repeated dosing is not recommended due to the risk of hypernatremia. Relative or absolute contraindications to hypertonic saline include preexisting dehydration, hypernatremia or hyperosmolar conditions (ex. hyperosmolar-hyperglycemic diabetes mellitus). To maintain the volume expansion derived from administration of hypertonic saline, it is often combined with a synthetic colloid such as hetastarch (10–20 mL/kg) and administered together.

Colloids have been used successfully in the resuscitation of patients in shock for years. However, controlled studies have not consistently shown that colloidal solutions are more effective at achieving resuscitation than isotonic crystalloids. Theoretically, the use of a colloid for resuscitation in patients with low serum protein or those with edematous diseases may be preferred. Incremental doses of 5 mL/kg of hydroxyethyl starch is a reasonable starting point, with a total shock dose equaling 10 mL/kg and 20 mL/kg for cats and dogs respectively. Clinically, the primary utility of synthetic colloids for resuscitation is to maintain the duration of volume expansion achieved with isotonic crystalloids. Synthetic colloids are almost never used alone for resuscitation of a patient. Rather, they are co-administered with either isotonic or hypertonic crystalloids. An effective resuscitation plan would include alternating administration of isotonic crystalloid and colloid solutions (1/4 volume aliquots of each) until resuscitation has been achieved. Significant debate exists regarding the impact of synthetic colloids on coagulation and platelet function. There is little debate that synthetic colloids can impair platelet function *in vitro*, but the clinical implications are less clear. Perhaps of more clinical import is the potential for synthetic colloids to induce dilutional coagulopathy. For these reasons, synthetic colloids should be used thoughtfully in patients with thrombocytopenia/thrombocytopathia or documented coagulopathy. Ultimately, the clinician should attempt resuscitation with the method they are most comfortable with rather than attempting to use a resuscitation strategy that is unfamiliar.

The use of blood products in shock resuscitation is not routine since most patients have adequate oxygen-carrying capacity. If a patient has been administered an adequate volume of fluid for resuscitation, has persistent clinical signs of shock and requires oxygen-carrying capacity, then the administration of blood is indicated. This can be in the form of packed red blood cells, whole blood or hemoglobin-based oxygen carriers. No agreed-upon transfusion trigger exists and the decision to administer blood depends on the chronicity of the anemia and the patient's clinical signs. For patients with an acute drop of 30–50% in packed cell volume (PCV), the administration of blood should be strongly considered. In these cases, a reasonable goal is to raise the PCV by 15–20% with a minimum PCV target of 20%. Typical doses of 10 mL/kg of packed red blood cells or 20 mL/kg of whole blood should be effective.

The actual rate of administration of blood products for resuscitation will depend on the patient's condition. Under ideal circumstances, blood products are administered slowly with careful monitoring for transfusion reactions. Patients in shock, however, do not often have the benefit of time and bolus administration may be needed. In this case, care has to be taken as techniques that apply pressure to the red blood cells or increase shear stress, such as administration with an infusion bag through a small-bore catheter, can result in significant lysis of transfused cells. When bolusing blood products, it is best to allow blood to flow by gravity as quickly as possible. Administration of blood should be through a dedicated IV catheter, meaning that other resuscitative fluids should be held during transfusion unless provided through a different catheter or lumen (in the case of multilumen catheters). It is safe to administer normal saline with blood products and co-administration may improve the fluid dynamics of the blood product and speed the delivery rate.

The treatment of pain may be needed in many patients with shock, and is mandatory if they have been traumatized. In unstable painful patients, pain control should be achieved with short-acting pure mu opioid agonists (ex. fentanyl, hydromorphone, oxymorphone or morphine) administered via the intravenous or intramuscular route. The dose should be adequate to effectively treat pain but not depress respiration. This will help the clinician evaluate the patient, as it will mitigate the contribution of pain to tachycardia. With pain controlled, the presence of tachycardia likely indicates shock or hypoxia in the traumatized patient. Typical doses of common analgesics are provided in Table 41.1.

Vasopressors and positive inotropes are rarely used during the initial resuscitation of shock but can be invaluable for the treatment or management of vasodilatory or septic shock that is refractory to resuscitation.

Table 41.1 Dosages of commonly used opioid analgesics in the patient with shock

Drug	Dosage	Frequency
Fentanyl (bolus)	2–5 µg/kg	PRN, q15 min
Fentanyl (CRI)	5–20 µg/kg/h	CRI
Hydromorphone/ oxymorphone	0.05–0.2 mg/kg	q4-6h
Morphine	0.5–2 mg/kg	q4h
Buprenorphine	0.01–0.02 mg/kg	q6-12h
Methadone	0.2–0.5 mg/kg	q4-6h

CRI, constant rate infusion; PRN, as needed (*pro re nata*).

Administration of vasopressors or positive inotropes should not be performed prior to adequate volume expansion, with the possible exception of treating cardiogenic shock due to systolic failure with a positive inotrope. Clinically, the most frequently used vasopressor during shock is epinephrine administered for the acute treatment of anaphylaxis. A more detailed discussion of vasopressors can be found in Chapter 43.

Some patients in shock will not be stabilized until the underlying disease process has been corrected, as is often the case with obstructive shock. Patients with significant amounts of pericardial effusion causing cardiac tamponade improve dramatically when even a small amount of fluid is removed, as do patients with GDV following decompression of the abdomen. Patients in obstructive shock often do not have an absolute volume deficiency, but increasing preload can transiently improve the diastolic filling of the heart while preparations for definitive treatment are under way.

Reevaluation and Endpoints of Resuscitation

The importance of reevaluating the patient during and after resuscitation cannot be overstated. When evaluating the efficacy of treatment, the clinician expects physiologic signs of shock to resolve. If resolution is not achieved, further resuscitation is needed or reconsideration of the diagnosis is necessary. As with all medical treatments, it is necessary to have predetermined endpoints in mind to decide when treatment is no longer needed. The optimal endpoints of resuscitation have been debated for a number of years and although recommendations and general agreement exist, no consensus has been reached. The ultimate endpoints of resuscitation should tell the clinician when the patient is out of shock, meaning adequate oxygen delivery to all tissues has been reestablished. Possible endpoints

Box 41.1 Endpoints of resuscitation. Each of these values must be interpreted within the clinical context as improvement in an isolated variable may not indicate complete resolution of shock

- Normalization of heart rate
- Normalization of respiratory rate
- Improvement of pulse quality
- Normalization of capillary refill time
- Blood pressure
- Improvement of blood lactate concentration
- $ScvO_2$

include physical exam findings or biochemical variables (Box 41.1). These should be evaluated before, during, and after therapy has been instituted.

Normalization of heart rate, respiratory rate, and CRT as well as improvement of pulse quality have been traditionally used by clinicians to judge if resuscitation is complete. These endpoints are intuitive because they coincide with the findings that are initially used to determine if a patient is in shock. It follows that when those findings normalize, resolution of shock has been achieved. The reality is more complex as physical exam endpoints can normalize while inadequate oxygen delivery is ongoing at the cellular and subcellular level. Therefore, the use of endpoints that include evaluation of cellular oxygen usage such as lactate, base excess, and hemoglobin saturation should be incorporated into all shock treatment plans. In practice, resuscitation should continue until there is resolution of the physical exam endpoints, at which time analysis of the biochemical endpoints should be performed. If those endpoints have been reached then resuscitation is complete; if biochemical derangements persist then resuscitation efforts should continue until resolution is achieved.

Blood Pressure

Blood pressure can be measured in a variety of ways but is most commonly performed using a Doppler with sphygmomanometer or a digital monitor with oscilllometric capability. Unfortunately, blood pressure is an unreliable predictor of perfusion as it is influenced by the compensatory mechanisms previously discussed. In fact, a patient can have significant microcirculatory hypoperfusion while maintaining normal blood pressure. However, hypotension does occur as shock progresses and when present should be aggressively treated with a target of returning the systolic blood pressure to at least 90 mmHg and MAP to 60 mmHg.

Lactate

Because lactate is a byproduct of anaerobic metabolism, has a relatively short half-life and can be measured readily, it is a very useful biomarker for shock. Lactate measurement is an inexpensive adjunct to traditional physical exam endpoints and its use has become standard of care in human medicine.

In most cases, elevations in lactate occur secondary to anaerobic metabolism, so by measuring the concentration of lactate in a blood sample, the clinician can form an idea of whether or not anaerobic metabolism is occurring. Occasionally, neoplastic or endocrine diseases can cause the production of lactate to be higher than the body's ability to metabolize it, leading to elevation of blood lactate concentration. Similarly, significant liver disease or liver failure can reduce lactate clearance and lead to hyperlactatemia. When lactate is elevated due to causes other than anaerobic metabolism, it is termed type B hyperlactatemia. Occasionally, strenuous exercise can cause hyperlactatemia. This appears clinically in patients with prolonged seizures or patients that require aggressive restraint during examination or blood collection. These possibilities should be considered when a patient has a high blood lactate concentration but no other clinical signs that would indicate the presence of shock. This is an uncommon occurrence in veterinary medicine and an animal presented in shock with blood lactate elevation should be assumed to have inadequate oxygen delivery until proven otherwise.

The finding of elevated lactate alone does not necessarily mean that global oxygen delivery is inadequate as local perfusion abnormalities can have significant impact on lactate concentration. Although absolute lactate concentration can be correlated with patient outcomes, lactate clearance following resuscitative efforts is probably a better prognostic indicator and patients with persistently elevated lactate concentrations despite aggressive treatment should be considered to have a worse prognosis. As with all resuscitation endpoints, the results of lactate measurement must be interpreted in light of the patient's clinical condition.

Mixed Venous or Central Venous Oxygen Saturation

Measurement of venous hemoglobin saturation can provide meaningful insight into the consumption of oxygen within the body. The hemoglobin saturation of venous blood is expected to be lower than that of arterial blood. If this difference is greater than expected, it may indicate that oxygen-starved tissues are removing more oxygen than usual from each hemoglobin molecule. This is best explained by the oxygen extraction ratio (OER), which is simply the mathematical ratio of the amount of oxygen

that is delivered to the capillaries via the arteries and the amount found in the venous blood draining the capillaries. This ratio indicates the proportion of oxygen that the mitochondria are using versus the amount supplied. If venous blood has high hemoglobin saturation, then the mitochondria did not consume as much oxygen as expected. This may indicate low metabolic rate or mitochondrial dysfunction, as seen in sepsis. However, if venous oxygen saturation is low, it suggests that the mitochondria are extracting more oxygen than expected and that an oxygen debt may be present.

Importantly, venous hemoglobin saturation only reflects the oxygen consumption that is occurring in the tissue bed that the blood is draining. As an example, if you were to draw blood from a cephalic vein, you will only be gaining knowledge about oxygen usage in the distal limb. Blood drawn from the jugular vein will provide information about oxygen consumption in the head, including the brain. Under most circumstances, samples drawn from the jugular vein are approximately reflective of oxygen consumption throughout the body, but a better representation of the global oxygen usage would be venous blood that has been mixed from all parts of the body. This ideal sample is retrieved from the pulmonary artery and is termed the mixed venous oxygen saturation (SvO_2). The pulmonary artery is not routinely catheterized in people and even less frequently in veterinary patients, but there is a strong correlation between mixed venous samples and central venous samples ($ScvO_2$) obtained from the cranial vena cava or right atrium. Obtaining an $ScvO_2$ sample is much more feasible in clinical practice and can prove very useful for guiding resuscitation efforts.

The most significant advantage of venous hemoglobin saturation monitoring is that increases in OER (i.e., lower than expected venous hemoglobin saturation) may be evident before the onset of anaerobic metabolism, giving the clinician an essential head start in the treatment of shock. An $ScvO_2$ of <70% indicates that a patient is experiencing tissue oxygen debt. When performing resuscitation, therefore, the goal is to maintain an $ScvO_2$ of >70%. If this is not possible with the administration of vascular expansion and vasopressor support alone then treatment with red blood cells may be indicated. Venous hemoglobin saturation may be low for several reasons, including slow capillary transit time (poor microperfusion), increased tissue demand for oxygen, low arterial hemoglobin saturation or anemia. Once again, venous hemoglobin saturation should be interpreted with the patient's overall condition in mind.

Conclusion

A simplified and systematic approach to the patient in shock is necessary for successful management. It is easy to become overwhelmed with the totality of clinical implications and lose sight of the ultimate goal. Approaching shock from the standpoint of oxygen delivery makes the interventions that need to be considered finite and easier to implement. Frequent reevaluation of the patient through the endpoints of resuscitation will allow determination of the efficacy of therapy.

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42

Cardiogenic Shock

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Pathophysiology

Cardiogenic shock occurs when oxygen delivery is insufficient to maintain normal aerobic cellular metabolism as a result of cardiac dysfunction in the presence of adequate intravascular volume. In other words, cardiogenic shock occurs when cardiac output is decreased despite adequate blood volume. Importantly, cardiogenic shock does not imply congestive heart failure (CHF) although CHF can be present in cardiogenic shock patients.

Cardiogenic shock occurs in two settings. Forward failure results from the heart's inability to adequately pump blood forward from either the left or right ventricle into either the aorta or main pulmonary artery respectively. Backward failure, on the other hand, results from inadequate ventricular filling of the heart during diastole with a subsequent reduction in stroke volume and cardiac output. Common conditions resulting in forward failure of the heart include rupture of one or more chordae tendinae or acute-onset severe pulmonary hypertension. Causes of backward failure include paroxysmal ventricular tachycardia or pericardial tamponade.

Cardiogenic shock is somewhat different from other forms of shock due to the greater potential impact on the myocardium. When cardiac dysfunction underlies the development of shock, coronary perfusion is often impaired as a result of increased right-sided pressures or decreased aortic root pressure. Because of the potential for decreased coronary perfusion and subsequent ischemic myocardial injury, it is imperative that cardiogenic shock is recognized early and treated aggressively.

When ventricular function or efficiency is acutely diminished, cardiac output declines rapidly. If ventricular dysfunction is a result of systolic myocardial failure (as seen with dilated cardiomyopathy), the force of ventricular contractions (inotropy) is not sufficient to eject a normal volume of blood from the ventricles. Since stroke volume is one of two determinants of cardiac output (cardiac output = heart rate × stroke volume), a decrease in inotropy will reduce cardiac output in a direct fashion unless compensation occurs by increasing heart rate. Perceived ventricular dysfunction also occurs when there is a sudden change in valvular integrity resulting in an acute increase in regurgitant fraction and decrease in cardiac output. If this occurs, a large portion of the ventricular load is directed backwards through the atrioventricular valve rather than the semilunar valves of the aorta or main pulmonary artery. Although this occurrence is uncommon in the general population, animals that have existing degenerative valvular disease are at an increased risk of suffering rupture of one or more of the chordae tendinae.

Bradycardia is an uncommon cause of forward failure and cardiogenic shock but can occur with third-degree atrioventricular block. This condition results in diminished cardiac output as a result of drastic reduction in heart rate (the other main determinant of cardiac output). Regardless of the inciting cause of forward failure, the end-result is an increase in the end-diastolic ventricular volume with subsequent increases in atrial volumes and pressures. Cardiogenic shock from forward failure states is often exacerbated by development of pulmonary edema and hypoxemia.

Backward failure results from diseases that cause decreased ventricular volume at end-diastole. Since the volume of blood pumped out of the heart is dependent on the volume of blood present at the beginning of the cardiac cycle, it follows that any decrease in this volume will result in diminished cardiac output. The Frank Starling law of the heart states that the greater the volume of the ventricle at end-diastole, the more forceful the corresponding contraction has to be to meet the demand for greater output, effectively tying preload (end-diastolic volume) to cardiac output.

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While it is convenient to consider the heart as consisting of two separate pumps (the left and right), it must be remembered that the two operate in a dependent manner. The right heart is obligated to pump the same volume of blood that is returned to it from the venous circulation in the same fashion that the left heart is obligated to pump the volume of blood that is returned from the pulmonary circulation. This interdependence means that dysfunction of either the left or right heart results in a decrease in total cardiac output. Therefore, sudden failure of one side of the heart will result in dysfunction of the entire heart and can lead to cardiogenic shock.

Once global oxygen delivery is insufficient to maintain aerobic metabolism, the pathophysiology of shock at the cellular level is identical regardless of the underlying etiology.

Epidemiology

Many of the conditions that cause cardiogenic shock in dogs are chronic, progressive diseases that have an acute worsening. Myxomatous mitral valve disease can predispose dogs to rupturing one or more chordae tendinae, leading to cardiogenic shock. Unfortunately, the severity of valvular lesions is not predictive of risk of chordae tendinae rupture in dogs so little can be done to predict which patients will suffer from this condition. When rupture of a first-order chorda occurs, patients will often exhibit acute, severe clinical signs. Rupture of second or third-order chordae may result in minimal to no clinical signs and may only be detected during routine echocardiography or necropsy.

Pericardial effusion is arguably the most common cause of cardiogenic shock in dogs and can occur more or less acutely. Chronic pericardial effusion is less likely to result in cardiogenic shock while acute pericardial effusion almost uniformly causes tamponade and subsequent cardiogenic shock. Acute pericardial effusion can occur secondary to a rapid bleeding event from a neoplastic lesion associated with the heart (hemangiosarcoma of the right atrium), or from rupture of one of the vascular structures within the pericardial sac (atrial rupture in dogs or cats with severe left atrial enlargement secondary to chronic cardiac disease). Idiopathic pericarditis is an uncommon cause of acute pericardial effusion but is a frequent cause of cardiac tamponade in dogs. Pericardial effusion in cats is rare and infrequently results in tamponade.

Canine heartworm disease can occur anywhere in the continental United States, but the incidence reaches 45% along the Atlantic and Gulf Coast regions and the Mississippi River region. Caval syndrome can manifest as cardiogenic shock when dogs have large heartworm burdens that mature rapidly. The severity of disease is directly related to worm burden and patient size and caval syndrome occurs most often when worm burdens approach 60–100 although it has been reported with worm burdens as small as 12.

Tachyarrhythmias can result from primary conductional abnormalities such as arrythmogenic right ventricular cardiomyopathy (ARVC) or may be secondary to structural changes within the heart, as is the case with dilated cardiomyopathy (DCM). In fact, sudden death due to ventricular tachycardia occurs in up to 50% of Doberman pinschers affected with DCM. A rare but severe form of ventricular tachycardia called Wolff–Parkinson–White syndrome can be seen in dogs or cats with ventricular preexcitation. These patients are at risk for development of paroxysmal ventricular tachycardia due to the establishment of a reentry circuit that allows for the establishment of a reciprocating tachycardia and are at increased risk of developing cardiogenic shock.

Third-degree atrioventricular (AV) block can result from progression of a chronic infiltrative cardiac disease, infectious disease (e.g., Chagas disease), myocarditis or ingestion of cardiotoxins, including prescription medications (e.g., beta blockers, calcium channel blockers) or plant alkaloids (e.g., digitalis glycosides). If acute in onset (not preceded by second-degree AV block), third-degree AV block can result in development of cardiogenic shock although this is uncommon and usually coincident with significant structural cardiac disease. Sick sinus syndrome is a disease that occurs primarily in miniature schnauzers and infrequently in other breeds. It is characterized by periods of severe bradycardia or sinus arrest with occasional paroxysmal tachycardia resulting in potentially significant perfusion abnormalities.

Myocarditis is an extremely rare cause of cardiogenic shock that can be caused by infectious organisms, trauma, immune-mediated diseases, and toxins. Infectious causes of myocarditis include viral (parvo, distemper), bacterial (various), rickettsial (*Bartonella*), and protozoal organisms (*Trypanosoma*, *Toxoplasma*), among others. Myocarditis can induce myocardial failure through a cycle of inflammation, myofiber dropout and fibrosis, the cumulative effect of which is a clinical syndrome that mimics dilated cardiomyopathy. In general, myocarditis results in a subacute to chronically progressive form of cardiac dysfunction, but patients with undiagnosed myocarditis can present with end-stage disease in cardiogenic shock.

Rarely, intracardiac neoplasia can result in development of cardiogenic shock by directly affecting blood flow within the heart itself. Neoplasia associated with the atrioventricular valves, semilunar valves, right ventricular outflow tract, and right and left atria has been described. Tumor types that have been reported include

ectopic thyroid carcinoma, hemangiosarcoma, and osteosarcoma, among others.

Cardiogenic shock in cats occurs infrequently. When it does occur, it is usually due to cardiomyopathy (dilated [DCM], restrictive [RCM) or hypertrophic [HCM] with or without left ventricular outflow tract obstruction [LVOT]). The clinical importance of LVOT obstruction in cats with HCM is not fully understood but in cats with severe LVOT secondary to HCM, the dynamic obstruction of the left ventricular outflow tract can result in significant decreases in cardiac output. A more common cause of cardiogenic shock in cats is a form of "low-output" heart failure, usually characterized by hypothermia, bradycardia, and severe hypotension. This form of heart failure appears to be more common in cats with RCM and may be the result of ischemic heart injury.

Signalment

Cardiogenic shock can occur in a patient of any age or breed, making it difficult to describe a typical signalment, but because myocardial failure or neoplasia is often the inciting cause of cardiac dysfunction, these patients tend to be older middle-aged to geriatric animals. Pericardial effusion occurs most commonly in large- and giant-breed dogs, although endocardial ruptures resulting in acute pericardial effusion appear to be more common in older male small-breed dogs, with dachshunds and cocker spaniels being overrepresented.

Young dogs and cats with congenital cardiac abnormalities can develop cardiogenic shock. These patients are often identified as having a cardiac abnormality during an early veterinary visit and have frequently exhausted most if not all management options by the time cardiogenic shock develops. Therefore, when it occurs in these patients, it is usually a terminal, irreversible event.

Canine heartworm disease occurs in middle-aged dogs of both sexes. Smaller dogs appear to be at greater risk of developing caval syndrome and subsequently would be at greater risk for development of cardiogenic shock, likely due to the smaller worm burdens required to cause significant clinical disease in these smaller patients.

Certain breed predispositions for cardiac disease exist and by extension, these breeds may be at increased risk for development of cardiogenic shock. Boxer dogs are much more likely than other breeds to develop arrythmogenic right ventricular cardiomyopathy while Doberman Pinschers are considered most at risk for development of dilated cardiomyopathy. Both of these conditions can lead to ventricular tachycardia with cardiogenic shock. Besides the potential for tachyarrhythmias, dogs with DCM are at risk for systolic failure. Large- to giant-breed dogs are at increased risk for development of atrial fibrillation. Cats are rarely able to propagate atrial fibrillation due to their relatively small atrial mass but cats with severe atrial enlargement due to cardiomyopathy (Maine Coon, Himalayans) should be considered to be at risk.

History and Clinical Signs

A common historical complaint for animals presenting with cardiogenic shock is collapse or syncope. Owners commonly describe "seizures" rather than syncope so a careful history must be taken to determine if intracranial disease or seizures are in fact a contributing factor. A thorough history includes the patient's activity and behavior immediately preceding and following the event, state of consciousness during the event, and frequency of events. Syncope can result from many different cardiac conditions but brady- or tachyarrhythmias and pulmonary hypertension are the most common. Often syncope in these animals is exercise induced and the occurrence of syncope at rest should be considered evidence of advanced disease. If a patient presenting in shock has a history of syncope or collapse or if the owner describes exercise-induced "seizures," the clinician should be alert to the potential for a cardiogenic cause of shock. Most, if not all, patients in cardiogenic shock will present with acute exercise intolerance or weakness.

Regardless of the underlying cause of cardiogenic shock, all of these patients will present with perceptible derangements in perfusion parameters. The mucous membranes may be pale (evidence of poor perfusion) or cyanotic (evidence of hypoxemia). Delayed capillary refill time is an indicator of poor peripheral perfusion. In cases of severe shock, the mucous membranes may fail to blanch altogether. Often, the distal extremities will be cooler to the touch than the trunk. As shock progresses from compensated to the early, then late decompensatory stages, the mental status will change and the patient will become obtunded. Patients presenting obtunded to stuporous are in the late stages of shock and without timely intervention are likely to die.

As a general rule, patients in cardiogenic shock will have one or more abnormal findings during cardiac auscultation. Animals with pericardial disease will often have decreased heart sounds. Auscultation of animals with myocardial dysfunction may reveal either brady- or tachyarrhythmias. When present, arrhythmias can either be regular (e.g., sustained ventricular tachycardia) or irregular (e.g., atrial fibrillation). Cats often have gallop rhythms although extra heart sounds can be present in the dog also and usually indicate structural cardiac disease. Increases in adventitial lung sounds (crackles) may be present in cases with forward failure that results in the

development of pulmonary edema. Occasionally, acute worsening of a previously detected murmur with or without development of a precordial thrill is present and may be indicative of rupture of a first-order chorda tendina.

In some instances, as in the case of cardiac tamponade, the history may be one of subacute progression. Physical exam findings suggestive of pericardial effusion include muffled heart sounds, decreased precordial impulse, detection of pulsus paradoxus (although weak pulses are also common), and presence of jugular pulses. The finding of ascites and a positive hepatojugular reflex is more likely to occur in cases of chronic pericardial effusion and may be absent in the patient presenting with cardiogenic shock.

Respiratory distress may or may not occur as a result of cardiogenic shock but respiratory failure is rare. Tachypnea is likely to be present as a result of normal compensatory mechanisms to improve oxygen delivery. Significant hypoxia or hypoxemia can occur in situations such as pulmonary hypertension or pulmonary edema due to chordae tendinae rupture. For a more in-depth discussion on respiratory failure, the reader is referred to Chapter 39.

Diagnosis

Unique clinical characteristics of cardiogenic shock include concurrent hypotension (systolic blood pressure <90 mmHg or mean arterial pressure <60 mmHg), decreased cardiac output, and elevated central venous or left atrial pressures. There is no single diagnostic test that will confirm the presence of cardiogenic shock. Rather, the clinician will be forced to reconcile available diagnostic results (limited by patient stability, availability within the clinic, and finances) with the patient's historical findings, presenting complaint, and physical exam findings to achieve a diagnosis.

When presented with a patient in cardiogenic shock, the clinician will be faced with the decision about whether or not the restraint required to perform a diagnostic test is going to be tolerated by the patient. Unfortunately, it may be necessary to delay or forego some diagnostic tests that require restraint due to the tenuous nature of the patient's condition and every effort should be made to limit stress to the patient. Staging of testing can be helpful, focusing efforts on performing tests in the order most likely to yield meaningful results. As an example, it would be best to delay collection of blood in order to obtain even a single thoracic radiograph or an electrocardiograph (ECG). Occasionally, it is necessary to accept less than ideal results for testing such as obtaining a single radiographic view rather than orthogonal views or performing a limited echocardiogram or thoracic ultrasound rather than a complete exam to preserve patient safety. In fact, thoracic ultrasound can often be performed in the ER with minimal restrain and can produce repeatable results with a small amount of training. It is extremely disappointing when patients die during diagnostic procedures so the patient's condition, stability, and the value of the potential information obtained should be taken into consideration prior to ordering or performing a test.

The use of ECG provides real-time evaluation of the electrical conductance of the heart and enables the clinician to determine the source of cardiac depolarization and if a conduction abnormality exists. When evaluating a patient with suspected cardiogenic shock, an ECG should always be obtained. Patients are usually tolerant of ECG leads placed with either alligator clips or pads. The goal of ECG evaluation in this setting is to determine which cardiac cells are acting as pacemaker cells and if electrical conduction is occurring in an organized fashion. Therefore, patients can often be allowed to remain in sternal recumbency with minimal restraint. Evaluation of a lead II ECG should enable the clinician to answer pertinent urgent questions. A more thorough six-lead ECG can be performed if the patient's condition is considered stable enough to allow for restraint in lateral recumbency. While the presence of sinus tachycardia will not enable diagnosis of cardiogenic shock (sinus tachycardia is expected to occur in most shock states regardless of etiology), the presence of paroxysmal ventricular tachycardia supports the diagnosis. Additionally, the finding of multiform ventricular ectopy or electrical alternans may increase the clinician's suspicion of a cardiac origin of shock.

Radiography is a useful diagnostic tool and is readily available in most veterinary facilities. When using radiography in the emergency setting, it is important to keep patient safety in mind, realizing that the quality and completeness of the study may have to be compromised to ensure patient safety. Diagnostic radiographs can often be obtained with minimal restraint. In fact, patients can often be allowed to remain in sternal recumbency while a dorsoventral (DV) projection is obtained. A single lateral or DV projection may provide clues regarding the cause of shock (e.g., a globoid cardiac silhouette) but orthogonal views are always preferred if possible. Animals with rupture of a first-order chorda may manifest fulminant pulmonary edema characterized by the presence of an alveolar lung pattern while animals with cardiogenic shock secondary to ventricular tachycardia may have no radiographic abnormalities.

Echocardiography can be used to diagnose many of the causes of cardiogenic shock. The minimally experienced ultrasonographer will be able to recognize the presence of

pericardial effusion and will likely correctly identify tamponade if present. Additionally, with a small amount of focused training, the emergency clinician can recognize acute systolic failure (e.g., dilated cardiomyopathy). Evaluation of ventricular function and filling pressures in patients with chronic valvular disease requires more training and is complicated by the fact that ventricular systolic and diastolic function changes with age and disease severity in dogs. The recognition of chordae tendinae rupture, mild to moderate valvular insufficiency, caval syndrome or pulmonary hypertension will likely require evaluation by a veterinary cardiologist. Echocardiography can also be used to identify rare causes of cardiogenic shock such as intracardiac tumors.

The use of biomarkers in veterinary medicine is an area of active investigation. While many biomarkers have been studied and show promise for distinguishing cardiac disease from respiratory disease or for stratifying severity of cardiac disease (NT-proBNP, troponin-I), most are not available as point-of-care (POC) tests, limiting the clinical usefulness of these assays for evaluation of the patient in cardiogenic shock. The exception to this is troponin-I, which is available as a POC test (iStat by IDEXX) and has been shown in several veterinary studies to correlate with myocardial injury. A high troponin-I level in a patient presenting for shock should prompt the clinician to further explore the possibility of an underlying cardiac cause. It should be noted, however, that troponin-I levels have been shown to increase in dogs with gastric dilation and volvulus and may be elevated in any patient that has cardiovascular instability. The degree of troponin-I elevation is likely greater in dogs with myocardial injury than in those with shock of noncardiac origin. Therefore, the true utility of troponin-I may be in its ability to rule out myocardial injury in the acute setting.

Determination of cardiac output would provide strong support for a diagnosis of cardiogenic shock, especially in the absence of other possible causes of shock. While cardiac output monitoring technology exists in veterinary medicine, its clinical use remains limited at this time.

Therapy

Cardiogenic shock is a unique form of shock that is not generally responsive to traditional treatments for other types of shock, (i.e., volume expansion and vasopressor support). In fact, intravascular volume expansion and vasopressor therapy can be detrimental or even fatal when administered to a patient with cardiogenic shock. Rather, cardiogenic shock must be treated primarily by improving cardiac performance and secondarily by altering vasomotor tone (usually reduction of vasomotor tone).

As with all forms of shock, oxygen administration should be started immediately upon recognition of the shock state in an effort to maximize arterial oxygen content as far as possible. Oxygen can be provided by a variety of methods. The use of flow-by oxygen with a mask is easy to perform but requires constant restraint of the patient. This method of oxygen supplementation is relatively inefficient unless a tight-fitting mask is used. Unfortunately, animals in shock are often intolerant of having a mask held over their muzzles and they may struggle or resist. Holding a tube attached to an oxygen source in front of an animal's face is an extremely inefficient method of providing oxygen but, recalling that perfect is the enemy of good, is probably better than not providing any supplemental oxygen. Occasionally, animals will tolerate placement of nasal prongs similar to those used in human medicine. Due to the large size of the prongs, this is most feasible in large-breed, no-brachycephalic dogs.

A less labor-intensive way of providing oxygen is through the use of an oxygen chamber or cage. Purpose-built oxygen cages are available but require a significant financial investment and utilize large amounts of oxygen. A less expensive alternative is a plexiglass door with a gasket attached to a standard cage that allows introduction of oxygen through a port. While this method is less expensive than installing purpose-made cages, the clinician has little control of the oxygen content and limited ability to reduce carbon dioxide accumulation within the cage. The amount of oxygen used in these cages is usually higher than in purpose-made oxygen cages due to leakage through imperfect seals.

When providing supplemental oxygen in the acute setting, the highest achievable F_iO_2 should be used. Once the patient begins to stabilize, the F_iO_2 can be reduced to below 60% to decrease the likelihood of oxygen toxicity developing.

Animals with confirmed or suspected pulmonary edema and cardiogenic shock should be given loop diuretics upon presentation. Loop diuretics are rapidly acting, effective diuretics that can quickly improve the clinical condition of patients with pulmonary edema. Furosemide (2 mg/kg) should be administered intramuscularly and repeated every 30–60 minutes as needed until clinical signs improve. Attempts at IV catheter placement or IV administration of diuretics can be considered but patient safety must always be kept in mind.

Sometimes it becomes apparent that without more aggressive intervention (i.e., IV administration of medications), the patient's condition will continue to deteriorate. If, in the clinician's mind, the patient is progressing irreversibly toward cardiopulmonary arrest unless such intervention is undertaken, all attempts should be made to minimize the stress and duration of restraint by carefully

choreographing the steps to be taken. The use of mild sedatives can facilitate catheter placement in this situation. Administration of butorphanol (0.1–0.3 mg/kg) is generally safe and is unlikely to have an untoward effect on cardiac performance. The use of diuretics is not expected to improve clinical signs in animals with pulmonary hypertension, tamponade, or tachycardia-induced cardiogenic shock but is also not likely to result in acute decompensation.

Medications that increase cardiac contractility (positive inotropes) should be considered in animals that have documented systolic dysfunction. It must be remembered that positive inotropes not only increase cardiac contractility but also increase myocardial oxygen consumption. Dobutamine, an injectable beta-adrenergic agonist, can be administered as a constant rate infusion to treat systolic failure. For dogs with strongly suspected or confirmed systolic dysfunction, dobutamine can be started at a rate of 2.5 µg/kg/min. The dose is uptitrated every five minutes until systolic function improves or to a maximum rate of 20 µg/kg/min. In certain clinical situations, systolic dysfunction cannot be confirmed due to the patient's condition or unavailability of echocardiography. In this situation, the clinician will rely on signalment and results of other diagnostic tests to determine if systolic dysfunction is likely.

Systolic dysfunction in cats can be difficult to confirm due to their rather tenuous condition when in cardiogenic shock, therefore inotropic support should be considered in any cat presenting with heart failure and bradycardia. The dose of dobutamine for cats ranges from 1 to 5 µg/kg/min and should again be uptitrated to effect. In some instances, it may be possible to use pimobendan to improve cardiac contractility. Pimobendan is a phosphodiesterase III inhibitor and a calcium sensitizer that increases inotropy while reducing vascular tone, making it an attractive treatment option for many causes of cardiogenic shock. Unfortunately, pimobendan is only available as an oral medication in the United States, limiting its use in emergency situations. Administering oral medications to patients in shock should be avoided due to the stress associated with pilling and concerns about absorption of the drug from the underperfused gastrointestinal tract. An injectable form of pimobendan has recently been approved for use in Europe with a labeled dose of 0.15 mg/kg.

As mentioned earlier, the use of vasoactive medications in cardiogenic shock is rare. Almost never,will a patient with cardiogenic shock benefit from an increase in vascular tone alone. The same cannot be said for decreasing vascular tone, however. Patients that are likely to benefit from afterload reduction include those with rupture of a first-order chorda tendina or dilated cardiomyopathy – in other words, patients with forward heart failure.

The most effective medication to achieve consistent, rapid vasodilation is nitroprusside, which acts by increasing nitric oxide (a powerful arterial dilator) primarily at the level of the arterioles. Due to the potential for profound hypotension, the use of nitroprusside should be reserved for patients with confirmed congestive heart failure and systolic or valvular dysfunction. When used, nitroprusside is most effective as a constant rate infusion (CRI) with doses starting at 1 µg/kg/min. As with dobutamine, nitroprusside dose should be uptitrated until the desired effect is achieved or a maximum dose of 10 µg/kg/min is reached. Patients being treated with nitroprusside should have their blood pressure monitored very closely. Ideally, blood pressure is checked every 10–15 minutes until the target pressure (mean arterial pressure [MAP] 70 mmHg, systemic arterial pressure [SAP] 90 mmHg) is achieved. Mean arterial pressures less than 60 mmHg or systolic pressures less than 90 mmHg should be avoided due to the potential for additional organ injury. An early sign of hypotension in patients on nitroprusside is vomiting and if this occurs the patient should have blood pressure checked immediately and the CRI rate adjusted accordingly. Fortunately, nitroprusside has a very short half-life so discontinuation of a CRI should result in rapid recovery of blood pressure. Inadvertent, abrupt cessation of nitroprusside should be avoided due to the risk of rebound hypertension.

The use of nitroglycerine paste has been advocated in the past. There is not good evidence to support its routine use and dosing of transdermal medications can be notoriously difficult, especially in low cardiac output states where absorption and perfusion are likely to be impaired.

Sildenafil citrate is a phosphodiesterase V inhibitor that has been shown to be useful for the treatment of pulmonary hypertension in dogs. While the use of sildenafil is well documented for management of chronic pulmonary hypertension, the benefits in the acute setting are less clear. Sildenafil has a rapid onset of action so administration in a crisis would be expected to result in at least some improvement in pulmonary pressure. Clinically, this appears to be the case. As with pimobendan, however, sildenafil is currently most widely available as an oral medication and its administration needs to be carefully considered prior to dosing. An injectable form of sildenafil is approved for use in human patients with pulmonary hypertension but there are no descriptions of clinical use in veterinary medicine. When given, the recommended dose of sildenafil for management of pulmonary hypertension is 1–2 mg/kg PO TID.

Treatment of acute pericardial tamponade involves immediate pericardiocentesis. Although the possibility of continued, uncontrolled hemorrhage exists, the morbidity and possible mortality associated with tamponade

cannot be tolerated. If complete drainage is not achieved, serial attempts can be made but may not be necessary. Because the pericardial sac is essentially an enclosed sphere, the removal of even a small amount of fluid will exponentially decrease the pressure within the sac. Observation of the pericardial space with ultrasound (if available) following every attempt at pericardiocentesis should be made. Often, the pericardium is lacerated during the attempt and although only a small amount of fluid is retrieved, tamponade has been relieved and pericardial fluid has been drained into the thoracic cavity where it is better tolerated. In cases where hemorrhage cannot be controlled or multiple attempts at percutaneous pericardiocentesis are unsuccessful, emergency thoracotomy may be required although this should only be attempted as a last resort when death is believed to be imminent or cardiac arrest has already occurred.

Treatment of tachyarrhythmias can be achieved through one of two mechanisms: conversion of the rhythm to a normal sinus rhythm or control of the rate of ventricular contractions. Administration of antiarrhythmic medications can be used in an emergency setting to treat patients with cardiogenic shock from tachyarrhythmias in an attempt to achieve either of these endpoints. Due to the urgency inherent in this condition, injectable antiarrhythmics are always preferred to oral formulations. Lidocaine or procainamide are considered first-line therapies for the treatment of ventricular tachycardia. Control of ventricular tachycardia begins with a 2 mg/kg slow bolus of lidocaine. If no response is seen, a second dose of lidocaine can be administered. Occasionally, rhythms that are refractory to lidocaine will respond to procainamide so if the rhythm has not improved with lidocaine, a dose of procainamide 5–15 mg/kg slow IV can be attempted.

Amiodarone has recently been incorporated into the human CPR guidelines developed by the American Heart Association for use during cardiopulmonary arrest as a treatment for pulseless ventricular tachycardia and ventricular fibrillation refractory to electrical defibrillation. Amiodarone has been used as an oral medication in veterinary medicine to treat many different arrhythmias, including atrial fibrillation and ventricular tachycardia. The use of injectable amiodarone is reported in veterinary patients but has been associated with development of anaphylactic or anaphylactoid reactions. Due to these potential adverse effects, it should be considered as a second-choice option for management of acute, life-threatening tachyarrhythmias. If amiodarone is going to be used, the recommended starting dose is 5–10 mg/kg as a slow IV bolus to effect and the amiodarone should be diluted prior to administration.

Occasionally, dogs will present with supraventricular tachycardia (SVT) or sinus tachycardia causing cardiogenic shock as a result of toxin ingestion. For dogs with ECG-confirmed sinus tachycardia (with a rate >180 bpm), the administration of beta-blockers should be considered once other causes of shock have been ruled out and the absence of congestive heart failure has been confirmed. Due to the need to urgently address cardiogenic shock, injectable, ultra-short-acting beta-blockers should be used as first-line treatment with oral formulations reserved for patients that have stabilized. Esmolol administered as a bolus of 0.2–0.5 mg/kg followed by a CRI of 50–200 µg/kg/min is preferred. If bradycardia develops, the CRI rate should be slowed or discontinued. Diltiazem (5–20 µg/kg/min) can also be used and may be more effective at managing nonsinus SVT. Because of their negative inotropic effects, the use of beta-blockers and calcium channel blockers should be avoided in patients with congestive heart failure.

Some cardiac rhythms are amenable to electrical cardioversion using a debrillator (atrial fibrillation, paroxysmal ventricular tachycardia). When used to perform cardioversion, the energy delivered is generally much lower (0.5–1 J/kg) than for defibrillation and the timing of energy delivery must be synchronized with the R-wave of the ECG. The synchronization function on the defibrillator should be activated and the energy dosage should be selected. Once the synchronization function has correctly identified the R-waves, defibrillation can be performed as usual. If the defibrillator is not equipped with a synchronization feature then electrical cardioversion should not be attempted as inappropriately timed delivery of the shock can result in ventricular fibrillation. Heavy opioid sedation or anesthesia should be used if electrical cardioversion is going to be attempted on a conscious patient to minimize discomfort associated with the procedure (see description for transcutaneous pacing).

Treatment of cardiogenic shock due to complete (third degree) AV block consists of temporary or permanent placement of a pacemaker. Temporary transcutaneous pacing can be used in emergency situations and requires little advanced training to be effective. Most modern defibrillators are capable of performing temporary transcutaneous pacing while temporary transvenous pacing may require the use of a pacemaker programmer or purpose-made generator. Transcutaneous pacing is an uncomfortable experience at best and requires general anesthesia. To perform transcutaneous pacing, the patient is prepared while awake. The fur is clipped over the heart on both sides of the chest at the level of the costochondral junction. The temporary pacing pads are placed and plugged into the defibrillator base unit. Once the patient is instrumented, a rapid-sequence anesthetic induction (IV bolus premed followed immediately by IV bolus of induction agent) is performed and temporary

pacing is begun. Once pacing has begun, the voltage of the pacing leads is gradually increased until they are "captured" by the heart. Evaluation of ECG, pulse oximetry or digital palpation of the pulses can be used to verify capture. Transcutaneous pacing is always a stopgap measure to allow time for the placement of either a temporary transvenous pacing mechanism or a permanent pacemaker and should not be considered if these options are not available.

Management of caval syndrome secondary to heartworm infection often requires direct removal of the worms from the right heart. The use of a transvenous approach has been well described and, provided the dog survives the perioperative period, appears to be very effective for management of acute caval syndrome. Surgical management is also the best treatment for well-defined intracardiac tumors. Unfortunately, open-heart surgery requires total venous inflow occlusion or cardiac bypass, significantly limiting its availability in veterinary medicine at this time.

Prognosis

Published mortality rates for cardiogenic shock in veterinary patients are lacking, but many human studies report mortality rates of 50–80%. In most instances, the development of cardiogenic shock is a sequela to a severe underlying structural or progressive conductive disease. Therefore, both the short- and long-term prognosis should be considered guarded to poor. Patients that recover from cardiogenic shock are usually left with residual cardiac dysfunction that is irreversible in nature. The exception to this may be dogs that are treated for caval syndrome secondary to canine heartworm disease and animals receiving a pacemaker for bradyarrhythmias.

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43

Septic Shock

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Etiology/Pathophysiology

The ability of an organism to mount an inflammatory response is necessary for the survival of nearly all life forms. Through the simple interaction of the body with its internal and external environments, a constant bombardment with infectious agents and minor injuries occurs that is prevented from progressing to systemic disease by the innate immune system. This process is performed successfully on a continuous basis without any conscious effort on the part of the organism or need for prior exposure to offending antigens.

Unfortunately, these same mechanisms, which are protective when functioning normally, can become unregulated or overactive, resulting in added pathology, perhaps even worse than the original insult would have caused. This idea is reinforced by the fact that patients often die of sequelae to infections or systemic inflammation rather than directly from the primary insult.

The systemic inflammatory response syndrome (SIRS) is the systemic manifestation of a response to an insult and may result from anything creating inflammation. Importantly, this can be the result of a systemic condition (e.g., heat stroke) or a severe local insult (e.g., pancreatitis). While systemic inflammation may be necessary to combat the initial insult, when left unregulated it can lead to severe consequences. The presence of certain clinical findings is used to define SIRS and sepsis in both veterinary and human medicine. Definitions for SIRS have been proposed and are currently being used clinically (Table 43.1).

Since there is little difference between the clinical appearance of SIRS and uncomplicated sepsis, the two terms are often used interchangeably. When SIRS occurs due to an infectious cause, the term used to describe it is sepsis. As a result of these definitions, it means that sepsis always occurs in conjunction with SIRS while SIRS can exist without the presence of sepsis. As is the case with most aspects of veterinary medicine, sepsis/SIRS is not an all-or-nothing condition but rather occurs along a spectrum, the least severe form of which is a hemodynamically stable patient that fulfills the clinical criteria. Severe sepsis is defined as sepsis with acute dysfunction of one or more organs. Common examples of secondary organ dysfunction include the development of a coagulopathy or acute kidney injury. The worst permutation of the septic spectrum is septic shock in which a patient not only fulfills criteria for severe sepsis but also has hypotension and signs of shock that are not reversed with fluid therapy and is consequently vasopressor dependent.

Response to Infection or Injury

Innate Immunity

The immune system has evolved into two complementary systems that work together to fight infection and mitigate the damage that occurs in the host: the innate immune system and the adaptive immune system. For convenience, they are often discussed separately, but it should be remembered that neither branch works in isolation from the other and that cross-talk and feedback are constantly occurring between the two branches.

The innate immune system is the portion of the immune system that is nonspecific and responds to any insult that may be present without need for preexposure while the adaptive arm of immunity is a more specialized system that requires preexposure to an organism or antigen. The adaptive response can have infinite, very specific targets but unfortunately, the delay necessary to recognize an antigen and synthesize antibodies in order to mount a response makes adaptive immunity unsuitable as a primary means of defending the host from an acute injury or novel infection.

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Table 43.1 SIRS criteria for dogs and cats

Criterion	Cats	Dogs
Temperature	>103.5 °F <100 °F	>102.6 °F <100.6 °F
Heart rate bpm	>225 <140	>120
Respiratory rate	>40 breaths per minute	>20 breaths per minute
White blood cells/μL	>19 500 or <5000 >3% bands	>16 000 or <6000 >3% bands

Source: Adapted from Brady *et al.* (2000) and Hauptman *et al.* (1997).

As a consequence, most of the clinical manifestations associated with sepsis and SIRS, with few exceptions, are associated with the response of the innate immune system. It is important to note that the body makes no distinction between these two systems and they function synergistically. For instance, proinflammatory cytokines elicited as a result of an innate immune response help to augment the subsequent or concurrent adaptive response.

Innate immunity relies on recognition by the host of some very specific, evolutionarily conserved molecular patterns that are found in association with infection, inflammation, cell death or all of the above. Pattern recognition receptors (PRRs) are a relatively small set of receptors that are able to recognize a wide range of pathogens, including viruses, bacteria, and fungi. Many cell types that participate in immune function, including macrophages, monocytes, dendritic cells, neutrophils, and epithelial cells, express PRRs that allow the rapid recognition of pathogens at the site of infection. Numerous PRRs have been identified (Nod-like receptors, C-type lectin receptors, RIG receptors, and RAGE receptors) with remarkable homology across species in all parts of the phylogenetic tree. The fact that these PRRs are found in such diverse species highlights their importance for survival.

The most studied and best-known PRRs are the toll-like receptors (TLRs), which are expressed by many cell types including macrophages, dendritic, endothelial, and epithelial cells. TLR activation is generally considered to be proinflammatory and results in the production of antimicrobial peptides, inflammatory cytokines and chemokines, and adhesion molecules, all of which work together to coordinate the innate response.

As a result of PRR activation, there is a coordinated response by the immune system to recruit other cells into the fight against infection. This recruitment, the actions of the recruited cells, their associated killing mechanisms, and soluble factors have led some authors to compare the TLRs and other PRRs to keys on a piano. When one key is struck alone, the resultant note does not make a song, but when several keys are played at the same time and in different combinations, a piece of music emerges. The appropriateness or lack thereof of this process is the central driver in the pathology associated with sepsis and septic shock.

Dysregulated Immunity

Once a pathogen has been recognized and the immune response initiated, there are numerous opportunities for dysregulation to occur, adding to morbidity and possibly mortality of the patient. This dysregulated immunity was considered to be exclusively an overexuberant inflammatory response and in fact, the "inflammation only" theory explains most of the clinical signs observed in septic patients. It does not, however, explain all the clinical signs and it has subsequently become clear that hyperinflammation alone does not fully account for the morbidity and mortality experienced by septic patients.

A compensatory anti-inflammatory response syndrome (CARS) was proposed as an alternative that may occur in some patients as a result of systemic inflammation. The CARS theory states that in some patients, overcompensation by the anti-inflammatory arm of the immune system results from a combination of excessive anti-inflammatory cytokine production and, possibly more importantly, from the death and dysfunction of immune cells. This theory helps to explain some of the clinical manifestations of sepsis/SIRS. It is convenient to consider these conditions in the extreme as distinct identities but clinically most patients will lie somewhere in the middle.

Physiologic Consequences

Patients with sepsis can develop shock that often shares characteristics of hypovolemic, vasodilatory, and cardiogenic etiology due to the actions of inflammatory mediators and their cumulative effect on the circulatory system. In addition to tissue perfusion derangements, patients with sepsis or septic shock can suffer from cytopathic hypoxia or an inability to utilize oxygen at the mitochondrial level. This further complicates understanding the pathophysiology of sepsis and septic shock.

Hypovolemia often develops from vomiting, diarrhea or bleeding but can also occur due to accumulation of cavitary effusion or peripheral edema reducing effective circulating volume. Changes in vascular permeability, vascular hydrostatic pressure, decreased colloid osmotic pressure or lymphatic occlusion all occur in septic patients and result in a tendency for fluid to move out of the vascular space. As a result, significant "third spacing" of fluid can occur in the thoracic or abdominal cavities or interstitium of patients with sepsis or SIRS. The net effect of this fluid movement is decreased intravascular volume that contributes to lower cardiac output and impaired oxygen delivery.

Besides loss of effective circulating volume, sepsis can induce significant alterations in vascular tone. Because

these patients may have low intravascular volume, compensatory mechanisms are activated in an effort to maintain blood pressure. To minimize the effect of hypovolemia on organ systems in nonseptic patients, systemic vascular resistance generally increases to compensate for the lower cardiac output and maintain organ perfusion. In sepsis, however, numerous factors counteract these compensatory mechanisms to the detriment of the patient. This can result in decreased effectiveness of vasoconstriction or, worse, to pathologic dilation of the vessels.

The most well-understood vasodilatory agent in sepsis is nitric oxide (NO). In sepsis and septic shock, inducible nitric oxide synthase (iNOS) produces supraphysiologic levels of nitric oxide that interfere with myocyte calcium metabolism and impair the ability of vascular smooth muscle cells to contract. The end-result is vasodilation with a characteristically poor response to vasoconstrictive stimuli, including reduced vascular response to catecholamines. Additionally, the surplus of nitric oxide leads to production of reactive oxygen species, including peroxynitrite, which are directly toxic in the local environment and act to cause further damage to endothelium and smooth muscle myocytes. Nitric oxide is also responsible to some degree for the cardiac depression found in patients with sepsis or septic shock.

Endocrine abnormalities occur in sepsis and can also adversely affect the ability of the vascular tree to respond to stimuli. With the additional demand for vasoconstriction, the neurohypophysis (posterior pituitary) depletes its stores of vasopressin and is unable to meet the demand, leading to a well-documented deficiency in some septic patients.

A distinct cardiac failure component is present in some human patients with septic shock but is of unknown clinical relevance in veterinary medicine. It was believed that a circulating myocardial depressant factor was present in the blood of septic patients that decreased cardiac function. This myocardial depressant factor was subsequently identified as tumor necrosis factor (TNF)-alpha which, together with interleukin (IL)-1, has been associated with cardiac myocyte dysfunction. TNF-alpha and IL-1, both potent inducers of iNOS, are now known to be the offending molecules that lead to sepsis-induced cardiac dysfunction. If decreased systolic function is coupled with decreased systemic vascular resistance, as seen in septic shock, the cardiac output often stays the same or even increases although tissue perfusion is severely compromised. However, if vasoconstriction persists, as seen in uncomplicated or severe sepsis, decreased systolic function can lead to a significant reduction in cardiac output.

Sepsis-induced endothelial injury affects the lungs by allowing neutrophil migration into the lung parenchyma and increased vascular permeability that impairs gas exchange. This disease has been termed acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), depending on severity, with ALI describing a less severe manifestation than ARDS. Both are characterized by acute-onset bilateral pulmonary infiltrates with no evidence of left-sided heart failure. Classification is further determined by the degree of hypoxemia. For more information on ALI/ARDS the reader is referred to Chapter 38.

Significant alterations in normal gastrointestinal function, motility, and vascular permeability result from inflammatory mediators, altered blood flow, and oxidative stress. This may allow exposure of the bloodstream to the luminal contents of the gastrointestinal (GI) tract and allow bacteria access to the bloodstream or lymph, although the clinical significance and actual incidence of bacterial translocation are unknown.

Hepatic dysfunction in sepsis is manifested as hypoalbuminemia, icterus, hypoglycemia, and coagulation abnormalities and decreased detoxifying ability. The underlying cause of hepatic dysfunction is unknown but may result from hypoperfusion of the liver, or may be directly due to the systemic inflammatory process (i.e., inflammatory mediators) as many of the constitutive functions of the liver are downregulated as part of the acute phase response.

Coagulation abnormalities can be significant and can lead directly to the death of the patient. Sepsis-induced coagulopathy is a manifestation of the procoagulant nature of almost all proinflammatory mediators. In general terms, the procoagulant state in sepsis causes generation of microthrombi that result in inflammation within the vascular beds in which they lodge. This systemic activation of the coagulation system finally results in the consumption of coagulation factors and in the later stages ultimately induces a hypocoagulable state. This scenario has been termed disseminated intravascular coagulation (DIC) and continues to be a significant clinical complication in the management of sepsis. Unfortunately, due to clinical limitations in identifying patients in the procoagulant phase of DIC, this complication is often found in the last stages when profound bleeding tendencies predominate and it is extremely difficult to manage or reverse.

The discovery of renal dysfunction or acute kidney injury is an easily identified marker of multiple organ dysfunction syndrome. Acute kidney injury results from decreased renal blood flow secondary to systemic hypotension; alterations in renal blood flow from vasoactive substances, microthromboembolism, and poorly understood renal cellular apoptosis are also believed to contribute. Patients may exhibit a progressive increase in creatinine and decreased urine production despite normal intravascular fluid volume. Even small changes in

serum creatinine (within the reference range) can indicate renal impairment and emerging multiorgan failure.

The central nervous system manifestations of sepsis and septic shock may be due to the effects of systemic hypotension and decreased cerebral perfusion or may be related to the direct effects of sepsis-induced cytokines. Alterations in cerebral blood flow, increased capillary leakage, and disruption of the blood–brain barrier are thought to be mechanisms contributing to brain dysfunction in sepsis. In addition to primary intracranial causes, sepsis-induced hypoglycemia can cause neurologic dysfunction. The clinical signs seen with sepsis and septic shock are predominantly alterations in mentation (i.e., obtundation, stupor, coma) and seizures.

Epidemiology

The exact incidence of sepsis in veterinary medicine is unknown. However, sepsis is likely a common occurrence in clinical practice and remains among the most difficult to treat conditions. According to the NIH, about 750 000 people become septic in the United States each year with a mortality rate of 28–50%. In fact, the rates of hospitalization for human sepsis have become higher than those of myocardial infarctions. The death rate from sepsis eclipses that of prostate cancer, breast cancer, and AIDS combined.

Despite the difficulty in diagnosing sepsis, there are common veterinary diseases that can cause a patient to develop sepsis. Parvoviral enteritis, pyometra, pneumonia, and septic peritonitis are just a few of the diseases responsible for sepsis and septic shock in dogs and cats.

Septic peritonitis occurs in both cats and dogs and most commonly results from perforation of the GI tract. Because of the propensity of dogs to ingest foreign objects, septic peritonitis occurs more commonly in that species. Most frequently, perforation of the GI tract occurs from ingestion of foreign material that physically obstructs aboral flow or damages the walls of the GI tract to the point of rupture. Perforation of the stomach and duodenum can occur secondary to nonsteroidal antiinflammatory drug (NSAID) administration. Neoplasia can cause perforation in any part of the bowel.

Disease of organ systems other than the GI tract can cause septic peritonitis. This occurs most frequently when a normally sterile organ becomes infected and the infection extends into the abdomen via perforation or through translocation of bacteria to the blood or lymph. Extension of infection from the urogenital tract can occur because of prostatitis, prostatic abscess, pyometra, pyelonephritis or rupture of the urinary bladder containing infected urine or calculi. Septic bile peritonitis results from perforation of an infected biliary tree, most frequently the gallbladder. Less frequently, infection or abscessation of organs such as the liver or spleen, or necrotic tissue secondary to strangulation or torsion is the source. Spontaneous septic peritonitis can occur in cats with no evidence of gastrointestinal compromise or other identifiable source.

Numerous other diseases are capable of causing sepsis in dogs and cats. Penetrating trauma from animal bites is a common occurrence and contamination from bite wounds can result in sepsis. Blunt trauma without penetrating injury (e.g., being struck by a vehicle or falling from a height) frequently results in significant soft tissue injury that can result in sepsis if infection of the damaged tissue occurs.

Signalment

All species, breeds, sexes, and ages can develop sepsis. Consequently, there is no signalment specific to sepsis but there are populations that are susceptible to diseases that can be the underlying cause of sepsis. For example, young, unvaccinated puppies are at risk of contracting Parvoenteritis while intact female dogs and cats may develop pyometra. Dogs that develop septic peritonitis tend to be younger with indiscriminate eating habits that ingest foreign material, resulting in perforation of the GI tract. A report including nearly 75 000 dogs identified some distinct breed- and age-related differences in all-cause mortality, with younger patients having a significantly higher likelihood of dying of infectious disease or trauma. Geriatric dogs with chronic, progressive diseases necessitating treatment with NSAIDs, corticosteroids, or other immunosuppressive medications are also at higher risk than the general population for developing GI tract perforation. Ruptured neoplasia of the GI tract occurs in both geriatric dogs and cats.

Lifestyle of the pet can significantly affect the likelihood of developing sepsis. Pets that are primarily outdoors or that spend a significant amount of time outdoors and unsupervised are more likely to be exposed to injuries that can result in sepsis.

History and Clinical Signs

Patient historical information often relates to the underlying cause of sepsis. For example, animals with septic peritonitis may have historical complaints such as vomiting, abdominal pain or hemorrhagic diarrhea while patients with sepsis secondary to pyometra often

have polyuria, polydipsia, and vulvar discharge as part of their history. Many dogs with septic peritonitis secondary to gastrointestinal perforation will have a history of NSAID or corticosteroid administration. Some of the etiologies of sepsis are subacute to chronic in nature and subsequently the historical complaints may be somewhat vague. Regardless of the underlying cause of sepsis, it is common for owners to report decreased activity levels and loss of appetite for varying amounts of time prior to presentation. Travel history, exposure to any and all medications (including common over-the-counter drugs), housing (indoor vs outdoor), and exposure to other animals are all important historical facts to elucidate.

Just as sepsis/SIRS occurs on a spectrum, the clinical signs associated with sepsis/SIRS vary depending on the severity of the condition. By definition, all animals with sepsis have clinical signs consistent with SIRS. Additional clinical signs that may be present include lethargy, recumbency, vocalization, or seizures, with some patients even presenting moribund.

Once septic shock develops, clinical signs vary but are generally related to deficits in oxygen delivery. Patients with septic shock can have two different presentations: they can be in hyperdynamic (compensated) or hypodynamic (decompensated) shock. Hyperdynamic shock implies that there is greater than normal cardiac output with vasodilation and these patients will be tachycardic, have red mucous membranes, bounding femoral pulses, and warm extremities. Patients in the hypodynamic phase of shock can be tachycardic or bradycardic, have weak pulses, pale to gray mucous membranes, and cold extremities.

Diagnosis

The diagnosis of septic shock is made by fulfilling the SIRS criteria and key hemodynamic parameters in conjunction with identification of an underlying infection. Patients in septic shock will show similar physical exam findings to patients in shock for other reasons, but there will generally be additional abnormalities related to the underlying cause of sepsis. For instance, a patient with septic peritonitis will have traditional signs of shock (tachycardia, weak pulses, and pale mucous membranes) but will also often have abdominal pain and peritoneal effusion as evidenced by abdominal distension with the possibility of a palpable fluid wave.

When presented a patient with suspected sepsis or septic shock, it is important to first gather as much data as you can. The minimum database consists of a complete blood count, biochemistry profile, and urinalysis. Abnormalities in the minimum database generally reflect the underlying disease although specific sepsis-related changes could be present.

An inflammatory response is expected on the hemogram, although individual patients may demonstrate high, normal, or low leukocyte counts with or without toxic change or presence of band neutrophils. Patients may have a regenerative or nonregenerative anemia and may be thrombocytopenic.

The biochemistry profile can often be quite abnormal. Septic patients have a significant inflammatory component to their disease that can affect blood protein levels dramatically. Hypoalbuminemia is found frequently in septic patients as albumin loss into exudates occurs concurrently with downregulation of albumin production during the acute phase response. Other abnormalities identified on the biochemistry profile may include hypoglycemia, hyperbilirubinemia, hypocalcemia, and elevated creatinine and blood urea nitrogen. Of these, hypoglycemia is of particular concern since it contributes to morbidity or mortality if not identified and corrected rapidly.

Imaging studies are often key to the identification of the source of sepsis. Plain radiographs of the chest and abdomen are useful for identifying possible sources of sepsis and the finding of unstructured interstitial to alveolar pulmonary infiltrates, pleural effusion, obstructive intestinal pattern, free abdominal air, or loss of abdominal detail indicating free fluid should be considered significant and additional confirmatory diagnostic tests should be pursued.

Collection of free abdominal fluid, if present, is often the first step in diagnosing septic peritonitis and can be accomplished via blind four-quadrant paracentesis or ultrasound-guided needle aspiration. Ultrasound allows the clinician to bring imaging to the bedside and perform a rapid evaluation of the thoracic and abdominal cavities. This can help with the initial identification of disease, and can provide a method to monitor progression. Ultrasound is particularly useful for identifying pockets of fluid within the chest and abdominal cavities that can then be sampled. In clinical practice, ultrasound is more effective at identifying free fluid than is blind four-quadrant paracentesis, making it an objective and effective tool in the ER and ICU.

Once fluid is obtained, cytologic evaluation can confirm the diagnosis of septic peritonitis or prompt the clinician to investigate further. Identification of intracellular bacteria signifies that bacteria present in the peritoneal cavity are being phagocytized by inflammatory cells and indicates infection rather than sample contamination. The finding of even one intracellular bacterium is significant and is an indication for immediate

surgical exploration. While identification of even one intracellular bacterium confirms the diagnosis of septic peritonitis, the absence of this finding does not rule out sepsis. If the fluid obtained is highly cellular (composed of mixed inflammatory cells) or is turbid, flocculent or malodorous then further investigation may be needed.

Comparison of the biochemical values, specifically lactate and glucose, of abdominal fluid with blood can be invaluable for aiding in the diagnosis of septic peritonitis. The comparison of glucose and lactate concentrations of abdominal fluid and blood is both sensitive and specific for differentiating septic peritonitis from other causes of peritoneal effusion. Under normal conditions, the concentration of glucose and lactate in peritoneal fluid is essentially the same as that of blood. As infection progresses within the peritoneal cavity, bacteria and white blood cells utilize glucose for energy and produce lactate as a by-product. If the lactate concentration of abdominal fluid is 2.0 mmol/L higher than that of the blood or if glucose is 20 mg/dL lower in the effusion than in the blood, a presumptive diagnosis of septic peritonitis can be made and surgical exploration should be recommended.

Monitoring coagulation assists with identification of needed therapies rather than identification of sepsis or septic shock and coagulation assays may be normal or abnormal in these patients. A prothrombin time (PT) or partial thromboplastin time (aPTT) that is >50% prolonged indicates coagulopathy. Fibrinogen levels may be normal, low or high, depending on the chronicity of the disease. Patients that have a prolonged disease course tend to have higher fibrinogen levels, but it is not uncommon to find low fibrinogen due to active consumption. D-dimers are often elevated as a result of the underlying condition or inappropriate coagulation (i.e., DIC). Identification of three of the following in a patient identifies DIC: prolongation of PT or aPTT, hypofibrinogenemia, thrombocytopenia, elevation of fibrin degradation products (FDPs) or D-dimers, or documented antithrombin deficiency.

Treatment

Treatment of sepsis and septic shock must be aggressive and aimed at eliminating the underlying cause. In broad terms, treatment of sepsis and septic shock can be divided into several distinct components: resuscitation, source control (eliminating the cause of sepsis), antimicrobial therapy, and supportive care. The resuscitation of a patient with severe sepsis or septic shock is different from that of patients with other forms of shock. This is due to the multifactorial nature of the development of shock in the septic patient, meaning that in any one patient, low systemic vascular resistance, cardiac dysfunction, and hypovolemia may all be coexistent and may all contribute to failure of oxygen delivery (i.e., shock).

Resuscitation

Complicating septic shock resuscitation is the fact that vascular permeability may be increased, which can decrease the efficacy of crystalloid resuscitation or lead to overresuscitation and subsequent edema formation. The use of goal-directed therapy, consideration of other fluids options, and use of vasoactive agents as well as fastidious reevaluation can improve the efficacy of resuscitation.

The most important initial therapy in the resuscitation of a patient with septic shock is the administration of appropriate doses of IV fluids to restore effective circulatory volume and improve global perfusion. The appropriate amount and character of the fluids that should be administered are a matter of debate. The author prefers to give an initial bolus of 20–30 mL/kg of crystalloid fluids such as lactated Ringer's solution or 0.9% sodium chloride. This initial dose serves to act as a fluid challenge and will help the clinician determine if continued fluid resuscitation may be beneficial. If a positive response is seen, this dose can be repeated 2–3 more times until one of three endpoints occurs: signs of shock resolve, there is no further improvement in perfusion parameters or volume overload becomes evident. Signs of volume overload include development of peripheral or pulmonary edema or measurement of central venous pressures greater than 10 cmH_2O.

Colloidal solutions are commonly used as a primary or secondary resuscitative fluid in veterinary patients in shock. Colloids have several theoretical benefits, but one of the most important is that they discourage formation of tissue edema since they do not move out of the vascular compartment as quickly as crystalloid fluids. If colloids are used, total doses of 20 mL/kg are typically broken into aliquots similar to the technique used with crystalloids and are administered in incremental 5–10 mL/kg boluses until endpoints are achieved. Hetastarch (Hespan®, Hextend™) is the most commonly used colloid in veterinary patients and has replaced the dextran solutions that were in use previously. A newer generation of hydroxyethylstarchs, generally classified as tetrastarchs, is also available with a similar dosing schedule.

Patients in septic shock, by definition, have hypotension that is not responsive to fluid loading alone, meaning that vascular expansion has been completed without resulting in resolution of shock. Determining when patients are adequately volume expanded is difficult.

One method for determining if volume loading has been adequate is measurement of central venous pressure, with a target of 8–12 cmH_2O. Many of these patients will not have a central line in place, in which case lack of improvement in blood pressure following IV fluid boluses can be interpreted as evidence that volume expansion is complete. When this happens, vasopressors are needed to increase systemic vascular resistance in an effort to increase blood pressure and maintain vital organ perfusion. There is no consensus on which vasopressor is most effective and selection is largely based on clinician preference. The most commonly used first-line vasopressors are dopamine (5–20 µg/kg/ min) and norepinephrine (0.05–0.3 µg/kg/min). If normotension is not achieved at the upper end of the dose range for a single vasopressor then the addition of a second agent is needed. Typical secondary vasopressors include vasopressin (0.01–0.04 U/kg/h) or norepinephrine if not already used as a first-line agent.

While vasopressors function to increase systemic vascular resistance and improve perfusion of tissue beds, patients with sepsis or septic shock often have concurrent systolic dysfunction. Positive inotropes are drugs that increase inotropy (contraction strength) and chronotropy (contraction rate), resulting in an increased stroke volume and heart rate, and consequently cardiac output. The most commonly used inotropic medication is dobutamine. If evidence of systolic failure is present then dobutamine should be started (5–15 µg/kg/min) and the dose titrated up every 15 minutes until endpoints are reached or the top of the dose range is reached. If dobutamine fails to result in resolution or improvement in shock then the addition of a vasopressor should be considered. It should be remembered that many adrenergic drugs are positive inotropes in addition to being vasopressors (ex. dopamine and norepinephrine) and the primary effect is often dependent on the dose administered. For more information about resuscitation endpoints, the reader is directed to Chapter 41.

Source Control

Source control is important for the resolution of sepsis and septic shock and should be performed as soon as possible after the source is identified to improve the likelihood of recovery. Source control almost always requires some degree of surgical intervention, ranging from lancing of an abscess to resection of perforated bowel. Good source control for wounds includes early and aggressive debridement of devitalized or infected tissue. Dogs with necrotizing fasciitis may require radical resection of affected tissue and the use of vacuum bandaging or application of wet to dry bandages for continued debridement following the initial surgical intervention.

If the septic source is an abdominal viscus such as the uterus or bowel then laparotomy should be performed as soon as the patient is stable enough for anesthesia with the goal of eliminating ongoing bacterial contamination with dilution or removal of already affected tissue. Similarly, if the septic source is in the thorax (ex. pyothorax or lung abscess) then thoracotomy should be recommended. Pyothorax can be managed conservatively with placement of thoracostomy tubes acting as source control mechanisms and is reported to be effective 71% of the time. The decision to manage cases with thoracostomy tubes versus surgical intervention depends on geography, as well as clinician preference or training. In areas of the country where inhaled grass awns from foxtails are common, the frequency of surgery is expected to be higher than that of an area in which those plants are not found. Lung abscesses must be managed with lung lobectomy. For cases with severe sepsis or septic shock secondary to pyelonephritis, source control interventions to consider include percutaneous renal pelvis centesis or nephrectomy.

Antimicrobial Therapy

The early administration of appropriate antibiotics is key for successful treatment of patients with sepsis and septic shock. Every effort should be made to collect culture samples before antibiotics are administered; however, one cannot wait indefinitely to initiate treatment and the goal should be to begin antibiotics within one hour of recognition of septic shock. In patients with sepsis without shock, it is often much more feasible to withhold antibiotic therapy until appropriate cultures have been obtained.

Ideally, the antibiotic administered would be effective against the offending organism in question. Unfortunately, in most cases the antibiotic sensitivities or the identity of the organism are unknown prior to initiation of antimicrobial therapy. Even when appropriate culture samples are collected, the results are delayed by 48–72 hours or longer. Therefore, the initial antimicrobial selection should be effective against bacteria in all four quadrants (gram positive, gram negative, aerobic, and anaerobic). This usually requires the co-administration of two or more antibiotics. Unless a clear contraindication exists, the dose of all antibiotics should be at the high end of the dose range, they should be given IV, and penetrate the desired tissue bed. Examples of effective antibiotic combinations include combining potentiated penicillins (ex. ampicillin/sulbactam 30–50 mg/kg q8h or ticarcillin/clavulanate 40–50 mg/kg q8h) with fluorquinolones

(ex. enrofloxacin 10–mg/kg q24h) or aminoglycosides (ex. gentamicin 6–8 mg/kg q24h).

Once culture results are returned, the antibiotic spectrum can be narrowed based on the microbial sensitivity pattern. The duration of therapy required by septic patients is unknown and difficult to determine. A useful guide is to continue antibiotics therapy until one week after clinical resolution of infection.

Supportive Care

There are numerous additional components that are integral to the recovery of any critically ill animal. In septic patients, nutrition, monitoring, and high-quality nursing care cannot be emphasized enough. Diligent monitoring is necessary for these animals as their status can change quickly and with little notice. Heart rate, respiratory rate, respiratory effort, blood pressure, hemoglobin saturation, urine production, and blood glucose should be checked at regular intervals.

Due to the catabolic state that occurs during sepsis, nutritional support is a very important component of treatment for these patients. In addition to helping prevent hypoglycemia, nutrition allows for some anabolic activity to occur and enables synthesis of components of the immune system. In patients with severe sepsis or septic shock, dextrose supplementation is often necessary to treat hypoglycemia. When possible, it is always preferable to provide these patients with enteral rather than parenteral nutrition. Early enteral nutrition (defined as consistent caloric intake within the first 24 hours) has been shown to decrease length of hospitalization in dogs with septic peritonitis. This can be accomplished through voluntary alimentation by the patient or through the use of feeding tubes. The use of feeding tubes is becoming more common in the management of critically ill patients as more diets specifically formulated to be used in small-caliber tubes are developed. While most feeding tube options require heavy sedation or general anesthesia for placement, nasoesophagal tubes are small-caliber tubes that can be placed with little to no sedation and are therefore very useful for providing enteral nutrition to those patients that are unwilling to eat voluntarily. Although patients with sepsis as a rule have a negative energy balance, the goal with nutritional support should be to meet the resting energy requirement. There is little to no evidence that hyperalimentation improves clinical outcomes and it has been associated with development of complications including feeding intolerance and hyperglycemia.

Critical illness-related corticosteroid deficiency (CIRCI) is a multifactorial deficiency in circulating cortisol in critically ill patients. This condition was first described when it was found that a subset of patients with refractory hypotension improved following administration of physiologic doses of corticosteroids. Initially CIRCI was diagnosed by determining if patients responded appropriately to an adrenocorticotropic hormone (ACTH) stimulation test. It was found, however, that even some patients with normal response to ACTH stimulation benefited from corticosteroid supplementation. This led to the recommendation for supplementation of hydrocortisone in critically ill human patients with unresponsive hypotension regardless of ACTH stimulation results and in fact, ACTH stimulation tests are no longer considered necessary for the diagnosis of CIRCI.

Corticosteroid administration should be considered only if fluids and vasopressors do not correct hypotension. If used, the author prefers hydrocortisone 1–4 mg/kg/day divided q12h or once every 24 hours. Corticosteroids should be discontinued when the patient is no longer vasopressor dependent.

Prognosis

The prognosis for septic shock is tremendously variable in both veterinary and human patients. Severity and reversibility of the underlying disease process as well as the presence of comorbid conditions affect prognosis of sepsis and septic shock. However, it must be recognized that the farther along the septic spectrum (toward development of septic shock) that a patient goes, the worse the prognosis will be. Veterinary survival data are difficult to interpret as the practice of euthanasia complicates the evaluation of outcome, but survival rates of 50–60% are commonly reported. This correlates with studies showing mortality rates of nearly 50% in humans with septic shock.

Patients with sepsis or septic shock have significant disease and regardless of the cause, this condition is considered serious. Every effort should be made to set realistic owner expectations with the understanding that the prognosis is guarded to poor (especially in the case of septic shock). The financial and emotional cost of treating a dog with sepsis can be very high. The long-term prognosis for patients that survive sepsis and septic shock is unknown although good long-term outcomes appear to be common.

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44

Disorders of Heat and Cold

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Normal Thermoregulation

Body temperature is closely maintained in mammals around an optimal set point at which ideal cellular function can occur. This is a complex process that ultimately results in a balance between heat production and heat loss. The hypothalamus acts as the main regulator of this process with multiple sensors throughout the body in the skin, thoracic and abdominal viscera, and spinal cord. The body can be viewed as two thermal divisions: the core and peripheral compartments. The core compartment is well perfused with a mostly constant temperature. The peripheral compartment is composed of the extremities and peripheral temperature is dependent on heat transmission from the core via blood flow, heat conduction from adjacent tissues, and heat loss to the environment.

Heat is generated by muscle activity and metabolism, with the brain, heart, and abdominal organs being the main generators of metabolic heat. Changing blood levels of thyroxine, epinephrine, and norepinephrine can change the basal metabolic rate, and subsequently body heat. Increased muscular activity (i.e., shivering) is also used as a means of generating heat. Heat retention occurs by physiologic responses including piloerection and peripheral vasoconstriction, as well as behaviors such as seeking shelter and warmth and curling up.

In order to prevent hyperthermia, methods of heat dissipation are necessary to maintain an ideal body temperature. The four main mechanisms of heat loss from the body are evaporation, conduction, convection, and radiation. *Evaporation* is loss of heat from moisture on the body surface. In canine and feline patients, the main source of heat loss by the evaporative route is from the respiratory tract, with panting providing a means of increasing heat loss from the body. *Conduction* is the transfer of heat from body surfaces to objects contacting the body, such as exam tables or cage floors. *Convection* occurs when body heat is transferred to the air surrounding the body and *radiation* is the transfer of heat from the body to distant surfaces without direct bodily contact. In small animals, conduction and convection are the primary means of heat dissipation. Individual patient factors that contribute to increased heat loss may include increased relative surface area in a neonate, decreased fat insulation in a thin patient, inability to prevent excessive heat loss to a conductive surface or decreased heat seeking due to weakness or altered mentation.

Hypothermia

Hypothermia is defined as body temperature of less than 38 °C (100.4 °F) and is classified by severity as mild (32–37 °C/89.6–98.6 °F), moderate (28–32 °C/82.4–89.6 °F), or severe (<28 °C/82.4 °F). With the onset of hypothermia, compensatory responses including peripheral vasoconstriction and shivering are stimulated. Once body temperature reaches <34 °C (93.2 °F), vasodilation occurs and metabolic rate is decreased. Below 31 °C (87.8 °F), thermoregulation ceases completely and if hypothermia is allowed to continue unabated, death shortly follows.

Primary hypothermia is the result of prolonged exposure to low environmental temperatures, where the processes of heat production and retention are insufficient to maintain normal body temperature. Some patients may be more vulnerable to developing primary hypothermia due to decreased body condition, increased relative body surface area or a decreased ability to generate heat. Neonates, geriatrics, and patients suffering from chronic illnesses that result in decreased body fat and lean mass may be more susceptible to primary hypothermia.

Secondary hypothermia is a result of disease, anesthesia, and/or surgery, or other processes that cause alterations

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in heat production, heat retention or thermoregulation. A common cause of secondary hypothermia in small animal patients is general anesthesia. Perioperative hypothermia consists of three phases, starting with an initial rapid decrease in the core temperature of 1–1.5 °C during the first hour. Most anesthetics cause vasodilation, which results in venous pooling and redistribution of heat from the core to the periphery. This is accompanied by a decrease in the temperature threshold needed to cause reflex vasoconstriction. This phase is followed by a slower decrease in temperature over the next 2–3 hours as heat loss exceeds the rate of metabolic heat production that is decreased 20–30% by anesthetics. Heat loss during this period is more profound in patients undergoing open cavitary surgical procedures due to increased heat loss by all means of heat transfer as a result of the increased surface area available for heat exchange. The plateau phase is the final phase where metabolic heat production is equivalent to continued heat loss. At this point, the core temperature has decreased to a point where vasoconstriction occurs and heat loss is decreased.

The consequences of primary and secondary hypothermia are similar, although patients with secondary hypothermia are generally more symptomatic at higher temperatures. In the anesthetic setting, postoperative hypothermia has been associated with increased mortality in humans.

Hypothermia has many physiologic effects and consequences. One major effect of hypothermia is a decrease in the overall metabolic rate. This includes decreased hepatic metabolism, which may prolong the effects of anesthetic medications and consequently anesthesia-associated hypothermia. In the kidneys, hypothermia initiates cold diuresis due to increased glomerular filtration rate (GFR) and decreased sensitivity to antidiuretic hormone (ADH). During severe hypothermia, renal effects can progress to decreased renal blood flow, decreased GFR and ischemic renal tubular damage, which can lead to acute renal tubular necrosis.

Besides the effects on abdominal viscera, hypothermia can lead to a hypocoagulable state due to thrombocytopenia, thrombocytopathia, alteration in coagulation factor function and disruption of fibrinolysis. Hypothermia has also been documented to cause suppression of the immune system, resulting in increased surgical site infections and altered wound healing in human and veterinary patients.

Cardiovascular consequences of hypothermia include an initial catecholamine-stimulated increase in heart rate and blood pressure that increases myocardial oxygen demand and consumption. Hypothermia induces a left shift in the oxygen–hemoglobin dissociation curve resulting in decreased oxygen release to the tissues. Combined with reflex vasoconstriction, this results in significant tissue hypoxia, especially to the skin and extremities. During more severe hypothermia, there is decreased catecholamine responsiveness resulting in bradycardia and hypotension. Arrhythmias can occur due to myocardial ischemia as well as myocardial irritation, with ventricular fibrillation as a commonly documented rhythm.

Hypoxia is propagated by a decrease in respiratory rate and tidal volume. While mild hypothermia may protect the brain from ischemia in cases of cardiopulmonary resuscitation and traumatic brain injury, in normal patients the negative consequences of hypothermia are likely greater than the benefits. Even mild hypothermia can result in altered mentation due to decreased cerebral blood flow. Prolonged recovery from anesthesia due to hypothermia and decreased drug metabolism can potentiate altered mentation.

Therapy

The primary treatment goal of hypothermia, regardless of cause, is the restoration of normal body temperature. The main difference between the treatment of primary and secondary hypothermia is that since it can be anticipated, the best treatment for secondary hypothermia is prevention. Prevention of perianesthetic hypothermia requires close patient monitoring with rectal or esophageal thermometers. Indwelling probes allow for continuous temperature monitoring.

Prevention of hypothermia utilizes the same therapies and techniques as treatment of hypothermia. Heat loss can be prevented with passive surface rewarming in the form of a blanket covering the patient and placed between the patient and conducting surface. Extremities can be wrapped in insulating material. Active surface rewarming increases the temperature of the air and surfaces surrounding the patient to minimize heat loss. Forced warm air blankets and circulating water blankets significantly decrease heat loss from anesthetized patients and should be used on all patients undergoing general anesthesia of any significant duration (i.e., greater than 30 minutes).

Active core rewarming increases the temperature of the core by introducing heat centrally and can be performed by administration of warmed IV fluids, warm pleural or peritoneal lavage, warm water enemas, warm saline urinary bladder lavage, and inhalation of warm, humidified air. Warmed IV fluids are helpful in preventing hypothermia but are of minimal assistance in rewarming hypothermic patients. IV fluids can be warmed to 40 °C (104 °F) in a microwave for 2.5 minutes (microwave variation exists and each clinic should verify individual microwave time) or stored in an incubator for immediate use. In-line fluid warmers help to maintain the temperature as the fluid is being administered. Peritoneal and

pleural lavage fluids should be warmed to 40–43 °C and are invaluable in rewarming and preventing further heat loss in surgical patients.

When rewarming hypothermic patients, all these measures can be employed based on the severity of the hypothermia. When hypothermia is mild (>32 °C/89.6 °F), passive surface rewarming may be sufficient. With moderate hypothermia (>28 °C/82.4 °F), active external rewarming is required with the main efforts aimed toward the core region rather than the extremities. Once hypothermia becomes severe (<28 °C/82.4 °F), active core rewarming is mandatory. Warm lavage allows heat transfer from the fluids to the bowel and heart and can help prevent further decrease in temperature. Heat transfer is able to occur as long as the lavage fluid temperature exceeds the core temperature, ideally 40–43 °C (104–109 °F). Warm peritoneal or pleural lavage can be performed in nonsurgical patients but is technically more difficult than in animals with an open body cavity in the operating room. If necessary, a peritoneal catheter or thoracostomy tube is placed using sterile technique and 10–20 mL/kg of warmed lavage fluid (0.9% NaCl) is infused. The amount of time that fluid is allowed to remain within the body cavity (dwell time) will determine how much heat is transferred. Dwell times should be of sufficient duration to allow for maximum heat transfer, with typical dwell times lasting 2–5 minutes. Transfers can be repeated as needed until the target body temperature is reached.

Similar to peritoneal or pleural lavage, warm lavage of the urinary bladder and colon is an option but is of unknown benefit due to limited surface area available for heat exchange. However, urinary bladder lavage and warm water enema administration is less invasive and does not require placement of catheters within the peritoneal or thoracic cavities. If used, the dwell times, exchange volumes, and temperature of the infusate are the same as for the cavitary lavage techniques.

Hypothermic patients require cautious IV fluid resuscitation to assist in restoring blood pressure and effective circulating volume. As hypothermia progresses, the decreased affinity of catecholamines for receptors leads to reduction of cardiac contractility and vasodilation. This may manifest as a minimal response to IV fluid therapy and does not automatically indicate the need to continue volume expansion with fluids in the absence of ongoing hypovolemia. As the body temperature returns to normal, rebound vasoconstriction and increased contractility may result in fluid overload as the intravascular fluid volume is centralized. When IV fluid therapy is needed, warm IV fluids are recommended so fluid resuscitation does not potentiate hypothermia. The ideal rate at which to rewarm a hypothermic patient is unknown but a general recommendation is 1–2 °C per hour. Active rewarming efforts are stopped once the patient has reached 37 °C (98.6 °F) to prevent hyperthermia.

Primary hypothermia is less common than secondary hypothermia. When it does occur, the decrease in body temperature is generally more severe; however, the recovery may be less complicated due to the absence of concurrent diseases, surgery or anesthetic drugs.

With rewarming, there is an increase in the metabolic rate and oxygen consumption that may not be appropriately compensated for in patients that are hypotensive or hypoventilating. Supplemental oxygen may be beneficial in preventing hypoxia from this increase in oxygen demand. When utilizing external warming techniques, a condition known as afterdrop can occur in which the core temperature actually continues to decrease as peripheral vasodilation allows movement of warm core blood to the periphery and return of cold peripheral blood to the core. Afterdrop may be prevented by instituting core rewarming techniques concurrent with external rewarming, and by directing rewarming techniques at the trunk rather than the limbs. At the far end of the afterdrop spectrum lies rewarming shock, which occurs when rapid vasodilation from external warming results in significant venous blood pooling and circulatory collapse. Thermal burns due to active rewarming efforts can occur if excessive heat is used (>42 °C/107.6 °F), prolonged contact time between patient and heat source is allowed, or there is a lack of insulation between the heat source and patient.

Prognosis

Rewarming complications can affect the prognosis of hypothermic patients.

Hyperthermia

Hyperthermia is defined as an increase in body temperature greater than 38 °C (100.4 °F) and can be due to an alteration of the set point of the hypothalamus to a higher temperature with deliberate efforts of the body to raise itself to that temperature (true fever) or can result from loss of the thermoregulatory balance of the body in which heat production is increased or heat loss is inhibited but the set point remains the same. Hyperthermia can be induced by extreme muscular activity. Sustained exercise, especially in an underconditioned or overweight patient, sustained seizure activity or frequent cluster seizures can induce severe hyperthermia if not controlled.

An uncommon cause of hyperthermia in dogs and cats is malignant hyperthermia. This is a condition of disturbed calcium metabolism that is initiated by drugs, most commonly volatile anesthetic gases, that results in

a myopathy with increased metabolic heat production. Clinical signs include elevated body temperature and often muscle rigidity. In patients under anesthesia, an increase in end-tidal CO_2 may be noted due to the increased metabolic rate associated with this condition. Various pathologic conditions, including endocrine disorders (hyperthyroidism, pheochromocytoma), can induce an increase in metabolic rate and heat production, as well as decrease heat loss due to peripheral vasoconstriction. Hypothalamic lesions that result in an increase in the temperature set point will create hyperthermia.

Prolonged extreme elevations in body temperature can increase the metabolic rate and demand for oxygen, water, and calories that may exceed the body's ability to supply them. When this occurs, protein denaturation occurs and resulting cellular dysfunction is manifested as cardiac arrhythmias, liver dysfunction, kidney failure, and damage to the gastrointestinal barrier with secondary bacterial translocation. Acid–base and electrolyte derangements occur due to dysfunction at the cellular and organ level. Muscle damage from high temperatures and hypoxia causes rhabdomyolysis, hyperkalemia, and myoglobinuria, leading to further renal injury. Significant alterations in systemic coagulation manifest as disseminated intravascular coagulation (DIC) with thrombosis adding to organ dysfunction. Consumption of clotting factors results in inappropriate bleeding that may produce clinically significant anemia.

Treatment

Treatment of hyperthermia should be directed at correcting the underlying cause and returning the body temperature to normal through the use of active cooling. Active cooling techniques include placing the patient in front of a fan to improve convective heat transfer, removing bedding to allow contact with cool cage or floor surfaces to maximize conductive heat loss, and application of alcohol to the foot pads to enhance evaporative heat dissipation. These techniques are generally sufficient for treatment of hyperthermia of less than 41 °C (106 °F) and should be started on animals with hyperthermia greater than 40 °C (104 °F). If these mechanisms are ineffective or if hyperthermia is more severe, then dousing the patient (wet to the skin, not just the hair coat) in cool water and placing them in front of a fan is the best way to transfer heat from the core to the skin and subsequently to the environment. Ice water should be avoided as it will induce peripheral vasoconstriction and inhibit heat transfer from the skin and delay core cooling. Application of ice water may also induce shivering which can result in heat generation. Cooling should be closely monitored and active cooling stopped when the core body temperature is still above 39 °C (102.2 °F)

Hyperthermia secondary to seizure activity requires aggressive medical management of the seizure activity with antiepileptic drugs (diazepam 0.5 mg/kg IV) and active cooling. Treatment of malignant hyperthermia includes stopping the causative medication, active cooling, and administration of dantrolene (2.5–5.0 mg/kg IV).

Fever

Hyperthermia in the form of fever is part of the systemic acute phase response to a pathogen or tissue injury and is aimed at decreasing the ability of infectious agents to replicate and survive. The response may be triggered by a variety of infectious agents including bacteria, fungi, and viruses, as well as tissue injury from trauma or surgery. Neoplastic cells are also capable of inducing fever. A substance that is created by the body and induces fever is an endogenous pyrogen, the most significant of which are the cytokines interleukin (IL)-1, Il-6, and tumor necrosis factor (TNF)-alpha. A substance released by an infectious agent that induces fever is known as an exogenous pyrogen and includes lipopolysaccharide (LPS) of gram-negative bacterial cell walls. LPS and other exogenous pyrogens bind to immune cells and result in cytokine release and initiate the acute phase response. Infectious agents also create tissue damage that leads to the release of cytokines. Once released, cytokines stimulate the arachidonic acid pathway and result in the production of prostaglandin-E_2 (PGE_2). PGE_2 is the main mediator of the fever response through its action on the hypothalamus that results in vasoconstriction to prevent heat loss and catecholamine release (among other mechanisms) to increase thermogenesis.

The cause of fever may be obvious based on history and physical exam, as in the case of an infected wound or surgical site, or an abscess from a bite wound. If not readily apparent, an extensive work-up may be required to identify the underlying cause. A tiered approach to working up a fever is often proposed, starting with a minimum database including complete blood count, chemistry profile, and urinalysis. Thoracic and abdominal radiographs with ultrasound are also often included in the initial work-up. If these tests do not provide a diagnosis, further diagnostics including relevant infectious disease titers (based on geographic area), urine culture, blood cultures, echocardiogram, joint taps, and cerebrospinal fluid analysis may be required.

Treatment

Identifying and eliminating the cause of true fever is the mainstay of treatment. Therapeutic treatment with IV fluids to maintain hydration and electrolyte balance may

be necessary. Broad-spectrum antibiotics are recommended if a bacterial infection is suspected and when possible, antibiotic therapy should be deescalated based on culture results. Prolonged fever with no response to antimicrobials and a thorough, inconclusive work-up may indicate an immune-mediated process that requires immunosuppression, a viral process that requires continued monitoring and supportive care, or a neoplastic process that has yet to be identified. Treatment with antipyretics that inhibit prostaglandin synthesis, such as nonsteroidal antiinflammatory drugs (NSAIDs), is controversial as inhibiting the fever may allow continued propagation of an infectious agent. Possible side-effects of these medications in each individual patient should also be considered carefully prior to their administration. Although uncommon, true fevers exceeding 41 °C (106 °F) require more aggressive intervention with active cooling to prevent organ damage and other systemic effects.

Heat Stroke

Heat stroke is probably the most common cause of life-threatening hyperthermia (>40 °C/104 °F) encountered in veterinary medicine and results from inadequate heat dissipation from the body. Classic heat stroke is caused by exposure to high environmental temperatures, which overwhelm the body's ability to offload heat by means of convection and radiation. The most common situation causing classic heat stroke occurs when an animal is locked in an enclosed vehicle where the temperature can rapidly increase past the outside ambient temperature due to solar heat and poor interior ventilation. This situation develops more rapidly in larger dogs that produce greater body heat and have less relative surface area for heat dissipation than smaller dogs.

Exertional heat stroke is the result of physical activity in a hot and/or humid environment and is often seen in working dogs. Increased environmental humidity decreases respiratory evaporative heat loss while increased work of breathing promotes heat production and further exacerbates this condition. Many cases of exertional heat stroke occur early in the warm weather season due to lack of acclimatization to the change of temperature. Dogs with altered means of respiratory evaporative heat loss, such as brachycephalic dogs and dogs suffering from laryngeal paralysis, may be more vulnerable to exertional and classic heat stroke. Obesity and a thick hair coat can further decrease the ability to dissipate heat from the body in both forms of heat stroke.

Some dogs may have a genetic resistance to heat stroke due to increased levels of heat shock proteins (HSP), which protect and repair essential cellular proteins from heat damage. NSAIDs upregulate HSPs and may confer protection against heat stroke in patients that are on NSAIDs at the time of the heat stroke incident. In fact, in humans, NSAIDs may be indicated for heat stroke prevention during heat waves although there is no published research on this in dogs. Importantly, NSAIDs are contraindicated after a heat stroke event has occurred due to the risk of negative effects on the kidneys, coagulation system, and gastrointestinal tract.

The clinical signs of heat stroke depend on the degree and duration of temperature elevation, as well as a significant contribution by individual patient factors. Diagnosing heat stroke is often based on a history of confinement or exertion on a hot, humid day. Most animals will present with an elevated body temperature although it may be normal or low, especially if external cooling has been initiated prior to presentation or the patient is in the advanced stages of shock. On initial physical exam, tachycardia, panting, and injected mucous membranes may be noted. Cardiac arrhythmias may be ausculted or suspected due to the presence of pulse deficits. Neurologic deficits ranging from obtundation to coma and seizure may occur. Skin and mucous membranes should be examined for evidence of petechiae and ecchymosis and venipuncture sites should be monitored for appropriate hemostasis.

Initial work-up includes an electrolyte panel (including blood glucose), packed cell volume (PCV) with total solids (TS), complete blood count, chemistry profile, and coagulation assays. Common abnormalities include hemoconcentration with elevations in PCV and TS, elevations in liver enzymes (ALT, AST, alkaline phosphatase, bilirubin), renal and prerenal azotemia, elevated creatine kinase, prolonged clotting times, and hypoglycemia.

Treatment

The initial therapy for heat stroke should be aimed at rapidly returning body temperature to normal and correcting hypovolemia and acid–base and electrolyte derangements. Immediately upon recognition of a heat stroke crisis, owners should be instructed to thoroughly wet a patient with tepid water. Support staff should be trained to instruct owners in this crucial step provided it will not unnecessarily delay transport to a veterinary hospital. Upon presentation, the previously described active cooling techniques should be initiated. At least one peripheral IV catheter should be placed and room-temperature fluids administered to increase effective circulating volume and improve perfusion, enhancing peripheral heat loss.

During fluid resuscitation, heart rate, blood pressure, lactate, PCV/TS, and urine production should be monitored to guide therapy. A description of goal-directed resuscitation targets is found in Chapter 41. If hypoproteinemia

is present (albumin <2.0 g/dL, TP <5.0 g/dL), colloid therapy with natural colloids may be needed to support intravascular volume and prevent third spacing of fluids. If hypoglycemia is present (blood glucose <70 g/dL), an initial bolus of 50% dextrose (0.5–1.0 mL/kg, diluted to 25% with crystalloids) should be administered, then a constant rate IV infusion of a crystalloid solution with 2.5–5% dextrose initiated for continued glucose support. Blood glucose should be monitored and dextrose supplementation titrated to prevent hyperglycemia. If coagulation parameters indicate a hypocoagulable condition (prolonged prothrombin time [PT] or partial thromboplastin time [PTT]), appropriate blood products (ideally fresh frozen plasma 10–20 mL/kg) may be indicated. If bleeding is evident or the degree of derangement is great enough to raise concern for spontaneous hemorrhage then plasma is administered as needed until coagulation times rechecked 1–2 hours after transfusion are normal.

Continuous ECG monitoring is recommended to allow rapid identification of the development of cardiac arrhythmias. In patients with severe neurologic deficits or seizure activity, diazepam (0.5 mg/kg IV), phenobarbital (12–16 mg/kg), or levetiracetam (60 mg/kg) should be administered to achieve seizure control. If neurologic evaluation suggests increased intracranial pressure then mannitol (0.5–1.0 g/kg IV over 15 min) may be considered for possible treatment of cerebral edema although hyperosmolar agents should be used with care in animals that have acute hypernatremia, as often happens with heat stroke. Coverage with broad-spectrum antibiotics is advised due to the concern for bacterial translocation from a disrupted gastrointestinal (GI) barrier. If evidence of GI injury is present in the form of hematemesis or hematochezia then GI protectants, including histamine-2 blockers (famotidine 0.5 mg/kg IV BID) or proton pump inhibitors (omeprazole 1 mg/kg PO BID, pantoprazole 1 mg/kg IV BID) are indicated.

Nonsteroidal antiinflammatories have been associated with preventing or decreasing the severity of a heat stroke episode when given prior to the incident. There is no evidence of any benefit to administering NSAIDs in the face of an active heat stroke episode and there is warranted concern for adverse effects on the already compromised renal, gastrointestinal, and coagulation systems. Similarly, there is no supporting evidence for the administration of corticosteroids during or after a heat stroke episode.

Additional treatments are indicated based on diagnostic test results and individual patient needs. For more information on general critical care considerations, see Chapter 35.

Prognosis

Heat stroke is a serious condition and the prognosis is dependent on many factors, including duration of temperature elevation, extent of temperature elevation, rapidity of initiation of treatment, and development of complications. Poor prognostic indicators include coma or hypothermia at the time of presentation, progressive decline in neurologic status, worsening azotemia, hyperbilirubinemia, persistent hypoglycemia, DIC, cardiac arrhythmias, and pulmonary edema. Hypoglycemia has been found to be more profound in nonsurvivors and persistent hypoglycemia despite treatment with dextrose has been associated with increased mortality. Increasing creatinine level despite IV fluid therapy has also been associated with increased mortality. The presence of nucleated red blood cells at the time of presentation may indicate more severe heat stroke and correlates with outcome.

In general, animals with moderate to severe heat stroke should be given a guarded to poor prognosis. Animals that survive an episode of heat stroke are expected to make a full recovery although lasting neurologic deficits or renal dysfunction may occur. Survival of heat stroke does not confer protection from future events and owners should continue to be aware of environmental conditions to minimize the chances of occurrence.

Further Reading

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45

Acute Poisoning

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Veterinarians are frequently presented with patients who may have been exposed to a toxin. Often the suspected toxicity is based on known exposure to a toxin. In other situations, patients exhibit symptoms (such as muscle tremors, central nervous system [CNS] dysfunction, spontaneous intracavitary hemorrhage, acute liver failure in the absence of an obvious cause, etc.) that lead the clinician to suspect toxicity. A basic understanding of common toxins, diagnostic testing for toxic compounds, general decontamination procedures, and available antidotes is important for the practicing small animal clinician. Prompt diagnosis and treatment of the intoxicated patient can lead to good clinical outcomes while failure to recognize toxicity may lead to death.

History

Obtaining a detailed history is extremely important whenever a patient may have been poisoned. Owners often fail to recognize a substance as possibly toxic, especially when the onset of clinical signs is delayed or the intoxicants are common items. Asking general questions such as "Has your pet been exposed to any toxins?" may lead to a quick response of "No" if clients do not identify medications (e.g., ibuprofen, phenazopyridine ["AZO standard"], etc.) or plants (lilies in cats, sago palms in dogs, etc.) as toxicants. Asking specific questions may help to identify a possible exposure. It is often useful to ask if the patient has been given *any* medications or ingested *any* plants. It is necessary to ask clients about toxic exposure *over the past few weeks*, as they may not recognize the delay between ingestion and symptoms that can be seen with toxins such as vitamin K antagonist rodenticides.

Physical Examination

A thorough physical examination of any patient suspected to have been poisoned is important. Ensuring a patent airway, verifying respirations, and assessing circulation (the basic "ABCs" of examination) should always be the first part of the physical exam. Many toxins target the CNS or the gastrointestinal (GI) tract, and symptoms such as mental obtundation or severe vomiting and diarrhea may be obvious. Stimulants and cardiotoxins may cause tachyarrhythmias, bradyarrhythmias, or signs of poor perfusion, including pale or gray mucous membranes, cool extremities, and poor pulse quality. Careful physical examination may uncover subtle symptoms such as pain on palpation of the kidneys of a patient who has ingested a nephrotoxin. Cats who exhibit acute, severe muscle tremors often have recent exposure to topical parasiticides such as pyrethrins or permethrins. Veterinary patients poisoned by a vitamin K1 antagonist frequently exhibit signs of hemorrhagic shock, including tachycardia, pale gums, and tachypnea. Signs of hemorrhage may include muffled ventral lung sounds, a palpable abdominal fluid wave, hematemesis, hemoptysis, hyphema, hematuria or ecchymoses of the skin. If history or physical exam suggests poisoning as a possibility, treatment should proceed according to a plan designed around the suspected toxin.

Clinical Approach

Diagnostic Testing

Every patient who is known or suspected of having been exposed to a poison should have a minimum database of complete blood count (CBC), blood chemistry profile,

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and urinalysis. The urinalysis is often incorrectly omitted in clinical practice. Failure to perform a urinalysis may prevent the clinician from uncovering evidence of renal injury (casturia, crystalluria, etc.) prior to the onset of azotemia. Once azotemia develops, the window of opportunity for successful therapeutic intervention may have closed for some patients. More specific diagnostic testing may be recommended on a case-by-case basis, depending on the specific toxin suspected. For instance, blood ethylene glycol testing and determination of anion gap and measurement of blood osmolality (if possible) are recommended if ethylene glycol ingestion is suspected. Coagulation testing, such as prothrombin time (PT) and activated partial thromboplastin time (aPTT), is recommended for suspected cases of rodenticide ingestion.

The use of urine testing kits for illicit drug intoxication in veterinary patients has been described. One study comparing urine test screen results with the gold standard of urine toxin detection (gas chromatography/mass spectrometry) found that an on-site urine toxin screen (QuickScreen Pro Multi-Drug Screening Test) accurately detected the presence of amphetamines, barbiturates, benzodiazepines, and opiates in canine urine but did not reliably detect THC (the main psychoactive substance in marijuana) or methadone.

Certain Exposure to a Known Toxin

When a patient is known to have ingested a specific substance, the clinician has a unique opportunity to intervene. Contacting an animal poison control service (such as the Animal Poison Control Center Hotline [888-426-4435] or Pet Poison Helpline [855-764-7661]) provides access to a database containing all known pharmacokinetics of the toxin, including toxic dose, routes of metabolism, and excretion. Expected symptoms and recommended therapies to offset the toxicity are also provided by these hotlines. A one-time fee is charged by the providers of these services.

If contacting a poison control center is not an option, an internet-based search utilizing a veterinary-specific network (such as the Veterinary Information Network [VIN.com]) often provides much of the same information. Even a search of free, nonveterinary websites such as www.pubmed.gov can help locate useful information or publications regarding treatment of a known toxin. If the toxin is a manufactured product (i.e., not a naturally occurring toxin such as a plant), the manufacturer of the product can be contacted. The manufacturer will have information regarding the toxic potential of the substance and may be able to provide treatment recommendations based on the type of exposure.

When considering the approach to a patient known to have ingested a toxin, many factors must be considered. If a patient is asymptomatic, the clinician must consider the likelihood of toxic symptoms developing. Although the exact dosage of toxin exposure is not always known, treatment should proceed according to the maximum possible dose. Let us consider, for example, an 80-pound Labrador retriever with exposure to a bottle of 200 mg ibuprofen tablets. The bottle initially contained 100 tablets, but it had been opened prior to this exposure. Twenty tablets were counted following the ingestion but the owner is unsure how many tablets are missing. In this scenario, the clinician should approach the treatment of the dog as if 80 of the tablets were ingested, constituting a toxic exposure dose of 220 mg/kg, even though the actual exposure was likely less than this amount. Ibuprofen dosages above 125 mg/kg have been reported to cause acute kidney injury in dogs, so the clinician in this case should warn the client of this risk and treat accordingly.

Every attempt should be made to establish a likely timeline of exposure. When the development of significant symptomatic toxicity is a possibility, decontamination should be considered. Ingestion is the most common route of toxin exposure so GI decontamination is often needed. GI decontamination is no longer recommended for every case of ingestion of a known toxin, but decontamination should be considered if there is a likelihood of toxic symptoms developing (see "GI decontamination" later in this chapter).

When the specific toxin and dosage are known and symptoms are expected or present, available antidotes should be administered as soon as possible. Timely administration of an antidote following toxin exposure is of utmost importance. Examples of common toxins for which antidotes exist include ethylene glycol, anticoagulant rodenticides, organophosphates, acetaminophen, and opioids.

Two Common Examples: Timing is Everything

An in-depth discussion of all known toxins is beyond the scope of this chapter, but vitamin K antagonist anticoagulant rodenticides and ethylene glycol are two of the most common toxins encountered in small animal practice. The importance of establishing a timeline of exposure whenever possible is highlighted by these two poisons, because a successful outcome following intoxication depends on timely diagnosis and intervention.

Vitamin K1 antagonists inhibit activation of the vitamin K-dependent clotting factors II, VII, IX, X, protein C and S. These toxins typically take up to 48 hours to cause prolongation in clotting times; clinical symptoms of bleeding may take 4–5 days or longer to develop. Factor VII has a significantly shorter half-life than factors II, IX,

and X, so factor VII depletion results in the initial clotting test abnormalities detected in animals with anticoagulant rodenticide ingestion. However, significant hemorrhage does not begin until factor II depletion occurs 3–4 days after toxin ingestion. Diagnosing anticoagulant rodenticide toxicity in the initial 3–4 days following exposure allows for successful treatment prior to major bleeding.

Many patients present for veterinary care very shortly (e.g., one hour) after ingestion of anticoagulant rodenticide. Unless a concurrent disorder of hemostasis is suspected or clinical bleeding is present, coagulation testing is unnecessary in these patients as long as the client is absolutely certain that exposure occurred recently (e.g., within the past few hours). If exposure has occurred more than 24 hours prior to presentation, or if timing of exposure is unknown, diagnostic testing is indicated. Common testing recommended for anticoagulant rodenticide toxicity includes packed cell volume (PCV), total solids (TS), and clotting times (PT and aPTT). Activated clotting time (ACT) can be tested if PT and aPTT are unavailable. PT prolongation, which usually occurs 48 hours after ingestion, occurs prior to aPTT prolongation due to the short half-life of factor VII (6.2 hours) compared with factor II, IX, and X. aPTT prolongation is typically seen after depletion of factor IX, whose half-life is 13.9 hours. Prolongation of both PT and aPTT is expected prior to significant clinical bleeding following anticoagulant rodenticide exposure. These different test results at various time points after ingestion of anticoagulant rodenticide highlight the critical importance of establishing a timeline of exposure whenever possible.

The "proteins induced by vitamin K antagonism" (PIVKA) test and specific blood tests for anticoagulant rodenticide levels are typically not useful in the acute diagnosis and treatment of the routine small animal patient with anticoagulant rodenticide ingestion because plasma samples must be sent to a diagnostic lab and there is delay in test results. These tests may be indicated when anticoagulant rodenticide toxicity is suspected but the patient has no known exposure; however, samples must be collected prior to treatment, and the clinician must proceed with treatment before test results are available.

Treatment for a patient exposed to anticoagulant rodenticide invariably involves enteral or parenteral vitamin K1 therapy, but the timeline of exposure and symptoms dictates the specific therapeutic plan for each patient. Vitamin K1 (2.5–5 mg/kg/day IM, SC, or PO for up to six weeks) can be started orally in the asymptomatic patient with recent exposure (<48 hours ago). If more than 48 hours have passed since exposure and coagulation tests are prolonged, but clinical bleeding is not observed, a single dose of parenteral vitamin K1 can be given prior to starting oral vitamin K1 therapy. Patients experiencing clinical bleeding secondary to vitamin K antagonists should be treated with fresh frozen plasma (FFP) transfusion in addition to parenteral vitamin K1 administration.

Patients who may have ingested ethylene glycol (EG) present a unique clinical challenge due to the extremely time-sensitive and dangerous nature of this toxicity. Cats exposed to EG less than three hours prior to presentation (and dogs exposed less than eight hours prior to presentation) must be aggressively tested and/or treated. The presence of EG can be proven by blood tests, but available tests are imperfect. Bedside tests include the Kacey Ethylene Glycol Test Strips (Kacey Inc., Asheville, NC) and the Catachem VetSpec Ethylene Glycol Qualitative Test Kit (Catachem Inc., Oxford, CT). These tests are subjective and based on visual determination of color change, and the presence of other substances such as proplylene glycol or ethanol may cause false-positive test results. The results of two small studies led to some concern regarding the sensitivity and specificity of these tests. One study evaluating the Kacey Ethylene Glycol Test Strips published in 2008 reported a sensitivity of only 56–67% for detection of 20 mg/dL EG (a potentially lethal dose for cats) in blood. This study also reported a specificity of 25–50% for detection of 80 mg/dL EG in blood. The authors of the study concluded that the test should not be used as a sole determinant of intoxication due to the risk of both false-positive and false-negative results.

The results of a second study were published in 2014 in the Journal of Veterinary Emergency and Critical Care. This study compared the Kacey Ethylene Glycol Test to the Catachem VetSpec Etylene Glycol Qualitative Test Kit. EG was added to canine blood at concentrations ranging from 0 to 100 mg/dL, and 30 samples were evaluated separately by two individuals. The tests were assigned a score of less than 20 mg/dL, 20–50 mg/dL, or greater than 50 mg/dL. Sensitivity and specificity were 100% for the Kacey test, with good agreement between two readers. In this study the VetSpec test performed less well. Sensitivity and specificity were only 65% and 70% respectively for one reader and 95% and 40% for the other.

A separate publication evaluated an EG test kit designed for use on a chemistry analyzer found in major clinical pathology laboratories (the Hitachi P-modular 800 chemistry analyzer). This test was found to accurately measure blood EG, and results were not significantly altered by the presence of propylene glycol.

Although the development and assessment of new tests continue, most veterinary hospitals do not, at this time, have a reliably sensitive and specific way to measure blood EG levels. Woods' lamp evaluation of the oral cavity, face, vomitus, and urine can provide evidence of

exposure to EG since many formulations contain a fluorescent dye. Unfortunately, since some formulations do not contain added dye, Woods' lamp evaluation cannot be used as a sole diagnostic test. Diagnosis of EG toxicity must therefore be made based on clinical suspicion and the presence of certain findings on any of the following tests: osmole gap, anion gap, urinalysis (calcium oxalate crystalluria), blood chemistry, or abdominal ultrasonography. Ethylene glycol is an effective osmole, and the presence of significant ethylene glycol levels in the blood can result in neurologic symptoms (e.g., ataxia and stupor) due to hyperosmolality.

The presence of significant amounts of EG in the blood leads to an increase in the "osmole gap," which is the difference between measured blood osmolality and calculated blood osmolality (equation 1).

$$\text{Osmole gap} = \text{Measured osmolality} - \text{Calculated osmolality} \quad \text{(Eq. 1)}$$

Osmolality can be estimated using equation 2.

$$\left[\left(1.86\times\left(\text{Na}+\text{K}\right)\right)+\left(\text{BUN}/2.8\right)+\left(\text{Glu}/18\right)\right]/0.93 \quad \text{(Eq. 2)}$$

The normal whole-blood osmole gap has been reported as 3.49 mOsm and the normal plasma osmole gap as −2.01 mOsm. A significant increase in the osmole gap in a patient who may have been exposed to EG or who is showing symptoms should raise clinical suspicion for EG poisoning.

Fatalities due to EG toxicity are caused by acute renal failure as EG metabolism leads to accumulation of metabolic acids such as glycolic and oxalic acid. This accumulation leads to a metabolic acidosis and an elevated anion gap (AG) seen at approximately three hours after ingestion, peaking at six hours, and lasting up to 48 hours. AG can be determined using equation 3.

$$\text{Anion gap} = \left(\text{Na}^{+} + \text{K}^{+}\right) - \left(\text{Cl}^{-} + \text{HCO3}^{-}\right) \quad \text{(Eq. 3)}$$

Normal AG is 12–24 mEq/L in dogs and 13–27 mEq/L in cats. An elevated AG indicates accumulation of unmeasured anions. An elevated AG is not specific to EG intoxication, but an elevated AG 3–6 hours or more after possible exposure to EG may be considered a sign of EG exposure. The oxalic acid formed during metabolism of EG binds calcium, resulting in calcium oxalate monohydrate crystalluria as early as three hours after ingestion in cats (six hours in dogs).

In some cases, EG toxicity may not be diagnosed prior to the development of oligoanuric renal failure. Progressive azotemia may help establish a diagnosis of EG poisoning, but this finding almost always indicates a grave prognosis. Diagnosis of EG toxicity must be made prior to the development of azotemia to allow the best chance at survival. The different clinicopathologic findings at different time points following EG ingestion again demonstrate how important it is to establish a timeline of possible exposure.

The treatment of EG toxicity is similarly dependent on timing of exposure. Definitive treatment of EG ingestion revolves around preventing accumulation of toxic metabolites. Metabolism of EG to glycolic acid by the enzyme alcohol dehydrogenase (ADH) is the most important step in the development of EG toxicity. Veterinary patients have traditionally been treated with IV ethanol administration. Ethanol is metabolized by ADH, and ADH has a higher affinity for ethanol than EG. Administration of ethanol, therefore, can limit glycolic acid accumulation. At the same time, high rates of IV fluids can be given to drive urinary excretion of unmetabolized EG molecules. Ethanol administration can be an effective treatment for EG ingestion, but long courses of treatment are needed and side-effects (including hyperosmolality, CNS signs such as sedation, and GI signs such as vomiting) are frequently observed. ADH inhibitors such as 4-methylpyrazole (4-MP, also known as fomepazole) prevent metabolism of EG to toxic metabolites while offering less risk of side-effects than ethanol. The primary drawbacks to 4-MP are limited availability and relatively high cost compared with ethanol. Cats require very high doses of 4-MP compared with dogs, making cats more likely to develop side-effects such as CNS depression and ataxia following treatment with 4-MP. Treatment of cats with ADH inhibition using ethanol or 4-MP is typically ineffective if not begun within three hours of ingestion, whereas treatment of dogs is typically successfully if started within eight hours of ingestion.

Hemodialysis is a very effective treatment for removal of EG and glycolic acid; 90–95% of circulating EG can be removed in a single hemodialysis session. Intermittent hemodialysis may also effectively treat azotemia and hyperkalemia in patients with acute kidney injury from EG toxicity, allowing time to determine if recovery of kidney function occurs over the span of several weeks.

Regardless of the mode of treatment, prompt intervention is of utmost importance due to the time-dependent nature of this lethal toxin.

Uncertain Exposure to a Known Toxin

When treating a patient who may or may not have been exposed to a known toxic substance, the clinician must formulate a diagnostic testing and treatment plan based on the presence or absence of clinical symptoms, the likelihood of clinical symptoms developing if toxic exposure did in fact occur, and the danger of the toxin involved. The clinician should consider contacting an animal poison control center to obtain the most extensive and up-to-date information regarding the probability of toxicity from any possible exposure to the substance in

question. Patients exhibiting symptoms consistent with toxicity from the substance should be treated as if they have been poisoned, even if exposure cannot be completely confirmed. If symptoms of toxicity are not present and the possible toxicity is not life-threatening, then a "wait and see" approach of close monitoring may be all that is needed. If signs of toxicity are not present, but the toxin to which the patient was possibly exposed carries some risk of significant morbidity, then decontamination (see "Decontamination" later in this chapter) should be considered if appropriate, and close monitoring should be recommended. If the possible exposure involves a toxin conferring serious risk of organ failure and/or death, then aggressive testing to confirm or rule out exposure is recommended. Decontamination and treatment should also be instituted, even if toxic exposure cannot be definitively confirmed.

Certain Exposure to an Unknown Substance

Frequently, small animal veterinarians are presented with a patient who was observed to lick, ingest or otherwise contact an unknown substance. This situation typically involves ingestion of a plant while outdoors. A good familiarity with the local flora will prove useful to the clinician in this instance. Even if the client has obtained a sample of the ingested plant, it may be difficult or impossible for the clinician to identify whether or not the plant is dangerous. If clinical symptoms are present and consistent with a poison known to be present in the local environment, then treatment should proceed as if the poisonous compound in question caused the symptoms.

One commonly encountered situation utilizing this approach is the young, otherwise healthy dog presented for muscle tremors after being exposed to rotten food or compost. In this situation, the clinician cannot be completely certain that there has been toxin ingestion, and even if ingestion is strongly suspected, the exact toxic compound is unclear. The patient in this scenario is typically assumed to have ingested a tremorgenic mycotoxin. Diagnostic testing of the patient should aim to rule out other causes of muscle tremors (hypocalcemia, hypoglycemia, etc.). Once these other common causes have been ruled out, treatment of this patient should involve centrally acting muscle relaxants such as methocarbamol and supportive measures such as IV fluids to prevent dehydration resulting from increased muscle activity in a patient who is unable to drink properly. The client should be informed that tremorgenic mycotoxin toxicity is suspected but cannot be confirmed. If initial diagnostic testing reveals no obvious cause of the symptoms, and if symptoms do not improve over 24–48 hours despite appropriate treatment for tremorgenic mycotoxin toxicity, then further diagnostic testing is recommended to search for a separate cause of the muscle tremors.

Decontamination

Topical Decontamination

Topical exposure to a toxin most often involves parasiticides such as permethrins or pyrethrins. Patients with topical poison exposure should be bathed thoroughly in a mild soap (such as Dawn® liquid dishsoap) as soon as safely possible. Minimum protective equipment for veterinary personnel should include rubber gloves. Eye protection and a rubber apron may be needed, depending on the nature of the toxin involved.

Ocular Decontamination

Eye injury may occur when ocular surfaces contact a caustic irritant. The resultant corneal damage can be minor (only resulting in discomfort) or severe enough to cause melting corneal ulceration. The pH of the ocular irritant strongly influences the severity of corneal injury. Acid compounds injure the corneal epithelium, but alkaline compounds are associated with more severe damage and a higher likelihood of anterior chamber changes and permanent vision impairment. The pH of an ocular irritant can be checked by applying litmus paper to the conjunctival fornix. This may help the clinician prepare the client for the likelihood of severe damage.

Regardless of the specific chemical toxin, the degree of damage is also related to the duration of exposure, so the eye must be flushed as soon as possible. Continuous flushing of the cornea should continue for at least 15 minutes following ocular surface exposure to a toxin; many resources recommend a full 20–30 minutes of flushing. The eye can be flushed using a balanced fluid such as 0.9% NaCl or lactated Ringer's solution (LRS). Tap water is an acceptable flushing solution, but the hypoosmolality of tap water may contribute to corneal edema formation following toxic injury. Bottles of eye wash solution are typically too small (i.e., contain too little volume) to effectively flush the surface of the eye for 15 minutes or longer. The damage caused by severe chemical burns of the cornea can be reduced by using buffered eye wash solutions such as Diphoterine®, but these solutions are not available in most veterinary hospitals.

Gastrointestinal Decontamination

Emesis

Induction of emesis may be indicated whenever a toxin has been ingested and may still be in the stomach. If ingestion has occurred within the previous 4–6 hours, it is reasonable to consider inducing emesis. While usually a safe procedure, there are potential risks associated with inducing emesis, including aspiration pneumonia and esophageal or oropharyngeal injury. In general,

only asymptomatic patients should be made to vomit, as the risk for aspiration pneumonia is greatly increased by CNS dysfunction or neuromuscular weakness. The risk of esophageal or oropharyngeal injury is increased if large or sharp objects have been ingested along with the toxin. Though uncommon, these possible complications must be considered and discussed with the client when deciding whether or not to induce emesis in a patient that has ingested a toxin. Patients that have ingested caustic substances (e.g., bleach) or hydrocarbons (e.g., gasoline) should never be made to vomit. Ingestion of zinc phosphide rodenticide leads to liberation of phosphine gas in the acidic environment of the stomach; induction of emesis following zinc phosphide rodenticide must be done carefully in a well-ventilated area (ideally, outdoors) to reduce the risk of dangerous phosphine gas inhalation by veterinary staff.

Hydrogen peroxide and apomorphine are the two most common agents used to induce emesis in dogs. Due to an increased risk of side-effects, the use of syrup of ipecac, sodium chloride salt, dishwashing liquid or mustard powder is not recommended. Inducing emesis is typically easy in canine patients. Hydrogen peroxide (3%) can be given PO at a dose of 2.2 mL/kg (up to a maximum of 45 mL) and repeated if vomiting has not occurred within 10–15 minutes of administration. Hydrogen peroxide causes vomiting by acting as a local irritant in the oropharynx and stomach. Rarely, protracted vomiting can occur after administration. Occasionally, mild side-effects such as lethargy and diarrhea can occur. Very rare instances of symptomatic gastric ulceration or even gastric dilation and volvulus (GDV) have been anecdotally reported following administration of hydrogen peroxide. A prospective observational study reported a relatively low incidence of mild side-effects (14%) in 70 clinical canine patients following induction of emesis using hydrogen peroxide; no serious or life-threatening side-effects were reported in this study.

Apomorphine is a centrally acting emetic agent that reliably induces emesis in dogs by stimulation of the chemoreceptor trigger zone. It can be given as a 0.03–0.04 mg/kg intramuscular (IM) or IV injection. Vomiting typically occurs soon after apomorphine injection. If vomiting does not occur, dosing can be repeated once or twice more, but the drug may depress the vomiting center in the medulla, so repeat administration may be unlikely to induce vomiting if the first dose was unsuccessful. Conjunctival application of apomorphine is also a very effective way of inducing emesis in dogs. The conjunctiva should be thoroughly flushed after emesis to limit further absorption of apomorphine and decrease the risk of CNS depression or protracted vomiting. PO administration of apomorphine to induce emesis is not recommended due to slow absorption and high first-pass clearance by the liver. If prolonged vomiting occurs after apomorphine treatment, administration of an injectable antiemetic (e.g. maropitant, metoclopramide, or ondansetron) is indicated. Rarely, significant sedation will occur after apomorphine administration. The sedative effects of apomorphine can be reversed using naloxone.

Induction of emesis in cats is more challenging than in dogs. Injectable administration of an alpha-2-adrenergic agonist is currently the method of choice. Xylazine is commonly given at a dose of 0.44 mg/kg IM for this purpose; as much as 1.1 mg/kg can be given. Dexmedetomidine (20–40 µg/kg IM) can also be used. One major drawback to the use of alpha-2-adrenergic agonists for this purpose is that profound sedation may occur. Reversal of the alpha-2-adrenergic agonist using yohimbine (0.1 mg/kg IM or IV) or atipamezole (50 µg/kg IM) is recommended following emesis to prevent sedation from interfering with interpretation of symptoms of poisoning.

Gastric Lavage

When induction of emesis is unsuccessful or contraindicated and an ingested toxicant is likely to cause significant morbidity or mortality, gastric lavage may be considered. Gastric lavage should always be done under general anesthesia (unless the patient is already unconscious), and a cuffed endotracheal tube should always be placed to guard the airway against aspiration of gastric contents. Lavage is performed using warm (body temperature) water given through a large orogastric tube, keeping the head below the level of the chest throughout the procedure to discourage aspiration of gastric contents (which can occur even in the presence of a cuffed endotracheal tube). Initial lavage volumes are typically 5–10 ml/kg, and lavage is repeated until the fluid obtained from the stomach is completely clear. If indicated, a dose of activated charcoal can then be given through the orogastric tube prior to its removal. The tube should be kinked in more than one place during removal from the stomach to prevent fluid within the tube from spilling into the airway. Gastric lavage carries risks, including anesthesia and aspiration pneumonia; careful consideration of the risk:benefit ratio must precede this intervention.

GI Adsorption

Activated charcoal (AC) has been, and will likely continue to be, one of the most common treatments administered to veterinary patients who have ingested a toxin. The use of AC in human medicine has recently been critically reevaluated, and routine use has been discouraged due to a lack of evidence that its administration affects outcome. There have been no published veterinary studies comparing conventional therapy with AC versus conventional therapy alone. Inherent differences

between veterinary small animal patients and human patients make the veterinary application of human guidelines questionable. Veterinary patients may be more likely than human patients to ingest large quantities of toxins, and paradoxically veterinary patients may present for medical care sooner after ingestion than human patients due to the intentional nature of many human intoxications. Furthermore, advanced treatments such as hemofiltration for toxin removal or prolonged, aggressive hospital-based care for treatment of organ dysfunction are more readily available and more often pursued in human medicine than in veterinary patients, making it that much more important to limit toxin adsorption in veterinary patients as much as possible prior to signs of intoxication.

Products containing AC are administered at a dose of 1–5 g/kg body weight PO or via orogastric intubation to bind any remaining toxin within the GI tract and prevent further absorption of the toxin. AC administration is indicated when the ingested poison binds to AC, is likely to cause significant toxicity, and has been recently ingested (within the past 4–6 hours) and/or undergoes enterohepatic recirculation. Repeated dosing (every 4–6 hours for four total doses) is recommended for dangerous toxins for which enterohepatic recirculation is known to occur and no antidote is available. The use of AC-containing products may lead to vomiting, and aspiration of gastric contents or charcoal creates a risk of pneumonia. Injection of an antiemetic prior to AC administration may help decrease the incidence of emesis. AC may bind water within the GI tract, and repeated doses have been associated with dehydration and hypernatremia in rare cases. When repeated doses of AC are needed, many sources recommend the repeat doses be given at a lower dose (for instance, half the initial administered dose), and IV fluid administration is recommended to help prevent significant dehydration. It is also important that veterinarians and clients know which patients have received AC so that the resultant black stools are not misinterpreted as melena.

Activated charcoal binds to most but not all toxins; it does not bind alcohols, heavy metals, or small organic molecules. Use of AC is therefore not indicated for toxic ingestions of xylitol, ethylene glycol, zinc, nitrates, or sodium chlorate, among others. It is important to confirm that the suspected toxin binds to AC prior to administration of AC. If the binding affinity of a poison to AC is unknown by the clinician, a poison control hotline should be contacted prior to administration. Studies have shown that the timing of AC administration in relation to toxin ingestion directly influences the percentage of ingested toxin that is bound within the GI tract. If AC use is indicated, it is important that the treatment be administered as soon as possible.

Few dogs (and almost no cats) willingly ingest AC solutions. One commonly utilized clinical method of administration involves combining the charcoal with a small amount of highly palatable food. While the food binds to the charcoal and reduces binding capacity, a published veterinary study suggests the reduction in toxin-binding capacity is clinically insignificant.

Cathartics

Cathartics are given to speed GI transit times in an effort to decrease the time a toxin is available for absorption within the GI tract. The two types of cathartics used in veterinary medicine are saccharides (e.g., sorbitol) and saline (e.g., magnesium sulfate); sorbitol is the most commonly used cathartic, and it is most commonly stocked in veterinary hospitals as an AC-sorbitol combination product. Because cathartics such as sorbitol act by drawing water into the GI lumen, significant risk of dehydration and hypernatremia exists with repeated use of these products. When a cathartic is used, it is typically only administered as a one-time dose. The most common clinical practice is to give only the first dose of AC with sorbitol, utilizing AC products *without* a cathartic for repeated doses.

Decontamination of Blood

Extracorporeal Therapies

One of the most effective methods to treat certain poisonings is removal using extracorporeal therapies such as hemodialysis and hemoperfusion. Hemodialysis involves circulating blood through an extracorporeal circuit and allowing for transfer of solutes and water across a semipermeable membrane. Toxins are good candidates for removal via hemodialysis if they are relatively small (<1500 daltons), poorly protein bound and with a low volume of distribution. Ethylene glycol and aspirin are examples of compounds that are readily cleared by hemodialysis. Hemoperfusion refers to the direct exposure of blood in an extracorporeal circuit to an adsorbent column of charcoal or (less commonly) a different adsorbent specially designed to bind a specific toxin. Hemoperfusion greatly increases the number of poisons that can be removed using extracorporeal therapy. Hemodialysis and hemoperfusion require specialized, often expensive, equipment and highly trained personnel. The availability of hemoperfusion is currently limited in veterinary medicine, but the number of facilities offering this potentially life-saving intervention will likely increase in the future.

Intravenous Lipid Therapy

Administration of intravenous lipid emulsions (IVLE) is a common therapy for the treatment of poisoning with lipophilic toxins. IVLE therapy was first used to treat

cardiotoxicity secondary to local anesthetic administration in humans. The proposed mechanism of action involved overriding the local anesthetic-induced inhibition of myocardial carnitine acylcarnitine translocase, potentially by mass effect or competitive inhibition, allowing fatty acids to reach the mitochondria and be used for energy production.

Since its initial introduction into the arsenal of available medical treatments, IVLE therapy has proven beneficial in the treatment of lipophilic toxins other than local anesthetics. Many of these lipophilic toxins cause dysfunction to organs other than the heart, yet their effects may still be reversed by IVLE administration, suggesting that IVLE treatment has a different or additional mechanism of action beyond improved free fatty acid availability or intracellular calcium accumulation. The most widely proposed mechanism of action for the beneficial effects of IVLE treatment of patients poisoned by liphophilic substances is the "lipid sink" theory. This theory states that increasing the plasma lipid content "sequesters" lipophilic toxins within the plasma, decreasing movement out of the bloodstream and into target organs such as the brain.

Anecdotal and published reports describe successful IVLE use in the treatment of a wide variety of toxins ranging from local anesthetics (bupivacaine) and vasoactive drugs (amlodipine, propranolol) to antiparasitic drugs (ivermectin, moxidectin) and antidepressant medications (bupropion, etc.). IV lipid emulsions are available as 20% formulations. The optimal dose is unclear at this time, but recommendations have been extrapolated from available human literature, animal research, and veterinary case reports. Current guidelines suggest 1.5–4 mL/kg IV bolus be given over one minute and followed by a constant rate infusion (CRI) of 0.25 mL/kg/min over 30–60 minutes. Patients who fail to respond to this protocol may require additional boluses of 1.5 mL/kg every 4–6 hours for 24 hours. Continued CRI doses of up to 0.05 mL/kg/h for up to 24 hours can be considered for patients who remain severely symptomatic. Utilizing a "lowest effective dose" approach is recommended due to the general lack of information regarding adverse effects of IVLE therapy in veterinary patients.

Reported side-effects in human medicine include infection due to contamination of the lipid product, anaphylactoid reactions, and allergic reaction to the egg or soybean component of the IVLE. A syndrome known as "fat overload syndrome" (FOS) has been observed in humans. FOS is associated with fat embolism, liver dysfunction, or coagulation system dysfunction (thrombocytopenia and prolonged clotting times). These side-effects have not yet been reported in clinical veterinary patients, but the use of IVLE as a treatment for lipophilic toxins is still somewhat new in veterinary medicine. When considering IVLE administration, the clinician must carefully weigh the severity and duration of toxic symptoms against the cost and potential complications associated with this intervention.

Conclusion

Small animal veterinarians commonly encounter acute poisoning. A sound, comprehensive approach to patient care (building on the fundamentals of a good history, physical exam, and diagnostic work-up) is important for diagnosing toxic exposure. A solid understanding of common toxins and appropriate utilization of available resources such as poison control hotlines help the clinician to establish the treatment plan most likely to result in a successful outcome. Exciting new therapies such as hemoperfusion and IVLE administration continue to evolve, making it important for the practicing small animal clinician to remain up to date on the most current available treatments.

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46

Medical Management of Trauma and Burns

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Etiology/Pathophysiology

The pathophysiology of trauma and burns is complex and explains why trauma and burn wounds are capable of affecting organs distant from the original insult and why the clinical course of disease can be so variable. Our current understanding of the pathophysiology of trauma is based on the theory that both primary and secondary insults contribute to morbidity and mortality. This is termed the *two-hit theory*. Primary insults (first hits) result in direct tissue injury from the trauma or burn (fractures, soft tissue destruction, organ rupture or vascular disruption). These factors are not under the control of the veterinarian. Secondary insults can be further divided into endogenous or exogenous causes. Typical endogenous second hits include shock, hypoxia, ischemia/reperfusion injuries, and infection. Exogenous (interventional) second hits include surgical trauma, anesthetic complications, and transfusion of blood products.

Systemic Inflammatory Response

The magnitude of the primary and secondary insults determines the systemic inflammatory response of the host. Immediately following a trauma load, the patient begins mounting a systemic response composed of both pro-inflammatory and anti-inflammatory components intended to limit entry of microorganisms, on the one hand, and limit secondary tissue damage, on the other. The balance, or lack thereof, determines if the patient will mount an appropriate response, or whether a pro-inflammatory or anti-inflammatory state will predominate.

Plasma levels of primary pro-inflammatory cytokines rise within 1–2 hours following trauma. Secondary pro-inflammatory cytokines begin to rise several hours following trauma and contribute to the systemic inflammation and activation of immune cells associated with severe trauma. The culmination of this activation is an increased number of circulating polymorphic nucleic cells (PMNs) and additional tissue injury.

Concurrent with the systemic inflammatory response (SIRS), an anti-inflammatory response called the compensatory anti-inflammatory response syndrome (CARS) is taking place. The purpose of this response is to minimize the tissue damage induced by the pro-inflammatory response and is achieved through release of anti-inflammatory mediators that reduce the synthesis of pro-inflammatory cytokines by their action on transcription factors necessary for their production.

Coagulation and Inflammation

Activation of the inflammatory system is closely tied to activation of the coagulation and complement cascades. Complement activation occurs through both the contact phase pathway and the classic pathway and results in recruitment and activation of phagocytic cells, induction of the hepatic acute phase response, and degranulation of mast cells. Mast cell degranulation releases vasoactive mediators including histamine, leading to leukocyte adhesion and increased vascular permeability (edema). Activation of the complement system also results in activation of the coagulation cascade although the most important inciting cause of activation of the coagulation cascade in the context of trauma is through the tissue factor pathway. Direct and secondary tissue injury exposes tissue factor (TF) on the endothelial cell surface which then complexes with factor VII (FVII) and activates the coagulation cascade. In severely traumatized patients, activation of the coagulation cascade can result in development of disseminated intravascular coagulation (DIC).

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Acute Phase Response

The release of pro-inflammatory cytokines tumor necrosis factor (TNF)-alpha, interleukin (IL)-1-beta, and IL-6 following trauma induces the acute phase response in the liver which results in up-regulation of positive acute phase proteins, including fibrinogen and prothrombin. At the same time positive acute phase proteins are being up-regulated, the production of negative acute phase proteins albumin, protein-C, protein-S, and antithrombin (AT) is reduced. The net effect of the acute phase response is generally in the direction of enhanced coagulation through the increased production of prothrombin, fibrinogen and the decreased production of endogenous anticoagulants protein-C, protein-S, and AT. The resultant hypercoagulable state can contribute to the development of DIC in patients following severe trauma or burns.

Ischemia and Reperfusion

Systemic ischemia can occur following trauma and is attributed to hypoxemia and hypotension immediately following trauma and during the early resuscitative period (<24 hrs). Local ischemia can occur due to blunt trauma, disruption of local blood supply or compartment syndrome. During periods of ischemia, several important intracellular changes occur. As energy stores are depleted, adenosine triphosphate (ATP) levels decrease and ATP is degraded to adenosine diphosphate (ADP) and hypoxanthine. As ischemia continues, intracellular pH decreases and lactate, hypoxanthine and sodium and calcium ion concentrations increase, leading to cellular swelling. Upon reperfusion, oxygen interacts with hypoxanthine, resulting in the formation of reactive oxygen species (ROS). This occurs within seconds of reintroduction of oxygen to ischemic tissues. Reactive oxygen species are capable of causing lipid peroxidation and cell death. The release of ROS into the systemic circulation and their subsequent delivery to the lungs following reperfusion may form the basis for the development of acute lung injury associated with trauma.

The liver and gut may be particularly sensitive to ischemia/reperfusion injury. In fact, ischemia and reperfusion of the gut following shock and subsequent resuscitation result in the gut becoming a source of proinflammatory mediators capable of inducing SIRS.

Traumatic Brain Injury/Spinal Cord Injury

The response of the brain and spinal cord to trauma is unique. Similar to general trauma, brain injury consists of primary (direct result of trauma) and secondary injury (subsequent to primary injury). Secondary brain and spinal cord injury is composed of hemorrhage, edema, vasospasm or enzymatically induced neurotoxicity. As an organ, the brain is particularly sensitive to injury by ROS due to high levels of unsaturated fatty acids and low antioxidant capacity. Periods of hypoxia and hypotension lead to the accumulation of the excitatory neurotransmitter glutamate in the interstitial compartment. High extracellular levels of glutamate in addition to intracellular depletion of ATP lead to accumulation of calcium and sodium ions within the neuronal cell and culminate in cellular dysfunction and death. Because of this, several autoregulatory countermeasures have been developed, including the brain's ability to regulate blood flow across a wide range of blood pressures. However, if hypoxia or shock is severe enough in magnitude or duration, these defense mechanisms are overcome and secondary neuronal injury occurs.

It is important to remember that primary brain injury can impair the autoregulatory functions of the brain, making it susceptible to secondary injury that would otherwise not occur. For this reason, initial resuscitative measures should be focused on improving oxygen delivery to the vital organs, especially the brain.

Burns

Local burns covering less than 30% of total body surface area (TBSA) rarely cause severe systemic effects while severe burns (those covering more than 30% of TBSA) are capable of inducing a syndrome called "burn shock" that is characterized by decreased intravascular volume, reduced cardiac output (CO), and increased systemic vascular resistance.

The physiologic response to burns is generally divided into two distinct phases. The resuscitation phase begins immediately following burn injury and is characterized by depleted circulating volume with increased vascular permeability and protein-rich fluid loss into the interstitial space, resulting in edema formation of both burned and unburned tissue. This phase coincides with a systemic response similar to that observed in severe trauma patients as described above. Hypoproteinemia in burn patients occurs secondary to protein loss in the form of edema fluid and fluid loss from the affected skin surface and can develop during the resuscitative phase of burn management.

Following the resuscitation phase of burn injury (3–5 days), a hyperdynamic/hypermetabolic phase, primarily mediated by counter-regulatory hormones including cortisol, glucagon, and catecholamines, begins. During the hyperdynamic phase, cardiac output is increased and vascular permeability begins to return to normal. In addition to the circulatory changes, an increase in metabolic rate occurs that results in negative

energy balance with protein catabolism, gluconeogenesis, glycogenolysis, hepatic insulin resistance, lipolysis, decreased lean body mass, and fever. Ultimately, energy requirements during this period can be increased threefold above basal metabolic rate.

Patients that suffered burn injuries in an enclosed structure fire are also at risk for developing inhalation injury. The inhalation of hot gas and particulate debris results in direct thermal injury to the airway mucosa and chemical irritation. Patients are at risk for developing upper airway obstruction, bronchospasm, small airway occlusion, pulmonary infection, and respiratory failure. The effect of direct thermal injury and chemical irritation is development of an inflammatory response resulting in interstitial edema formation. The damaged mucosal surface generates large amounts of cellular and necrotic debris, leading to further inflammation and distal migration within the bronchial tree with resultant lower airway plugging. This typically occurs 3–5 days post inhalation injury and, in conjunction with mucociliary dysfunction, can lead to development of bronchopneumonia.

Epidemiology

The incidence of trauma in veterinary medicine is relatively unknown with one large retrospective study finding that trauma accounted for 13% of admissions to an urban referral hospital. When it does occur, trauma in veterinary patients appears to be more likely to affect dogs than cats, with dogs comprising approximately 80–90% of trauma patients. In dogs, the mechanism of trauma is most likely to be blunt trauma associated with vehicular injury followed by sharp trauma and animal attacks. In the feline population, the mechanism of trauma is often unknown. In cases where the mechanism behind the trauma is known, cats are essentially equally as likely to suffer from blunt vehicular trauma, falls from height, crush injury or weapon-related trauma. The prehospital mortality rate of veterinary patients suffering trauma is unknown; in hospital, mortality ranges from approximately 10% to 20%.

Blunt trauma in the canine patient is more thoroughly described. The thorax and extremities are the most likely sites of injury from blunt trauma in dogs, with pelvic fracture, head trauma, and abdominal trauma occurring less frequently. The most common thoracic injuries incurred are pulmonary contusions, pneumothorax, and chest wall trauma/rib fractures. In blunt abdominal trauma, the most commonly encountered injuries are hemoperitoneum (25%), body wall hernia (5%), and rupture of the urinary system (3%). The two most commonly encountered orthopedic injuries are pelvic fractures and long bone fractures. Axial orthopedic injuries are relatively uncommon. Head trauma is more likely to be encountered in animals with a higher total trauma load and is associated with a worse outcome

Little is known about the incidence of penetrating ballistic injuries in dogs and cats although a recent study of military working dogs sheds some light on the topic. Obviously, military and law enforcement working dogs are at a higher risk than the general pet population of ballistic trauma and that trauma is more likely to be due to high-velocity/high-energy projectiles (rifle bullets). A higher incidence of penetrating ballistic injury is also likely in young, male dogs of the working breeds with lower velocity/energy ballistics (shotgun pellets) more likely.

Signalment

Young (1–3 years) large-breed dogs of both sexes are more likely to suffer blunt trauma (hit by car) than small-breed dogs. Conversely, small-breed dogs are more likely than large-breed dogs to be victims of animal attacks, with males being more commonly affected than females. Male cats are more likely to suffer trauma associated with vehicles or animal interaction than female cats while female cats appear more likely to fall from heights. Burn injuries most often occur in the veterinary hospital setting (heating pads) or structure fires; there is no species, breed or sex predilection.

History and Clinical Signs

The diagnosis of trauma is generally made based on history and physical exam findings rather than diagnostic test results. Often, the medical history is incomplete and it is not uncommon for the animal to be presented by a Good Samaritan rather than the owner. Cats frequently present with no history but with physical exam findings that are consistent with trauma.

Clinical signs associated with trauma will be dependent on the mechanism behind the trauma and the location on the body at which that trauma was inflicted. Typical injuries following trauma include fractures, contusions and abrasions, bruising or bleeding. Any animal presenting with one or more of these findings should be considered to have suffered trauma until proven otherwise. Blunt trauma patients are frequently presented with few outward signs of trauma but often have difficulty breathing, reluctance or inability to ambulate or decreased mentation. Initially, clinical signs may be mild and the animal may appear stable due to the catecholamine surge associated with the fight or flight response. Animals suspected of

suffering blunt trauma should be reevaluated frequently for new clinical signs or progression of existing clinical signs.

Penetrating trauma is much less difficult to diagnose, as these patients will have visible external wounds consistent with sharp or ballistic injuries. Very often in penetrating trauma, the amount of apparent external blood loss is small and animals with thick coats should be closely inspected for small penetrating wounds.

Diagnosis

Trauma is not often a diagnostic challenge. However, elucidating the extent of injuries can be. In all cases of suspected trauma, a complete medical history and a detailed description of the traumatic event, if possible, are essential. Owners should be asked about the patient's behavior immediately following the traumatic event. Specifically, the owner should be questioned about loss of consciousness, ambulation status, and whether the pet has urinated since the event. The owner should be asked to estimate the speed of the vehicle, height of the fall, and size of attacking animal, as applicable. Additionally, the owner should be asked to describe where on the pet they believe most of the trauma occurred. If a car hit the pet, the owner should be asked if the pet was seen traveling under the car or tire. If the pet was attacked by an animal, it should be determined if the pet was bitten and released or clenched and shaken. Finally, if a patient fell from height, the type of substrate upon which they landed should be ascertained.

A complete physical examination should be performed, with special attention paid to the neurologic system and thoracic and abdominal cavities. When evaluating the neurologic system in a trauma patient, a stepwise approach targeting life-threatening injuries first is utilized. The patient's mentation and level of consciousness (LOC) should be evaluated and their motor activity should be noted. Decerebrate rigidity (extension of all four limbs and opisthotonus) is associated with brainstem compression and altered LOC. Decerebellate rigidity (extension of forelimbs with hindlimb flexion) indicates cerebellar herniation and may be associated with normal or altered LOC. Motor function should be noted, taking care to discriminate between spinal reflexes and voluntary movement. Finally, brainstem reflexes are assessed. Pupil size, symmetry, and responsiveness are evaluated. Attempts should be made to elicit an occulocephalic reflex, taking care to avoid exacerbating possible cervical injuries.

Following evaluation of the neurologic system, the thorax should be evaluated for evidence of trauma. A visual inspection of the thorax should be performed and any lacerations, puncture wounds, abrasions or bruising should be noted. The patient should be observed while breathing prior to auscultation. Careful attention should be paid to the rate, depth, and pattern of breathing. Paradoxical movement of the thoracic wall inward during inspiration (flail chest) is indicative of segmental fracture of contiguous ribs. Thoracic auscultation should be performed in a quiet environment. The presence of breath sounds should be evaluated. Decreased breath sounds ventrally may indicate the presence of pleural fluid whereas decreased or absent breath sounds dorsally may indicate the presence of pneumothorax. In addition to ventral and dorsal differences, the breath sounds in each hemithorax should be compared to determine if unilateral pleural space disease (e.g., tension pneumothorax) is present.

Once the presence of breath sounds is confirmed, the quality of the sounds should be evaluated. Increases in bronchovesicular sounds or the presence of focal or diffuse crackles may indicate pulmonary contusion or hemorrhage. Detection of borborygmi within the thoracic cavity indicates herniation of abdominal contents through the diaphragm. Auscultation of the trachea should also be performed. Tracheal injury may result in loud guttural sounds while laryngeal injury may result in higher pitched wheezes (stridor).

The oral mucous membranes should be evaluated for color and capillary refill time (CRT). Pale mucous membranes can be present from anemia or peripheral vasoconstriction and decreased cardiac output, as seen with shock. Cyanosis may be observed if severe pulmonary or pleural space disease is present. Normal CRT is 1–2 seconds. Prolongation of CRT is consistent with decreased cardiac output and early to late decompensated shock. Patients in compensated shock may have a brisker than normal CRT and mucous membrane color may be bright pink to red.

The presence of cardiac sounds should be confirmed and the rate and regularity of the rhythm should be noted. Tachycardia can occur secondary to shock, pain or anxiety. Bradycardia may occur during shock in cats, but its presence in dogs is a harbinger of circulatory collapse and cardiopulmonary arrest. The absence of heart sounds may indicate pleural space disease (hemothorax), pericardial effusion or cardiac arrest. Pulses should be palpated during cardiac auscultation and should be evaluated for strength and synchrony with the heart. Heart sounds that do not generate a palpable pulse or pulses of varying strength are abnormal and electrocardiography should be considered. Severe peripheral vasoconstriction as seen in shock states results in the distal limbs being cooler to the touch than the trunk. A rectal temperature below normal is consistent with decompensated shock and should be considered a negative prognostic indicator.

Evaluation of the abdomen consists of visual inspection and palpation. Small puncture wounds over the abdomen, especially puncture wounds associated with animal bites, may belie severe trauma to the abdominal wall or abdominal viscera. Abdominal distension with or without a palpable fluid wave may occur with traumatic hemoabdomen. Palpation of the urinary bladder should be attempted although the presence of a palpable urinary bladder does not exclude the possibility of uroabdomen. A rectal exam should be performed in any animal that suffered blunt trauma to the caudal half of the body. Palpation of the pelvic ring for fractures and evaluation of anal tone are important components of a complete physical exam.

Assessment of the abdomen with ultrasound is becoming commonplace and has been shown to be a more sensitive indicator of free abdominal fluid than blind four-quadrant abdominocentesis or diagnostic peritoneal lavage. To perform an abdominal focused assessment with sonography for trauma (FAST) exam, the patient is placed in either left or right lateral recumbency. The ultrasound probe is placed at the first location on midline just caudal to the xyphoid process (diaphragmatico-hepatic position). The probe is then rotated cranially, caudally, and laterally in both directions. If no free fluid is observed then the probe is moved to the second site. The process is repeated, targeting the four points of investigation: diaphragmatico-hepatic, spleno-renal (left body wall over the left kidney), cysto-colic (midline over the urinary bladder), and hepato-renal (right body wall over the right kidney). If free fluid is found, the test is considered positive and an attempt should be made to obtain a sample for evaluation.

In most cases, orthopedic and cutaneous wounds are not immediately life threatening and their evaluation should complete the physical examination when the patient is deemed stable. The patient should be fully evaluated for the presence of lacerations, puncture wounds, abrasions or bruising. Gross deformity of limbs is assessed followed by a detailed orthopedic exam targeting long bones and joints of the appendicular skeleton. If not already done, the animal should be observed ambulating, if able. Radiographs of any areas of pain or instability should be obtained to determine the extent of the injuries. Wounds should be gently clipped to facilitate assessment.

Burn-Specific Considerations

When evaluating patients that have been burned, it is important to assess both the depth of the burn and the TBSA affected. Burn depth is classified as follows: superficial burns, superficial partial thickness, deep partial thickness, and full thickness. This terminology has supplanted the older classification scheme of grading burns by degree and provides a better description of burn severity. It is important to remember that the depth of the burn may vary across the affected area. Superficial wounds are erythematous and may have a dry, flaky appearance. Superficial partial-thickness burns are erythematous and moist. They blanch and blisters may be present. Deep partial-thickness burns are characterized by an absence of blisters and they appear waxy with reduced pain sensation. Full-thickness burns are white and may have eschar formation. Hair is easily plucked from the burn site.

Special attention should be paid to the airways of patients that have suffered burns in fires. The oropharynx should be evaluated for the presence of soot and the thorax should be carefully auscultated for evidence of airway or pulmonary parenchymal injury. If the animal smells of smoke then there is a high likelihood that some degree of inhalation injury is present. Notation of respiratory rate and effort should be made immediately and respiratory patterns and oxygenation status should be reevaluated regularly.

Therapy

The treatment of trauma patients can be divided into two distinct phases. The primary or acute phase of trauma management is focused on restoration of systemic and local oxygen delivery to preinjury levels to minimize secondary ischemic injury. The second phase of trauma management lasts until the patient is discharged and centers on maintaining oxygen delivery, definitive treatment of wounds or fractures, provision of nutritional support, and pain management.

Primary Phase

Successful resuscitation begins with recognition of its need. Resuscitation should be directed at reexpansion of effective circulating volume and re-establishment of systemic and local blood flow. The exact method of resuscitation is less important than the goals that are targeted. Classic resuscitation endpoints have focused on macrocirculatory findings such as heart rate, pulse quality, and blood pressure. Recent developments in shock treatment have identified microcirculatory markers that may be better for determining when resuscitation is complete (i.e., adequate oxygen delivery and usage has been restored).

Beyond the traditional resuscitation endpoints, the evaluation of biochemical markers such as base deficit, lactate, and central venous oxygen saturation has been advocated for use in veterinary medicine. The rationale

for using biochemical markers depends on the fact that cellular hypoxia may continue despite normalization of traditional resuscitation endpoints and the selected markers can detect this ongoing oxygen debt. If undetected, occult shock can be prolonged and can lead to further secondary injury. The best approach for determining when resuscitation is complete is one that incorporates both traditional and goal-directed endpoints.

Volume expansion should be achieved using replacement crystalloid fluids, hypertonic crystalloid fluids, synthetic colloids or blood products (packed red blood cells, fresh frozen plasma, fresh whole blood) as needed, although low-volume resuscitation (hypertonic saline and synthetic colloid) should be considered as the best choice for patients suffering head trauma or pulmonary contusions to minimize the likelihood of overresuscitation and exacerbation of vascular leak. There is no evidence that achieving supraphysiologic values for any of the macrocirculatory variables confers a benefit; on the contrary, overresuscitation may lead to increased morbidity (wound edema, fluid overload, dilutional coagulopathy) and should be avoided. Once normalization of macrocirculatory variables occurs then biochemical analysis should be performed to determine if oxygen debt is ongoing.

The provision of supplemental oxygen should be considered in any patient that has suffered trauma to the thorax or head, any patient in shock, or any patient that may have suffered inhalation injury. The ideal method to provide supplemental oxygen would allow the animal to move freely without restraint and would not contribute to stress. Oxygen cages or chambers approach this ideal. Flow-by oxygen or oxygen provided by facemask may prove useful during the initial evaluation period when it is imperative that the animal be handled. Nasal cannulation using purposemade nasal oxygen prongs is well tolerated by some patients and may allow for provision of supplemental oxygen without significant restraint. In rare circumstances, it may be necessary to secure an airway via orotracheal intubation or tracheostomy. In these cases, 100% oxygen is provided via an anesthetic circuit or self-inflating rescue bag.

Early analgesic management is an important part of the resuscitation phase of trauma management. Once it is determined that the patient's life is not in immediate danger, analgesia should be administered. In general, veterinary patients are less sensitive to the respiratory depressant effects of opioid medications and due to the minimal impact on cardiac indices and their reversibility, pure opioid agonists (morphine, hydromorphone, oxymorphone or fentanyl) should be considered the analgesic of choice in the acute setting. Head trauma patients should be treated for pain once it is determined that their neurologic status is stable. Completely withholding analgesia from head trauma patients is no longer advocated. Adequate analgesia improves patient comfort, facilitates examination, and improves healing.

Primary Wound Management

The goal of wound management during the primary phase of treatment is to prevent further contamination of the wounds and prevent additional tissue injury from occurring. Wounds should be clipped, cleaned with an antiseptic solution (chlorhexidine or betadine) and lavaged with saline. Following lavage, the wounds should be gently probed for depth and extent and then covered with a nonadherent sterile dressing until the patient has been stabilized and definitive treatment is possible. Very recent thermal burn wounds should be lavaged with cool saline to arrest ongoing thermal injury and should then be covered with silver sulfadiazine and a nonadherent bandage. Most chemical burns can be immediately lavaged with tap water for 30 minutes although some alkaline agents may take longer to remove. Elemental metals, including solid sodium, can ignite when they come in contact with water and should instead be covered with mineral oil. Wounds should never be allowed to go unaddressed for longer than 2–4 hours.

Any gross deformities suggesting luxation or fracture should be identified. If fractures are present distal to the stifle or elbow, the limb should be immobilized with a soft bandage, ensuring that the joints above and below the affected area are incorporated. Attempts to reduce fractures are not necessary in the acute phase of management. Fractures of the humerus, femur, pelvis or scapula are not bandaged due to muscular coverage and inability to achieve adequate immobilization. Patients with suspected cervical or spinal fracture or luxation should be sedated, treated for pain, and immobilized using a backboard to prevent further injury to the spinal cord. If sedation or analgesia is inadequate, these patients often struggle and can exacerbate their injuries. Luxations are treated in a similar fashion to fractures and attempts at reduction should be delayed until the patient's condition has stabilized.

Secondary Phase

The secondary phase of treatment begins when the endpoints of resuscitation have been met and the patient is either admitted to the hospital or moved to surgery. As stated previously, the focus of the secondary treatment phase is ensuring adequate oxygen delivery is maintained and establishing definitive treatment for surgical wounds. Additionally, at this stage supportive care including nutritional support, analgesia, and preventive nursing care is considered.

Fluid Therapy

Arguably the most important part of medical management of trauma patients is fluid therapy. Trauma and burn patients have unique fluid needs that require special consideration. Judicious use of crystalloid fluids in patients that suffer thoracic trauma and, in particular, those that develop pulmonary contusions is needed. It should be remembered that endothelial cell dysfunction and perturbations in vascular integrity might contribute to fluid loss from the intravascular space. Excessively high volumes of crystalloid fluid may exacerbate pulmonary contusions due to their rapid redistribution into the interstitial space following administration. Patients with head trauma should be treated in a similar fashion. If brain edema develops secondary to exuberant fluid resuscitation, cerebral blood flow may be impaired. This concern must be balanced by the need to maintain adequate blood pressure for brain perfusion.

Hypoproteinemia is common in trauma patients, especially following burn injury, animal bites, or crush injury. The routine use of synthetic colloids in veterinary medicine is somewhat controversial due to concerns associated with development of coagulopathy and possibly renal failure. However, no clinical veterinary trials to date have demonstrated a negative association and their use should be considered to maintain colloid osmotic pressure and reduce edema formation in nonaffected tissue. In addition to its importance for maintaining colloid osmotic pressure (COP), albumin is an important carrier molecule and facilitates healing. Therefore, canine patients may benefit from receiving human serum albumin or canine-specific lyophilized albumin rather than synthetic starches for colloidal support.

Pain Management

The importance of effective pain management goes beyond the ethical consideration of ameliorating pain. The presence of pain causes increases in sympathetic tone and catecholamine secretion, leading to increased cardiac output, peripheral vascular resistance, and myocardial oxygen consumption. While important for the fight or flight response, these changes, if chronic, further impair oxygen delivery to tissues. In addition to the cardiovascular effects of pain, a neuroendocrine response occurs, resulting in elevated levels of catabolic hormones including cortisol while a concurrent decrease in the anabolic hormones insulin and testosterone is present. The net result of the neuroendocrine response is the development of a catabolic state characterized by hyperglycemia, type B hyperlactatemia, and ketogenesis. Treatment of pain reduces or eliminates these responses, facilitates patient evaluation, improves patient quality of life, and leads to more rapid healing and reduced morbidity.

Patients that suffer severe trauma or burns should be considered to be very painful and analgesia should be provided liberally. The best method of pain management in traumatized or burned patients utilizes a multimodal approach. Pure opioid agonists are the mainstay of pain management and should be provided early in the course of treatment. Opioid medications have no ceiling effect, meaning that there is no maximum dose at which further administration would not be expected to affect a result. In most cases, administration should be continued throughout the duration of hospitalization. While opioids are capable of depressing respiratory drive in veterinary patients, this is rarely clinically relevant. If there is concern over a patient's ventilatory drive then the dose of opioid can be reduced or broken into aliquots and administered to effect.

The dissociative agent ketamine has some analgesic properties, particularly for superficial pain. More importantly, perhaps, are the n-methyl D-aspartate (NMDA) antagonistic properties of ketamine that may alter spinal modulation and prevent or ameliorate central sensitization (wind-up). In order to derive the full benefit of ketamine with regard to sensitization prevention, it should be administered for at least 24 hours as a constant rate infusion (CRI) (5–15 μg/kg/min). The use of ketamine alone is not effective for deep or visceral pain and can result in behavioral changes, therefore ketamine should almost always be administered in conjunction with an opioid. When discontinuing ketamine for patients that have been on a CRI for longer than 24 hours, a gradual reduction of the infusion rate over several hours is used to prevent behavioral changes associated with abrupt discontinuation.

Clinically, the alpha-2-agonists are most commonly used for sedation although their use for pain management is becoming more common. Their short half-lives and reversibility make them theoretically attractive options in many trauma patients but careful consideration should be taken prior to their use since clinically relevant cardiovascular side-effects are possible. Animals in shock or with significant heart disease (especially diseases causing decreased systolic function) should not be administered alpha-2-agonists. A CRI is often employed to most effectively use this class of drugs as a component of the pain management protocol. When used at rates of 0.5–2 μg/kg/h, dexmedetomidine can result in anxiolysis and analgesia without significant cardiovascular side-effects.

Regional or local anesthesia should be considered as an adjunct to traditional, systemic analgesic methods. The use of regional or local anesthesia often requires coordination with the surgical team since these interventions often require general anesthesia or sedation to be performed. Placement of diffusion catheters for repeated administration of local anesthetic medication should be

considered at the time of surgery, if applicable; their use in contaminated wounds (bite wounds) should be avoided, however. Epidural administration or placement of an epidural catheter can provide excellent pain management for animals with pelvic limb or pelvic ring trauma. If sacral fracture or sacroiliac luxation is present or the landmarks used for epidural administration are disrupted then epidural administration should not be performed. Local anesthetic drugs can also be used systemically, with IV infusion of lidocaine being useful as both an analgesic adjunct and a promotility agent for management of ileus.

Both blunt trauma and burn injury are capable of inducing a very pronounced inflammatory state. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) can be very beneficial in these patients. However, animals that are severely traumatized or are in shock should not be administered NSAIDs until all tissue perfusion has normalized and is not anticipated to change abruptly. Patients with severe soft tissue injury or crush injury are at risk for development of myoglobinuria and renal failure. Any animal that has pigmenturia or evidence of renal insufficiency should not receive NSAIDs. The decision to use NSAID medications should be deliberate and if case selection is appropriate then NSAIDs may prove to be a very useful analgesic adjunct. Due to the risk of systemic side-effects, including further impairment of the already compromised immune system in these patients, animals that have suffered severe trauma or burn injury should not receive corticosteroid medications unless specifically indicated.

Many animals that suffer severe soft tissue injury require repeated sedation events on concurrent days or even multiple sedation events within the same 24-hour period. Patients that are going to require repeated sedation should be identified early in the course of hospitalization and measures should be taken to coordinate their care. Following repeated sedation with the same anesthetic medications it is common to see recovery times become more prolonged and patients require larger doses of drugs to achieve the same level of sedation due to the development of tolerance. It is good practice to alter the sedation protocol every few days to prevent development of tolerance or toxicity with repeated dosing such as reported with propofol administration in cats. Additionally, animals that are sedated serially are at risk for nutritional deficiency due to repeated fasting. Efforts should be made to sedate the animal at the same time every day to allow for the most opportunities to provide nutrition.

Nutrition

The benefits of enteral nutrition (EN) for critically ill patients are well documented and include stimulating production of local antibody, prevention of villous atrophy and prevention of gut-derived inflammatory complications. There are many ways of providing EN, including voluntary ingestion, force feeding or syringe feeding, nasogastric, nasoesophageal or nasojejunal tube feeding or surgically placed feeding tube (esophagostomy tube, percutaneous gastrostomy tube, surgically placed gastrostomy tube, jejunostomy tube or gastrojejunostomy tube). The best way to provide EN will likely vary on an individual case basis and consideration should be given to several factors when deciding the best method for each patient.

Nasoesophageal or nasogastric feeding tubes are useful for animals that are not stable enough for an anesthetic event or for those that need a temporary bridge to voluntary eating or placement of a longer term feeding tube option. Nasogastric tubes can be useful for gastric decompression in animals with severe ileus and delayed gastric emptying. One major limitation to the use of nasoenteral feeding tubes is the limited number of diets that can be administered through the small diameter of the tube. Although generally well tolerated in the hospital setting, these tubes are not particularly useful to send home with patients. Nasoenteral feeding tubes can be used in most veterinary patients but some small dogs and cats may not be able to accommodate the tubes comfortably within the nasal cavity.

Animals that require a definitive surgical treatment may benefit from placement of a longer term feeding tube option at the time of surgery. Esophagostomy tubes or PEG tubes can be placed quickly in patients under general anesthesia. Esophagostomy tubes can be used for provision of nutritional support immediately following placement but are often limited in the types of food that they can accommodate. Tube clogging is a common problem and may necessitate altering the food formula to a more watery consistency. Percutaneously placed gastrostomy tubes cannot be used for nutritional support for the first 24 hours to prevent leakage of gastric contents until a fibrous adhesion forms at the stoma. Surgically placed gastrostomy or gastrojejunostomy tubes can be utilized immediately.

The optimal timing of implementing nutritional support is not known but evidence suggests that earlier is better. The clinician should strive to provide nutritional support within the first 24–48 hours following severe trauma or burns. Patients that are hemodynamically compromised should not have nutritional support begun until they are fully resuscitated and stable.

When starting nutritional support, it is important to have a plan in place for meeting nutritional requirements. There is no evidence that provision of calories in excess of basal energy requirement (BER) is beneficial; in fact, it may be detrimental. Many formulas are available for calculating caloric requirements but the basal energy

formula 30(BW in kg) +70 = kcal/day is both easy to use and remember. When instituting a feeding plan, begin by feeding a fraction (1/3 to 1/2) of the calculated resting energy requirement (RER) for the first 24 hours with the goal of achieving full RER over the next 48–72 hours. It is common for the actual delivered kcal to be less than the calculated requirement due to the fact that animals may be intolerant of the volume or rate required to meet the RER, the need to water food down (reducing the caloric density) to prevent tube clogging, or the necessity to fast animals for sedation or anesthetic events. Selection of a calorically dense formula (≥1 kcal/mL) is best in most settings to ensure that the caloric target is being reached. If available, the use of immune-modulating formulas enriched with omega-3 fatty acids and antioxidants may be a good choice.

Parenteral nutrition (PN) has been associated with a variety of complications such as hyperglycemia, hyperlipidemia, electrolyte disturbance (hypophosphatemia, hypokalemia), and septicemia. Although enteral nutrition is always preferable to parenteral nutrition, sometimes it is not feasible due to intolerance of EN or nonfunctional GI tract (severe ileus, preexisting disease). For patients that were healthy prior to trauma, PN is not considered necessary for the first 5–7 days of hospitalization while the patient's progress is monitored. If anorexia persists or GI dysfunction becomes evident then PN should be instituted.

Trauma patients are at high risk for development of ileus due to voluntary or involuntary immobilization, opioid administration, pain, and general anesthesia. Aggressive management of ileus should be attempted with metoclopramide, cisapride, lidocaine, erythromycin or ranitidine. Consideration should be given prior to routine treatment with H2 blockers due to the potential for bacterial overgrowth in the proximal GI tract and subsequent complications. Ideally, the use of gastric alkalinizing medications would be based on evidence of gastric ulceration or esophagitis or the probability of either of these complications developing.

Transfusion

Severely traumatized patients may require red blood cell or plasma component therapy due to hemorrhage or development of complications such as DIC. Red blood cell transfusion increases the oxygen-carrying capacity of the blood and helps to reestablish the oxygen reserve normally present in health. Determining a transfusion trigger is clinician dependent and no clear guidelines have been established. The decision is made on a case-by-case basis, carefully weighing the pros and cons of each transfusion. As a general rule, the more acute the drop in hemoglobin, the higher the transfusion trigger since the necessary time to adapt to the decrease in blood oxygen content has not passed. If a patient is exhibiting clinical signs associated with anemia, is in hemorrhagic shock refractory to crystalloid or colloid resuscitation, or is undergoing a planned surgical procedure with anticipated blood loss then transfusion of red blood cells should be considered. The target packed red blood cell volume (PCV) for blood transfusion is also unknown but achieving a PCV of 25–30% is reasonable, with little evidence that higher values are beneficial. Improving blood oxygen content can subsequently improve wound healing and prevent or ameliorate secondary injury associated with ischemia or inadequate oxygen delivery.

Since blood transfusion is becoming more common in veterinary medicine, it is important to obtain a full transfusion history from the owner prior to administration of any blood product. Pretransfusion testing will vary by case according to how urgently the product is needed. If time allows then complete pretransfusion testing, including blood typing and major cross-match, should be performed. Blood typing of cats is mandatory in all cases regardless of time sensitivity due to the potential for fatal reactions to first-time transfusions. Cross-matching of cats should be considered in all transfusions if time permits due to the prevalence of preformed antibodies in this species. It is not necessary to cross-match dogs receiving their first blood transfusion, as the existence of preformed antibodies is very uncommon, and in the emergency setting a universal donor or DEA 1.1-negative donor unit can be given with little to no pretransfusion testing. Animals that require multiple transfusions during a hospitalization should have a major cross-match performed for all transfusions occurring 72 hours after the first due to the risk of severe hemolytic transfusion reaction.

The rate at which blood is administered is determined by the patient's volume status and cardiovascular stability. In patients that are in hypovolemic shock secondary to massive hemorrhage, blood can be administered as fast as it will flow into the patient. Under more controlled circumstances, most blood transfusions are started at reduced rates that are gradually increased with the goal of completing the transfusion over several hours. Close attention should be paid to vital signs in an effort to detect transfusion reactions early.

Fluid overload is an uncommon complication in dogs receiving packed red blood cells but may be a concern in cats (especially if underlying heart disease is present). In addition to volume concerns, each red blood cell transfusion will expose the patient to foreign antigen and will stimulate an immune response to a greater or lesser degree. In patients that are already experiencing systemic inflammation, this second hit may precipitate further injury, as in the case of transfusion-related acute lung injury.

Sepsis Prevention

While animals with penetrating injuries or with grossly contaminated wounds should be started on antibiotics, the use of prophylactic antibiotics in animals that have suffered blunt trauma without disruption of the integument is controversial. When necessary, first-generation cephalosporins are generally adequate for wounds not related to animal bites. Patients that suffer animal bites should be treated with potentiated penicillins or fluoroquinolones to cover common oral pathogens. Available evidence suggests that burn patients should not routinely be administered prophylactic antibiotics. If signs of infection develop, such as redness, new or worsening pain, or malodorous or purulent discharge, then antibiotic therapy should be instituted at that time. As always, antibiotic therapy guided by culture results is the best practice and when possible, cultures should be obtained prior to administration of antibiotics.

Strict adherence to catheter hygiene should always be followed (gloves worn, IV lines kept off the floor), and IV catheters should be monitored daily for signs of phlebitis or infection and should be replaced or removed if present. Any patient that develops a fever while in hospital should have all catheter and tube sites inspected for signs of infection. In addition to daily visual inspection, catheter wraps should be changed daily. Urinary catheters should be connected to a closed collection system upon placement and the collection system should be changed daily. IV fluid lines should be changed on a routine basis and disconnections of the IV fluid line from the patient should be avoided as much as possible. Any gross contamination of the IV line should be immediately cleaned and the line should be changed.

Severely traumatized or burned patients should always be handled with gloves to prevent colonization with bacteria from caregivers. Colonization with methicillin-resistant *Staphylococcus* species is common in healthcare professionals and can put patients at risk if normal barrier prophylaxis and hand hygiene are not followed.

Monitoring

Critically ill trauma and burn patients are at risk for decompensating acutely due to myriad causes including multiorgan failure, acute lung injury or acute respiratory distress syndrome (ARDS), pulmonary thromboembolism, pneumonia, DIC or sepsis. Diligent monitoring of these patients will allow the clinician to identify possible complications early and increase the likelihood of successful intervention.

Severe trauma patients, especially those that have suffered traumatic brain injury or thoracic trauma, should be placed on a respiratory watch and have both respiratory rate and effort evaluated at least hourly. Continuous electrocardiographic monitoring should be strongly considered in all trauma patients, especially those with thoracic trauma. If continuous ECG monitoring is not feasible then heart rate and pulse synchrony should be checked frequently. Blood pressure monitoring should be performed regularly. Monitoring mentation, central venous pressure, direct arterial pressure, pulse oximetry, urine output, and body weight can provide invaluable information on progression of the patient's condition. Laboratory monitoring should include serial blood gas analysis (venous or arterial), blood lactate and blood glucose measurement. Serum biochemistry analysis, complete blood count, and urinalysis should be performed at admission and then every 2–3 days as the patient's condition dictates. Coagulation assays should be considered if DIC is suspected or if the patient has had substantial blood loss or blood component therapy. Serial radiographs are useful for monitoring progression of pulmonary injury and serial ultrasound can aid in monitoring progression of abdominal disease.

The nursing staff is often the first to be aware of a patient's changing condition and the longer they work with a patient, the more attuned they become to subtle changes in status. Therefore, a good working relationship with the nurses providing treatments is imperative for successful monitoring of severely injured patients.

Preventive Nursing Care

It is important to prevent trauma patients from remaining recumbent for long periods of time. Nonambulatory patients should be repositioned several times a day to prevent pressure sores from developing. Mobility facilitates mucus clearance from the lower airways and supervised walks should be encouraged as soon as possible. If walks are not possible, patients should have passive range of motion performed several times a day. In addition to encouraging mobility, recumbent patients should be provided with soft bedding to distribute weight over pressure points and further decrease the likelihood of pressure ulcer formation.

A concerted effort should be made to keep the patient clean and free from fecal or urine contamination. Prompt removal of waste and bathing when necessary will aid in prevention of fecal or urinary scalding that can lead to compromise of the integumentary barrier. If urine or fecal scalding is present then the fur from the area should be clipped, the area should be cleaned with dilute antiseptic solution and a barrier ointment such as zinc oxide should be applied several times a day. Many of these patients may require urinary management such as intermittent bladder catheterization, indwelling urinary catheter placement or intermittent urinary bladder expression. The presence of an indwelling urinary catheter is a risk factor for development of urinary tract infection and can be an important contributor to patient morbidity. If a urinary catheter is present then

the collection system should be maintained closed to reduce the chances of ascending contamination and urinary tract infection.

Patients with bandages covering wounds should have the bandages changed immediately if strikethrough is present or if the bandage becomes contaminated with feces or urine to prevent bacterial contamination of the wound bed. Regardless of contamination, bandages should be changed at least daily initially.

Burn-Specific Therapy

In the early postresuscitation phase of burn management (2–24 hours), patient fluid needs are likely to be much greater than would normally be expected. With this in mind, care should be taken to avoid excessive fluid administration and the goals of fluid administration should focus on maintaining blood pressure and urine production within normal limits.

Due to decreased local perfusion, burn wounds should be treated with topical antimicrobial agents and covered with nonadherent dressings after initial decontamination to prevent bacterial colonization rather than relying on systemic antimicrobial therapy. The topical antimicrobial of choice is silver sulfadiazine (SSD), which has a broad antimicrobial spectrum and few side-effects. Manuka honey can be used as an alternative to SSD.

Rehabilitation

Comprehensive management of trauma and burn patients does not end with hospital discharge. These patients often require weeks to months of physical rehabilitation, which should begin in hospital, to regain lost mobility and to complete the healing process. Often patients are discharged earlier than planned due to financial limitations of the owner. In these instances, it is imperative that in-depth discharge instructions be provided to the owner on how to perform nursing care, including passive range of motion, tube feedings, bladder expression, medication administration, etc. Consideration should be given to referring the client to a certified veterinary rehabilitation specialist, especially if spinal trauma, long bone fractures or severe soft tissue injuries were present. Burn patients are at risk for development of contracture as burns heal and physical therapy can help to prevent severe contracture deformity and maintain functional mobility.

Prognosis

Euthanasia is always a confounding factor when determining prognostic factors in veterinary patients. However, factors that appear to be correlated with an increased mortality include higher injury severity score, presence of head trauma, requirement of mechanical ventilation, hemoperitoneum, and vertebral fractures. Many scoring systems have been recommended for both human and veterinary patients to help predict patient outcomes. While care should be taken when using scoring systems to predict likely outcomes for individual patients, they may be useful to assess risk of death.

The Animal Trauma Triage (ATT) Score (Box 46.1) was developed to estimate risk of death following trauma. The ATT is easy to use and has been validated in several patient populations. The score uses a numerical value from 0 to 3 in six categories with a total possible score of 18. For every one-point increase in ATT, the patient's risk of death increases by 2.3–2.6 times. While the ATT has proven useful in trauma patients, it fails to take into account the presence of preexisting disease or nontarget organ system evaluation.

The use of a Modified Glasgow Coma Score (MGCS) for prognostication following head trauma has been reported in the veterinary literature (Box 46.2). The MGCS assigns a conglomerate score from 3 to 18 based on scores ranging from 1 to 6 in three categories: motor activity, brainstem reflexes, and level of consciousness. The lower the score, the worse the patient's performance is within each category, and a total score of less than 8 correlates with 50% survival at 48 hours. While the utility of a one-time MCGS performed at presentation is open for debate, serial evaluation can be used and may help the clinician to make a more objective assessment of the progression of traumatic brain injury. A worsening MGCS during the first 24–48 hours should be considered a negative prognostic indicator. The short-term prognosis for dogs with traumatic brain injury is similar to mortality rates for blunt trauma in general (12–15%). The long-term neurologic outcome of dogs surviving after head trauma is generally considered to be good to excellent. However, it is reported that 7% of dogs suffering head trauma develop a seizure disorder.

The prognosis for animals suffering blunt trauma is generally good with aggressive supportive care. Animals that suffer blunt trauma secondary to vehicular injury have a reported mortality rate of approximately 15–25%. Negative prognostic indicators include cranium fractures, recumbency at admission, development of DIC, multiple organ dysfunction syndrome, the need for ventilation or vasopressor therapy and cardiopulmonary arrest.

Animals that suffer bite wounds from larger animals should be considered critically ill until proven otherwise. The amount of trauma to the underlying tissue is disproportionate to the amount of external injury visible during examination and all of these wounds should be considered contaminated with bacteria. Small dogs and cats that have been bitten by larger canids also are likely to have a component of crush injury associated with the wound. For these reasons, animals with severe bite injury

Box 46.1 Animal Trauma Triage Score (ATT)

Perfusion

MM pink/moist CRT 2 s, T ≥100F, strong or bounding femoral pulse quality	0
MM hyperemic OR pale pink, tacky, T ≥100F, CRT 0–2 s, fair femoral pulses	1
MM very pale pink and tacky, CRT 2–3 s, T <100F, detectable but poor pulses	2
MM gray/blue/white, CRT >3 s, T <100F, no palpable femoral pulses	3

Cardiac

HR canine 60–140 bpm, feline 120–200 bpm, normal sinus rhythm	0
HR canine 140–180 bpm, feline 200–260 bpm, NSR or VPC <20/min	1
HR canine >180 bpm, feline >260 bpm, consistent arrhythmia	2
HR canine <60 bpm, feline ≤120 bpm, erratic arrhythmia	3

Respiratory

Regular resp rate with no stridor, no abdominal component to resp	0
Mild incr resp rate and effort, +/- abd comp, mild upper airway sounds	1
Mod incr resp rate and effort, some abd comp, elbow abduct, mod incr upper airway	2
Marked resp effort OR gasping/agonal resp, little/no air passage	3

Eye/muscle/integument

Abrasion/laceration – none or partial thickness. Eye: no fluorescein uptake	0
Abrasion/laceration – full thickness. NO deep tissue involved. Eye: corneal lac, not perf	1
Abrasion/laceration – full thickness, deep tissue involved. Artery/nerve/muscle intact. Eye: corneal perforation, punctured globe or proptosis	2
Penetration of abdomen/thorax. Abrasion/laceration full thickness, deep tissue involved. Artery/nerve/muscle compromised	3

Skeletal

Wt bearing 3 or 4 limbs. No palpable fx/jt laxity	0
Closed limb fx/rib fx or any mandibular fx. Single jt laxity/lux (including SI), pelvic fx with unilateral intact SI-ilium-acetabulum. Single limb open/closed fx at or below carpus/tarsus	1
Multiple grade 1 conditions, single long bone open fx above carpus/tarsus with cortical bone preserved. Nonmandibular skull fx	2
Vertebral body fx/luxation except coccygeal, multiple long bone open fx above tarsus/carpus, single long bone open fx above tarsus/carpus with loss of cortical bone	3

Neurologic

Central: consciousness: alert to sl dull. Periph: normal spinal reflexes; purposeful movement and nociception in all limbs	0
Central: dull/depressed/withdrawn. Periph: abn. spinal reflexes with purposeful movement and nociception intact in all 4 limbs	1
Central: unconscious. Responds to noxious stimuli. Periph: absent purposeful movement with intact nociception in 2 or more limbs OR nociception absent in 1 limb. Decr anal or tail tone	2
Central: nonresponsive to all stimuli, refractory seizures. Periph: absent nociception in 2 or more limbs; absent tail or perianal nociception	3

Source: Adapted from Rockar *et al*. (1994).

CRT, capillary refill time; HR, heart rate; MM, mucous membranes; NSR, normal sinus rhythm; SI, sacroiliac; VPC, ventricular premature contraction.

Box 46.2 Modified Glasgow Coma Score (MGCS)

Motor activity

Normal gait, normal spinal reflexes	6
Hemiparesis, tetraparesis, or decerebrate activity	5
Recumbent, intermittent extensor rigidity	4
Recumbent, constant extensor rigidity	3
Recumbent, constant extensor rigidity with opisthotonus	2
Recumbent, hypotonia of muscles, depressed or absent spinal reflexes	1

Brainstem reflexes

Normal pupillary light reflexes and oculocephalic reflexes	6
Slow pupillary light reflexes and normal to reduced oculocephalic reflexes	5
Bilateral unresponsive miosis with normal to reduced oculocephalic reflexes	4
Pinpoint pupils with reduced to absent oculocephalic reflexes	3
Unilateral, unresponsive mydriasis & reduced to absent oculocephalic reflexes	2
Bilateral, unresponsive mydriasis & reduced to absent oculocephalic reflexes	1

Level of consciousness

Occasional periods of alertness and responsive to environment	6
Depression or delirium, responsive, but response may be inappropriate	5
Semicomatose, responsive to visual stimuli	4
Semicomatose, responsive to auditory stimuli	3
Semicomatose, responsive only to repeated noxious stimuli	2
Comatose, unresponsive to repeated noxious stimuli	1

Source: Adapted from Platt *et al*. (2001).

have a worse prognosis than animals with a comparable blunt trauma load. For small to medium-sized dogs with severe bite wounds, a mortality rate of approximately 20% has been reported although a subset of patients (those with crush injury and development of pigmenturia) appear to have a much worse prognosis.

The prognosis for veterinary burn patients is unknown. The overall mortality rate in human burn victims without inhalation injury is approximately 14%. This increases to 20% in humans with inhalation injury and burns. Factors that affect prognosis in humans include TBSA affected and concurrent inhalation injury. The mortality rate for dogs and cats with smoke inhalation alone is approximately 10%. Animals that have suffered burns in addition to inhalation injury should be expected to have a higher mortality rate.

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47

Venomous Snake Bites

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Etiology/Pathophysiology

The degree of pathology related to snakebites is determined by two main factors: the composition of the venom and the amount of venom injected into the victim. In veterinary medicine, there are two families of venomous snakes that are responsible for the vast majority of envenomations: the Viperidae and Elapidae. In general, vipers are capable of injecting venom through hollow fangs and once they (vipers) are mature, they have the ability to control the volume of venom injected with each bite. The Elapidae do not have such an advanced venom delivery system and rely on introduction of venom secreted from a venom gland through a wound created by biting. These snakes use their teeth and underdeveloped fangs in a chewing motion to create the wound. Therefore, elapid envenomation usually requires a snake to "adhere" or "chew" on a victim for some amount of time to allow adequate envenomation and consequently, these snakes strike and hold to allow for venom introduction whereas vipers strike and retreat, allowing the venom injected during the bite to immobilize the patient.

The composition of snake venom is extremely complex and it varies between species and within species based on geographic range. Venom composition also varies with age of the snake and the time of year. There are many potential effects of snake envenomation including flaccid paralysis, systemic myolysis, coagulopathy and hemorrhage, renal damage/failure, cardiotoxicity, and local tissue injury at the bite site. While the traditional view of venomous snakes was that vipers caused local and hemorrhagic effects (hemotoxic venom) and elapids caused systemic and nonhemorrhagic effects (neurotoxic venom), the reality is that any species of snake is capable of producing venom that can affect one or more of the body systems. Some Asian and African cobras (vipers) produce profound tissue injury while some South and Central American rattlesnakes (also vipers) produce primarily paralytic or neurotoxic venoms.

The venom of the North American pit vipers (Crotalidae) is typically classified as necrogenic/hemorrhagic and is capable of causing massive tissue damage and inducing life-threatening inflammation or hemorrhage. The venom is primarily composed of water, with proteins and peptides making up approximately 10% of the total volume. It is this portion of the venom that is responsible for most of the direct tissue injury and hemostatic perturbation seen with envenomation. It is also this portion that is responsible for inducing endothelial cell damage leading to endothelial dysfunction, cell lysis, and ultimately circulatory collapse. So far, over 60 purified polypeptides and approximately 50 enzymatic fractions have been identified with at least 10 enzymes and 3–12 nonenzymatic proteins and peptides present in any individual snake's venom.

Hyaluronidase and collagenase act to break down connective tissue, facilitating the spread of venom and beginning the digestive process. Together, these enzymes are capable of causing massive tissue damage and necrosis and are responsible for many of the outward sings of envenomation. The impact of envenomation on hemostasis is profound and can be considered in light of the areas of hemostasis that are affected.

Venom proteins acting directly on coagulation factors include procoagulant proteins such as factor V (FV) activators, FX activators, prothrombin activators, and thrombin-like enzymes. Anticoagulant venom factors also exist and include FIX/X binding proteins, protein C activators, thrombin inhibitors, and phospholipase A_2. Finally, factors acting on fibrinolysis include fibrinolytic enzymes (metalloproteinases and serine proteases) and plasminogen activator.

Many of the components of snake venom exert an effect on platelet function. The C-type lectins, disintegrins, and proteinases inhibit platelets by a variety of

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mechanisms, including interactions with von Willebrand factor (vWF) receptors and fibrinogen receptors. Platelet activation occurs through a thrombin-like effect of proteinases and phospholipase A_2, among other mediators.

Besides the effect of venom on primary and secondary hemostasis, proteins in the venom can affect the endothelium. Metalloproteinases, disintegrins, and C-type lectins degrade the blood vessel extracellular matrix, induce endothelial cell apoptosis, and inhibit platelet binding through interference with vWF. The net result of this combined action is consumption of fibrin and development of bleeding diathesis that is not generally characterized by thrombosis or intravascular coagulation.

Neurotoxins contained in snake venom exhibit a predilection for peripheral nervous tissue and relatively few are capable of crossing the blood–brain barrier. Venoms that exert a primarily neurotoxic effect act as either presynaptic (beta-neurotoxins) or postsynaptic (alpha-neurotoxins) neuromuscular blocking agents; most neurotoxic venoms contain toxins that affect both the pre- and postsynaptic neuron. Presynaptic or beta-neurotoxins have been isolated from members of the Elapidae and Viperidae (including Crotalidae) families. Most of these toxins inhibit neurotransmitter (acetylcholine) release although a small number have been identified that actually enhance neurotransmitter release. Postsynaptic or alpha-neurotoxins result in a curare-like syndrome by binding acetylcholine receptors on the postsynaptic membrane or interfering with acetylcholine interaction with its postsynaptic receptors. The degree of inhibition is related to the number of receptors occupied by toxin molecules. Most of these toxins bind irreversibly to the acetylcholine (ACh) receptor although treatment with antivenin seems to accelerate toxin–receptor dissociation.

A unique syndrome resulting in myokymia (spontaneous undulating fine contractions of multiple individual motor units) has been identified with venom from timber rattlesnakes (*Crotalus horridus*). Primarily neurotoxic snake bites result in much less local tissue inflammation and pain than their necrogenic counterparts. Large necrosing wounds are uncommon in these cases.

Epidemiology

Of the approximately 2300 species of snakes worldwide, about 420 are venomous. Venomous species can be found on every continent except Antarctica, with members of the Viperidae family found throughout the world. In North, Central, and South America, the Viperidae family is represented primarily by the pit vipers (Crotalidae) and is responsible for the majority of veterinary envenomations. The true incidence of veterinary patients bitten by snakes every year is unknown but it is estimated to be between 150 000 and 300 000. Animals that are most at risk are those that live in a rural or semi-rural environment although dogs that are taken on walks in wilderness areas are also at high risk, especially if allowed off leash. There is a strong seasonal influence on the incidence of snake bites, with the majority of bites occurring in the spring and summer months.

The severity of a bite depends on several variables, including the time that has elapsed since the snake's last meal (it takes approximately 20 days for pit vipers to replenish venom stores), the motivation of the snake (defensive or offensive), and its age. Bites from immature snakes in the spring months are often more severe than bites that occur later in the season since juvenile pit vipers have not developed the ability to control the amount of venom that is injected with each strike but rather deliver an "all or nothing" bite. Therefore, somewhat counterintuitively, it is arguably better for an animal to be bitten by a large adult pit viper than a juvenile. The metabolic demands required to synthesize venom are quite high so adult snakes will often deliver an initial "dry bite" (a bite containing no venom) as an attempt to deter a pet from further harassing them. Subsequent defensive strikes, however, are often very severe as the snake continues to feel threatened and is committed to finally deterring its assailant.

The most common location of bite wounds is the head (79%) followed by extremities (16%) while bites to the torso account for less than 2% of confirmed snake bites. Additionally, single bites are much more common than multiple bites, with multiple bites occurring approximately 15–30% of the time. The small puncture wounds typical of snake bites are often difficult to locate and can be easily overlooked, especially if no surrounding local tissue reaction is present. Only 20–25% of known rattlesnake bites are actually envenomating.

Cats appear to be inherently more resistant to pit viper venom than dogs. However, when cats do present for veterinary care, their clinical condition is generally more advanced. This may be due to cats' habit of hiding and avoiding human contact following a snake bite compared to dogs who are more likely to seek human interaction. Cats' smaller body size and inclination to "toy" with possible prey may also be contributing factors to explain these findings.

The species of snake is known in less than 50% of cases although this can often be inferred based on the known ranges of different species. Owners should be discouraged from attempting to identify the snake due to the danger that is posed with handling a live or very recently dead snake. Envenomating bites can occur from recently dead or decapitated snakes. These agonal bites typically inject the entire volume of the venom gland, making them very severe.

Coral snake envenomations are relatively uncommon in the United States and are most likely to occur in the southeastern US and Gulf Coast region. The infrequency of bites is due to the reclusive nature and physical limitations of the snake. North American coral snakes are small in size and have small fixed fangs that are incapable of penetrating thick undercoats. Coral snakes depend on venom being introduced through a chewing motion rather than being injected. This requires the snake to be attached to the victim for some time to allow sufficient venom delivery. Dogs may even present to a veterinarian with the snake still maintaining its grip on the victim.

Due to the rural location in which bites often occur and the relative proximity or distance to veterinary care, the time from bite to veterinary care is highly variable but is usually within the first 2–3 hours.

Signalment

Young dogs of both sexes are equally at risk of being bitten by a snake. Although a clear breed predilection has not been identified, the sporting and working breeds appear to be overrepresented. Any dog or cat that spends time outdoors, especially if off leash or unsupervised in a rural or semirural environment, is at risk for being bitten by a snake.

History and Clinical Signs

Pets that have been bitten by snakes will have a very short pertinent history that may include known exposure to snakes. Owners will often report the presence of a swelling on the face or limbs that seems to be getting worse rapidly. The pet will be exhibiting signs of pain and may be either seeking or eschewing attention. Snakes are reclusive animals and owners frequently do not see them interact with their pet, making observation of a strike uncommon. When presented with a patient that has clinical signs consistent with snake bite, the veterinarian should question the owner about observed snake activity and possible exposure. Signs of snake envenomation almost always occur within the first four hours but may be delayed up to 24 hours, making the possibility of determining when snake bite could have occurred relatively easy.

Patients with necrogenic snakebites will exhibit swelling or erythema around the puncture wounds. Localized swelling is present in approximately 90–95% of cases at the time of initial examination. If the patient is presented very early following the bite then outward clinical signs can be initially very mild and may easily be overlooked but signs reliably appear within 30 minutes from the time of bite. When evaluated early, these patients can be mistaken as having a hypersensitivity reaction as is commonly seen with Hymenoptera stings. If the owner cannot provide a history that supports a diagnosis of snake bite, these patients may initially be incorrectly treated for hypersensitivity reactions. A distinguishing feature of snake bite is significant pain associated with the swelling whereas severe pain is generally absent in hypersensitivity reactions. Petechiae may be seen at presentation about 20% of the time.

Diagnosis

The diagnosis of snake bite is usually suspected based on a history of snake interaction observed or suspected by the owner. Confirmation of the diagnosis is achieved through examination of the patient with the presence of characteristic puncture wounds and local, progressive lymphedema.

Initial biochemical laboratory evaluation is usually normal although creatine kinase (CK) and aspartate aminotransferase(AST) may be elevated secondary to muscular injury. Complete blood count may reveal thrombocytopenia. When present, thrombocytopenia is generally moderate (135 000–160 000 platelets/μL). Mild to moderate leukocytosis may also be present during the initial evaluation. Pit viper envenomation has been shown to cause echinocytosis and a blood film revealing significant echinocytosis is supportive of a diagnosis of envenomation. Coagulation assays performed at the time of hospitalization may reveal prolongation of prothrombin time (PT), partial thromboplastin time (PTT) or activated clotting time (ACT). When present, the prototypical venom-induced coagulopathy is defined by low fibrinogen and platelet counts, increased fibrin split products (FSP), normal D-dimer concentration, and prolonged PT and PTT. This characteristic coagulation profile is due to the defibrination of plasma without overt coagulation resulting in failure of D-dimer concentration to become elevated. Clinically, D-dimer levels are often mildly elevated, most likely reflecting systemic inflammation and clot formation at the site of the bite wound. Recently, thromboelastography has been used to evaluate dogs with snake bite and may prove a useful adjunct for both diagnosis and prognosis.

Although uncommon, snake venom is capable of causing cardiac arrhythmias. Routine monitoring of electrocardiographs (ECGs) is probably not necessary but any animal that has tachycardia and/or an audible irregularity should have an ECG performed to evaluate for the presence of potentially malignant arrhythmias. While not specific, the presence of an arrhythmia in a patient exhibiting signs of snake bite may support the diagnosis.

Diagnosing coral snake envenomation is complicated by the lack of local tissue reaction and the fact that signs may not develop for up to 12 hours following envenomation. Any patient exhibiting signs of a rapidly progressive ascending paralysis in coral snake endemic areas should be considered at risk and be treated appropriately. Owners may not be as aware of coral snake exposure due to the smaller size of the snakes and the lack of a warning system such as a rattle.

Therapy

First Aid

Appropriate veterinary care should not be delayed to allow first aid measures to be performed. First aid for snake bites has a long and storied past, including lancing and suctioning the wound, placing tourniquets, ice packing, warm packing, and administering electroshock, among other techniques. To date, none of these measures has demonstrated any improvement in outcome; in fact, some can significantly worsen the clinical course of disease. Placement of tourniquets may exacerbate the amount of tissue injury by preventing dilution of the venom as it is distributed throughout the body and prolonging the duration of time that venom is present in the affected tissue bed. Envenomation that would not otherwise induce tissue necrosis might therefore result in massive tissue loss if a tourniquet is placed inappropriately in the field. Cold packing can induce local vasoconstriction and exacerbate tissue injury through a similar mechanism. Incision and suction should never be performed. It is not likely to result in any improvement in outcome and may put the care provider at risk. The best first aid measure available is to immobilize the affected area if possible and to transport the patient to the nearest veterinary facility capable of treating snake bite. Due to the preponderance of snake bites being located on the head and muzzle of dogs and cats, immobilization is not often feasible and rapid transport is the best option.

While first aid measures in necrogenic snake bites do not include application of a tourniquet or compression bandage, coral snake envenomations do benefit from constriction. There is very little local tissue injury associated with coral snake envenomations, meaning the application of a tight compression bandage on the affected area should be performed if possible.

Antivenin Therapy

Regardless of the primary effect of the venom, the mainstay of treatment for snake bite is the administration of venom antibodies (antivenin) specific to the envenoming species if possible. Because the effectiveness of antivenin is dependent on binding circulating venom molecules, a molar dosing regimen is followed, meaning that the dose of antivenin is dependent on the volume of venom injected rather than the patient's body size. In fact, smaller animals often require higher doses of antivenin due to differences in the volume of distribution of venom in a small versus large dog. Antivenin therapy is most effective when instituted early in the disease course although it is effective as long as circulating venom is present and should be considered even many hours after an envenomation if clinical signs are severe or progressive or if a coagulopathy develops.

Unfortunately, the cost of antivenin therapy can be quite high and often results in patients receiving less antivenin than ideal circumstances would dictate. When faced with the predicament of whether or not to administer a dose of antivenin with the belief that it will not be a completely effective dose, the clinician should err on the side of treatment since binding even a portion of the free venom may improve the clinical course.

There are currently two major types of antivenin commercially available. Polyvalent whole molecule antivenin is derived from the serum of horses sensitized to several North, Central, and South American pit viper species and contains the entire IgG antibody and may contain equine albumin, depending on manufacturer. The second type of antivenin is composed of the F_{ab} portion only of an ovine- or equine-derived antibody rather than the complete immunoglobulin molecule. Whole immunoglobulin antivenin is generally less expensive and more readily available than F_{ab}-based antivenins but due to the presence of the entire IgG molecule and possibly additional foreign proteins (equine or ovine albumin), the possibility of hypersensitivity reaction is increased. Antivenins containing the smaller F_{ab} portion of the immunoglobulin molecule are less immunogenic and may be better able to diffuse into damaged tissue due to their smaller size. However, this smaller size results in a shorter elimination half-life than the larger complete molecule antivenins. This can lead to a situation in which the antivenin is eliminated more rapidly than it is capable of binding circulating venom molecules, resulting in recurrence of clinical signs. If using an F_{ab}-based antivenin, the clinician should be aware of this possibility and recognize the fact that repeated dosing may be needed every six hours to most effectively treat the patient.

While the F_{ab}-based antivenins are less immunogenic than the whole molecule formulations, both types of antivenin are capable of causing immediate and delayed immune reactions, with a reported incidence of 5–13%. Anaphylactic (type I) or anaphylactoid hypersensitivity reactions occur immediately upon administration of antivenin, are dose related and are due to either an

IgE-mediated response (type I) or direct activation of the complement cascade (anaphylactoid). Signs of anaphylactoid reactions are identical to signs of true anaphylaxis and can range from mild facial edema and pruritus to complete circulatory collapse. Premedication with antihistamines has been reported but has not been proven to be beneficial in reducing the incidence of reactions. Delayed (type III) hypersensitivity reactions have been reported up to several weeks after administration and are the result of immune complex formation and complement activation. Clinical signs associated with delayed type III hypersensitivity reactions include fever, lethargy, vasculitis, peripheral edema, and glomerulonephritis. Type III hypersensitivity reactions are generally self-limiting but can rarely be life threatening. The risk of hypersensitivity reactions, including acute anaphylactic reactions, increases in animals that have been previously treated with antivenin products.

When edema formation is severe or when the location of the bite wound is likely to result in life-threatening complications (airway obstruction), early and aggressive antivenin therapy should be instituted. Antivenin should be administered to effect until the progression of the signs abates (i.e., there is no further evidence of new edema formation, bruising has stopped spreading, and coagulopathy is controlled). Median doses of antivenin for dogs have been reported as one vial (range 1–10), and beginning with one vial given over 30 minutes is reasonable. Additional doses can be administered every 30–60 minutes as needed. It should be remembered that antivenin products have colloidal properties that can significantly expand the vascular space. Volume overload is a concern in small patients, especially those that require higher doses of antivenin.

Serial measurement of muzzle or limb circumference can help the clinician decide whether progression has in fact stopped. It is important to remember that as edema matures, it becomes gravity dependent. Recognition of edema migration rather than progression is difficult and is best achieved through good-quality serial evaluations. Cage-side rounds provide an opportunity for all staff to observe the site, decreasing interobserver variation in assessment. Similarly, maturation of bruising should not be confused with ongoing bruising. Clipping the fur from affected areas and marking the leading edge of bruising can help the clinician differentiate the two. The use of digital photography may aid the clinician in monitoring progression and can facilitate communication between team members if questions arise.

It should be emphasized that snake bite-induced coagulopathy is not identical to other types of consumptive coagulopathy, so treatments used for common coagulopathies are often ineffective if applied to snake bite coagulopathy. Because the coagulopathy observed in snake envenomation is the result of defibrination rather than disseminated coagulation, the treatment of choice is not factor replacement, at least not initially. The underlying cause of defibrination is the presence or persistence of venom components in the blood. As long as venom components are circulating, fibrin and fibrinogen will continue to be degraded and treatment with factor replacement therapy in the form of fresh frozen or frozen plasma is not expected to be beneficial. In fact, administration of plasma products in the presence of circulating venom may exacerbate coagulopathy by providing more substrate for degradation, leading to higher levels of FSP, which further inhibit coagulation. Consequently, the most vital treatment is inactivation of circulating venom components by administration of antivenin.

Even with early and aggressive antivenin therapy, bite wounds to the head can result in severe, progressive edema and swelling and may pose a threat to airways. Often, early placement of a temporary tracheostomy is beneficial. Once edema has stopped forming, it will become gravity dependent and can result in severe swelling of the ventral muzzle and neck. If the decision to perform a tracheostomy is made too late, the dissection through edematous tissue is significantly more difficult.

If open wounds develop, they should be treated like any other contaminated, large, soft tissue wound. Any areas of necrosis should be surgically debrided; the wound should be cleaned daily and protected with a sterile bandage. Consultation with a surgeon should be considered for large wounds or wounds involving the joints. Primary closure of these wounds is rarely feasible due to the large amount of tissue loss that occurs. When wounds are present on limbs, the affected limb should be immobilized in a functional position to reduce the likelihood of wound contracture resulting in decreased range of motion. Most snake bites result in venom deposition within subcutaneous tissue rather than muscle bellies, so fasciotomy is rarely needed in dogs and cats.

Antibiotic therapy for snake bite is controversial in both human and veterinary medicine. There is little evidence that prophylactic antibiotic therapy improves the clinical course or prevents wound infection. The rationale for antibiotic use is grounded in the fact that bacterial cultures of snakes' mouths document heavy pathogenic bacterial loads; however, the actual incidence of documented infection is small. Therefore, the routine use of prophylactic antibiotics is likely not necessary and the decision to treat with antibiotics is clinician dependent. If used, broad-spectrum antibiotics should be selected. Antibiotic therapy is less controversial once a necrotic wound is present. As always, antibiotic therapy should be guided by culture and sensitivity results when possible to allow for deescalation and more responsible antibiotic usage.

Analgesia is an important component of snake bite treatment and should be considered early in the treatment

course. Administration of antivenin can reduce the acute pain associated with the snake bite although antivenin alone is insufficient to provide adequate analgesia. The use of opioid analgesics has been discouraged due to the possible respiratory depressant effects of this class of drugs. However, clinically significant respiratory depression in veterinary patients is uncommon with opioid medications and should not be considered a reason for withholding their administration. Administration of bolus opioids may be insufficient to manage the severe pain associated with snake bite. Constant rate infusion (CRI) of fentanyl (3–5 µg/kg/h) or morphine (0.1–0.3 mg/kg/h) should be considered in cases of severe envenomation. As always, a multimodal approach to pain management may be more effective than reliance on a single analgesic protocol. Ketamine has good somatic analgesic properties and a CRI (5–15 µg/kg/min) can be a nice addition to the analgesic protocol for snake bite victims. Lidocaine (50 µg/kg/min) and dexmedetomidine CRI (0.7–1.5 µg/kg/h) have both been demonstrated to provide analgesia, especially when used in conjunction with opioids. The ultimate pain management strategy implemented should take patient factors such as age, conformation, location and severity of envenomation, and cardiovascular status into consideration.

Edema formation of the face can impair the pet's ability to prehend food and move the lips and tongue. Accumulation of mucus in the buccal pouch can lead to bacterial overgrowth and development of oral ulcerations. Good oral care, including rinses with water and/or antiseptic solution, should be instituted if muzzle swelling is severe.

Some components of snake venom have been demonstrated to result in mast cell degranulation. While theoretical benefits of antihistamine administration exist, the routine use of H1 and H2 blocking drugs is not currently recommended for human snake bite victims and their use in veterinary patients is up for debate.

As is often the case with corticosteroids, their use is controversial. There is little conclusive veterinary or human literature to either support or refute their use for snake bite. Due to the lack of evidence of a clear advantage to patients receiving corticosteroids and their well-documented side-effects, the routine use of corticosteroids in snake bite cannot be advocated. Administration of corticosteroids may be indicated if a patient develops signs of an acute or delayed hypersensitivity reaction to antivenin administration. Similarly, nonsteroidal antiinflammatory drugs (NSAIDs) should not be administered to snake bite victims until any venom-induced coagulopathy has been effectively managed due to the potential for NSAID-induced thrombocytopathia. Following appropriate management of coagulopathy and hemodynamic stabilization, NSAIDs may prove useful in the analgesic management of snake bite victims. Nonsteroidal antiinflammatory medications should not be administered if myoglobinuria is present.

A rattlesnake vaccine (Red Rock Biologics, Woodland, CA) is commercially available in the United States for use against western diamondback rattlesnakes (*C. atrox*). There are currently no peer-reviewed studies evaluating the clinical efficacy of vaccination in mitigating signs and none are likely to be performed due to the high incidence of dry bites and variability in venom dose between patients. In fact, owners who have had their pets vaccinated may have a false sense of security when it comes to snake bite and may be slower to seek veterinary care. For this reason, it is not recommended to vaccinate for snake bite. Aversion training is available but is also considered unreliable as this too may result in a false sense of security when in snake habitats.

Prognosis

Fatality associated with snake bite injury is generally uncommon although these patients experience significant morbidity. Reported mortality rates range from 4% to 20% and are correlated with antivenin treatment. Despite the overall favorable prognosis for survival from snake bite, many pets are euthanized due to the financial burden associated with hospitalization and antivenin therapy, which can easily reach several thousand dollars.

The prognosis is directly dependent on the severity of the envenomation and the treatment received. Progression of envenomation is subjective and can be difficult to assess. One tool that can be utilized is the assignment of a snake bite severity score (SSS) at the time of admission and then every 4–6 hours for the first 24 hours (Box 47.1). The SSS assigns a numerical value ranging from 0 to 4 in six categories, with a total possible score ranging from 0 to 20, with more severe bites having higher scores. While the SSS has not been validated in dogs and cannot be used to assess a particular patient's risk for death, it aids the clinician in evaluating progression by assigning value to objective findings.

The prognosis for patients exhibiting signs of neurotoxicity secondary to envenomation is less clear. The severity of signs depends on the volume of venom introduced through the bite. Because of the limited local tissue reaction associated with coral snake bites, the severity of envenomation may not be readily apparent at the time of presentation. If patients develop severe clinical signs then the prognosis is guarded to poor if mechanical ventilation is not available. Commercially available coral snake antivenin is difficult to obtain but has proven useful for treatment of elapid envenomation in the US. Fortunately the majority of coral snake bites are nonenvenomating (a consequence of the snake's primitive venom delivery system).

Box 47.1 Snake bite severity score

Pulmonary system

Signs within normal limits	0
Minimal – slight tachypnea	1
Moderate – respiratory compromise, tachypnea, use of accessory muscles	2
Severe – cyanosis, dyspnea, extreme tachypnea, respiratory insufficiency or respiratory arrest from any cause	3

Cardiovascular system

Signs within normal limits	0
Minimal – tachycardia, general weakness, benign dysrhythmia, hypertension	1
Moderate – tachycardia, hypotension	2
Severe – marked tachycardia, hypotension (systolic <80 mmHg), malignant dysrhythmia or cardiac arrest	3

Local wound

Signs within normal limits	0
Minimal – pain, swelling, ecchymosis, erythema limited to bite site	1
Moderate – pain, swelling, ecchymosis, erythema less than half of extremity	2
Severe – pain, swelling, ecchymosis, erythema more than half of extremity, rapid spread	3
Very severe – pain, swelling, ecchymosis, erythema beyond affected extremity, significant tissue slough	4

Gastrointestinal system

Signs within normal limits	0
Minimal – abdominal pain, tenesmus	1
Moderate – vomiting, diarrhea	2
Severe – repetitive vomiting, diarrhea, or hematemesis	3

Hematologic system

Within normal limits	0
Minimal – coagulation parameters slightly abnormal, platelets 100 000–150 000/mm^3	1
Moderate – coagulation parameters abnormal, platelets 50 000–100 000/mm^3	2
Severe – coagulation parameters markedly abnormal, platelets 20 000–50 000/mm^3	3
Very severe – coagulation parameters markedly abnormal with bleeding present or threat of spontaneous bleeding, platelets <20 000/mm^3	4

Central nervous system

Signs within normal limits	0
Minimal – apprehension	1
Moderate – chills, weakness, faintness, ataxia	2
Severe – lethargy, seizures, coma	3

Source: Adapted from Peterson *et al.* (2011).

Conclusion

The only proven effective treatment for snake bites is the early administration of antivenin therapy. When patients are presented very early following a bite, the clinical signs may be very mild. The astute clinician will recognize the risk of rapid progression of signs and will be prepared to intervene early and appropriately. Ultimately, the best treatment for snake bite is prevention. Veterinarians should have frank discussions with owners of at-risk pets about the need for leashing at all times when in snake habitat.

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Section 6

Gastrointestinal Disease

48

Gastrointestinal Imaging

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General Imaging Principles

Medical imaging is an important element of the clinical work-up of a patient with gastrointestinal disease. Plain radiography is commonly used to evaluate patients with suspected gastrointestinal disease, but plain radiography can often be unremarkable and abdominal ultrasonography or cross-sectional imaging techniques such as contrast-enhanced abdominal computed tomography might be required to further evaluate the etiology of the disease.

Plain Radiography

Plain radiography is a widely available imaging technique and in many cases, it is the principal method used to evaluate the abdomen. Numerous studies have evaluated the usefulness of this technique in cats and dogs with suspected lesions of the oral cavity, esophagus, and gastrointestinal tract, in patients with acute abdominal signs, gastrointestinal foreign bodies, and small intestinal obstructive disease. However, in the past decade, abdominal ultrasound and more recently contrast-enhanced computed tomography have become major imaging modalities in patients with acute or chronic gastrointestinal signs. When abdominal radiographs are obtained, they often are used as a screening test. Abdominal radiographs have demonstrated the greatest value in patients in whom intestinal obstruction and/or perforation and urinary calculi are suspected. Therefore, the major value of abdominal radiographs is to exclude intestinal obstruction or free air in the peritoneal cavity secondary to perforation of a hollow organ such as the gastrointestinal tract. Despite advances in other imaging modalities, plain radiography remains the first modality of choice in patients with suspected gastrointestinal perforation. Additionally, abdominal radiographs are often used to evaluate tube or drain placement.

The most commonly used views are ventrodorsal (VD) and right and/or left lateral recumbent views. The VD view is usually preferred over the dorsoventral (DV) view as it is easier to position the abdomen close to and aligned with the cassette than in a DV view. There are slight differences in the radiographic appearance between right and left lateral recumbent views, which mainly include the change of position of mobile viscera and of the gas and fluid in the gastrointestinal tract due to the effect of gravity. Additional views, dependent on the clinical question asked, may include DV for evaluation of gas, contrast agent or foreign material in the stomach. Lateral or VD views with a horizontal beam are occasionally used to evaluate for the presence of gas/air in the peritoneal cavity.

Imaging Contrast Agents and Pharmacoradiology

Contrast radiography or computed tomography are both valuable imaging techniques, often providing additional information in the management of patients with gastrointestinal signs. Typically, the greatest value is in patients where radiographic and clinical signs suggesting gastrointestinal obstruction are equivocal. Contrast imaging may help to identify the extent and cause of gastrointestinal obstruction. Contrast agents currently used for gastrointestinal imaging can be classified into three groups: (1) intraluminal contrast agents for gastrointestinal tract studies; (2) intravascular contrast agents for computed tomography (CT) and angiography; (3) contrast agents for magnetic resonance tomography (MRI). These various types of contrast agents are discussed separately in the following sections.

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Intraluminal Contrast Agents

Barium Sulfate

Barium sulfate suspension is the most commonly used contrast agent for gastrointestinal radiographic studies in veterinary medicine. Barium sulfate is a white crystalline powder, which is inert and does not support bacterial growth. Coating of the mucosa of the gastrointestinal tract or opacification of the lumen of the gastrointestinal tract can require different barium formulations. Throughout the gastrointestinal tract, the pH, type, and amount of mucus and type of mucosa vary and therefore optimal coating in one segment does not necessarily result in optimal coating in another segment.

Aspiration of small amounts of barium formulations is of very little clinical significance. Barium within the trachea and main bronchi is usually cleared within 30 minutes. If barium aspiration is more extensive, it is retained within the interstitium of the lungs and a very slow decrease of barium in the lungs might be noted over several months to years (Figure 48.1). If diffuse extensive alveolar infiltration of barium occurs throughout the lungs, though, this can lead to death of the patient. Therefore, if major concerns for aspiration exist before the study, nonionic iodinated contrast agents should be considered.

Hypersensitivity reactions to barium have not been reported in veterinary medicine, but have been reported rarely in human medicine.

Barium leakage into the peritoneal cavity can occur due to a preexisting perforation of the gastrointestinal tract or secondary to a procedure such as a barium enema. In veterinary medicine, it is commonly accepted that the suspicion of gastrointestinal perforation is a contraindication for barium studies in patients. Most of our knowledge regarding barium peritonitis is from human medicine but the small number of reported reactions in small animals seem to be similar. If large amounts of barium are spilled into the peritoneal cavity, profound hypovolemia can develop secondary to exudation of large quantities of fluid associated with the chemical peritonitis. Furthermore, bacterial contamination may lead to sepsis and shock within hours. If a barium leakage occurs, immediate treatment should be started, including intravenous fluid therapy and antibiotic administration due to the commonly associated bacterial contamination. Once the patient is stabilized, abdominal surgery is commonly performed. However, barium can be difficult to remove surgically as new barium formulations can adhere strongly to the peritoneum.

Negative Contrast Agents

Air is one of the cheapest contrast agents for gastrointestinal studies. In veterinary patients, it is most commonly used to outline the colon, especially in patients where a small intestinal foreign body is suspected. Another application is in double contrast studies of the gastrointestinal tract; the most common application of this technique is in evaluating the stomach for the presence of a foreign body or to identify the location of the colon and differentiate the colon from small intestine in cases of intestinal obstruction.

Iodinated Contrast Agents

Water-soluble, iodine-containing contrast agents are most commonly used for gastrointestinal imaging when esophageal or gastrointestinal perforations are suspected. However, the role of water-soluble iodinated contrast agents and the merit of these compounds for

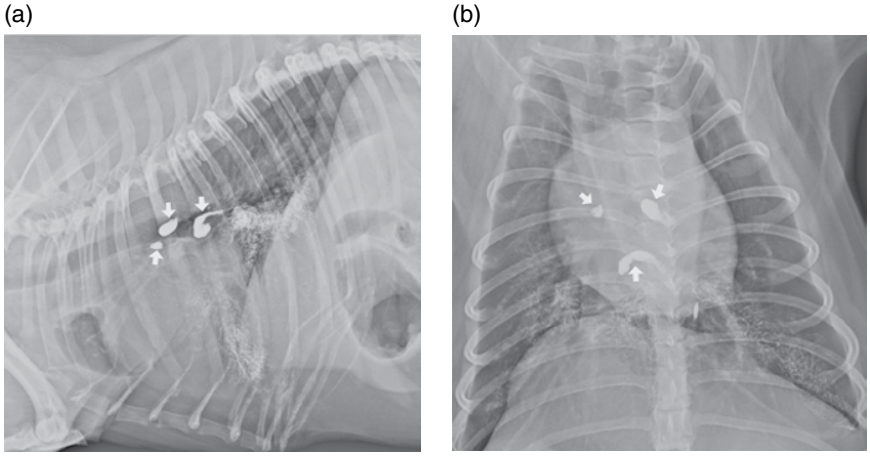


Figure 48.1 Left lateral (a) and ventrodorsal (b) radiographs of the thorax of a dog illustrating a previous aspiration of barium contrast agent, which occurred during a contrast radiographic study performed six years before. The barium is persistently present in the parenchyma of the right and left caudal as well as accessory lung lobes. Barium has localized to the tracheobronchial lymph nodes (*arrows*), which has no clinical significance.

general imaging of the gastrointestinal tract are areas of controversy. Water-soluble iodinated contrast agents do not coat the gastrointestinal mucosa. The most commonly used iodinated contrast agents formulated for the gastrointestinal tract are hypertonic and therefore pull fluids into the intestinal tract, resulting in distension of the intestinal lumen and better definition of the intestinal walls. The hypertonicity and fluid pull into the gastrointestinal tract can result in diarrhea and dehydration. If the contrast agent is aspirated or enters the lungs through a fistulous tract from the esophagus, severe pulmonary edema can result. If a perforation into the pleura or lungs is suspected, nonionic iodinated contrast agents can be used and are reported to be safer than ionic iodinated contrast agents.

Intravascular Contrast Agents

All currently used contrast agents used for vascular enhancement (except agents used for MRI) utilize iodine for X-ray absorption. Currently, the dominant areas for use of intravascular contrast agents are CT and MRI. No routine techniques have been described for evaluation of the gastrointestinal tract using radiography and intravascular contrast agents. Significant improvements in the composition of intravascular contrast agents have been made in the past decades, making them safer to use and better tolerated. As sodium iodide is toxic, it must be delivered in a molecule structure that is safe to use. The closer the osmolarity of the contrast agent is to water, the lower the toxicity of the contrast agent. When iodinated contrast agents are used, the patient should always be well hydrated as iodinated contrast agents can cause renal toxicity. Adverse reactions to intravenous iodinated contrast agents are rare in veterinary patients, but can range from anaphylactic shock to local reactions.

Ultrasonography

Ultrasonographic examination is one of the most useful techniques for evaluating the gastrointestinal tract in most veterinary patients. Ultrasound of the gastrointestinal tract is not only used to make an initial diagnosis, but also to monitor response to treatment or disease progression. Ultrasound can be used to evaluate superficial aspects of the esophagus in the cervical area and in the abdomen to evaluate the stomach to descending colon. Superficial structures are better evaluated with a high-frequency ultrasound probe, whereas deeper structures may require the use of low-frequency probes. Higher-frequency ultrasound probes have less tissue penetration but provide a better resolution of intestinal structures, including wall layering, compared to low-frequency ultrasound probes.

Ultrasound of the gastrointestinal tract provides information about the gastrointestinal wall and peristalsis of the gastrointestinal tract, which is information currently not provided by any other diagnostic technique, including radiography (plain and using oral or gastric contrast agents), CT, and endoscopy. One of the biggest limitations of the use of ultrasound when evaluating the gastrointestinal tract is its inability to penetrate air-filled structures, which can include air in the peritoneal cavity secondary to a perforation or recent surgical procedure or luminal air in the gastrointestinal tract. However, this limitation can often be overcome by repositioning the patient or ultrasound probe relative to the air-filled viscera or peritoneal air.

The ultrasound examination of the abdomen in the dog and cat is commonly performed in lateral or dorsal recumbency. Usually, the ultrasound exam is started cranial in the abdomen for evaluation of the gastrointestinal tract or other abdominal disease and then progresses caudally, usually in the anatomic order of the gastrointestinal tract.

Computed Tomography of the Gastrointestinal Tract

In small animals and humans, CT is used extensively to evaluate the abdomen, but veterinary reports of its use to evaluate the intestines, especially the intestinal wall, are rare. Gastrointestinal CT has been used in veterinary patients to diagnose intraluminal gastrointestinal foreign bodies. However, no significant improvement in sensitivity and specificity was reported in comparison to plain film radiography. Future veterinary applications using gastrointestinal CT are likely to develop, particularly with the advent of new multidetector row helical CT (MDCT) scanners. Faster scan times and greater spatial resolution are achievable with these new scanners, allowing for high-resolution multiphasic and multiplanar evaluation of the gastrointestinal tract, gastrointestinal wall, and lumen.

In human medicine, CT enterography and enteroclysis, in which oral contrast is used to distend and illuminate the gastrointestinal wall, are extensively used to evaluate the gastrointestinal tract as they allow evaluation of extraluminal pathology in addition to luminal disease. They are regularly used in the diagnosis and treatment of inflammatory bowel disease, to assess the severity and extent of disease, as well as inflammatory activity. CT without luminal contrast has successfully been used in dogs and cats to evaluate the anatomy of the gastrointestinal tract, to assess segments of the gastrointestinal tract for the presence of intraluminal or wall lesions, and to measure the intestinal width. The use of gastrointestinal CT examination to evaluate for foreign

bodies and obstructive intestinal disease in small animals has not been shown to have statistically significant increased sensitivity or specificity compared to plain radiography. In gastrointestinal CT without the use of intraluminal contrast agents, the lack of distension of the small intestine hinders evaluation of the intestinal wall throughout the entire gastrointestinal tract.

In human medicine, it has been well demonstrated that a critical technical requirement for CT of the bowel is full distension of a clear lumen with complete separation of the intestinal walls. In CT enterography, combinations of positive and neutral attenuation oral contrast agents are used, which allow distension of the intestinal tract and outlining of the wall. Conventional positive attenuation oral contrast media such as barium- or iodine-based agents are used for evaluation of the gastrointestinal tract similarly to their use in radiography or fluoroscopy (Figure 48.2). Conventional positive attenuation oral contrast agents allow visualization of the mucosal detail and assessment of mucosal enhancement. Neutral oral contrast agents, which are more commonly used in human medicine, have an attenuation close to water and are mainly used to distend the small intestinal tract and therefore better outline the intestinal walls, allowing for better evaluation for mural lesions. Commonly used neutral attenuation luminal contrast agents include water, milk, polyethylene glycol, 12.5% corn-oil emulsion, and methylcellulose.

Magnetic Resonance Imaging of the Gastrointestinal Tract

Magnetic resonance imaging is rarely used for evaluation of the gastrointestinal tract in human and veterinary patients. In human patients, new MRI applications for imaging of the colon are being developed. The most common use of MRI related to digestive disease in veterinary patients involves imaging of the oral cavity or cranial neck in patients where abscesses secondary to perforating injuries or foreign bodies are suspected.

Gastrointestinal Scintigraphy

Ultrasound and contrast radiography continue to be the most common imaging techniques used for the gastrointestinal tract. However, contrast radiography, similarly to contrast-enhanced CT, provides only very limited or no information about esophageal or gastrointestinal motility. It has been suggested that esophageal scintigraphy might provide valuable information in gastroesophageal

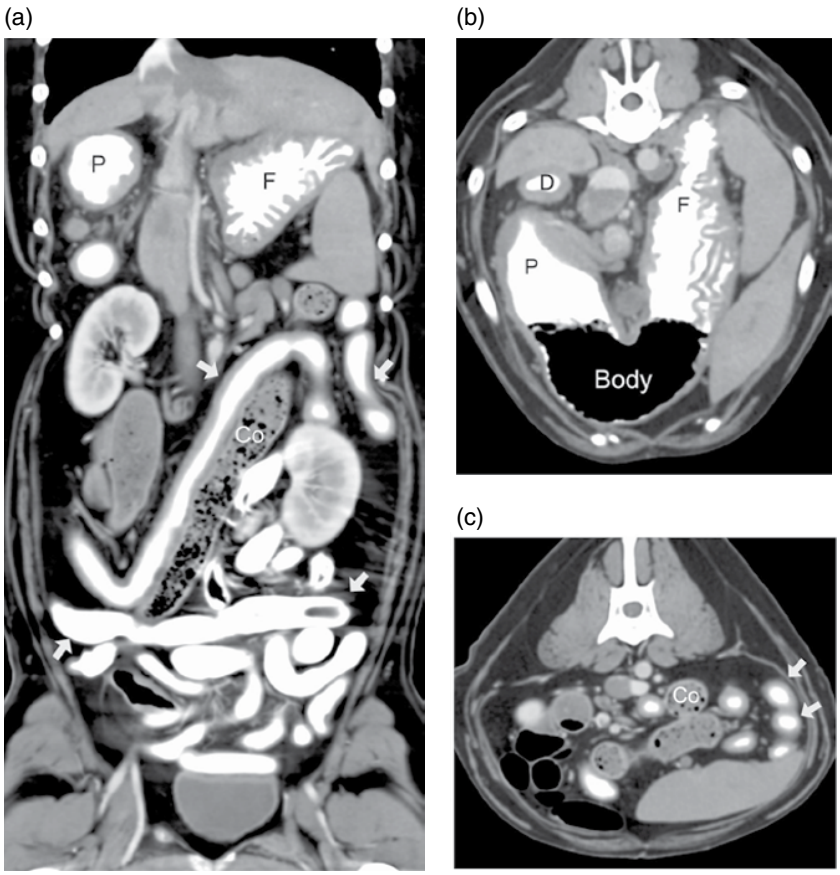


Figure 48.2 Dorsally reconstructed CT enterography image (a) and corresponding transverse CT images at the level of the stomach (b) and midabdomen (c). Iodinated contrast agent is noted in the stomach and small intestinal tract (*arrows*). The pylorus (P) and fundus (F) of the stomach are fluid filled and the gastric body is gas filled as the patient was scanned in dorsal recumbency. No contrast agent filling is noted in the colon (Co).

reflux patients. Scintigraphy is considered to be the gold standard for noninvasive evaluation of gastric emptying and intestinal transit times. Gastric emptying is evaluated by providing the animal with a standardized radiolabeled food and carrying out repeated nuclear imaging of the patient at defined intervals and in various positions for 4–6 hours. The variability of gastrointestinal transit times in dogs is very high, however, which limits the application of scintigraphy for clinical use.

Scintigraphy may have a use in clinical patients, if serial studies are done so that progression or response to treatment can be followed. However, in addition to the high variability of the gastrointestinal transit times, the lack of access to scintigraphy equipment and the need for the use of radiopharmaceuticals, which requires radiation safety precautions, limit the use of this technique in the daily clinical work-up of gastrointestinal disease.

The Pharynx

Normal Anatomy and Examination Technique

The pharynx is at a three-way crossroads of respiration, swallowing, and vocalization. The pharynx is located caudal to the oral and nasal cavities and cranial to the esophagus; this region allows transport of food from the mouth to the esophagus. During respiration, the pharynx allows the passage of air from the nasopharynx to the larynx. During vocalization, the pharynx functions as a resonating chamber and can alter sounds. Disorders of the pharynx may therefore result in dysfunction of swallowing, respiration or vocalization. Patients may therefore present with signs of dysphagia, choking, gagging and retching, or voice changes and the generation of unusual sounds.

Structural abnormalities of the pharynx are rare. The most commonly reported congenital abnormality of the pharynx is an elongated soft palate. Rarely, unilateral or bilateral hypoplasia or aplasia of the soft palate or midline clefts have been reported. Even less commonly, nasopharyngeal or intrapharyngeal stenosis has been described.

Head and neck survey radiographs are often a first step to evaluate for problems in the oropharyngeal phase of digestion. The most common radiographic views include a lateral and DV or VD view of the head and neck. In the VD and DV view, the pharyngeal and cricopharyngeal structures can be difficult to evaluate due to the complexity of the anatomy and the summation with adjacent skeletal and soft tissue structures. Survey radiographs are evaluated for the presence of anatomic abnormalities, including clefts, fractures of the adjacent osseous structures including the hyoid apparatus and abnormalities or fractures of the temporomandibular joints. With a cleft palate, an abnormal connection between the oral and nasal cavity exists, allowing food to enter the nasal cavity from the oral cavity. Radiographically, lack of air filling of the nasal cavity and abnormal content within the nasal cavity may be noted. Neuropathies are less commonly encountered reasons for oropharyngeal dysphagia. Survey radiographs mainly provide morphometric information in neuropathy patients, as there is often no anatomic abnormality present. Although survey radiographs followed by contrast radiographs with barium administration can provide valuable information, fluoroscopy is often needed to identify functional abnormalities.

Commonly, contrast imaging for pharyngeal motility studies is performed by administering liquid barium sulfate contrast agent; this should always be followed by administration of a mixture of solid food coated with barium sulfate. Patients may exhibit more signs when swallowing liquid or solid material and therefore both aspects should be evaluated. Additionally, thoracic radiographs should be considered, as secondary lung disease might be present.

Ultrasound Examination of the Pharynx

Ultrasound is infrequently used to evaluate the pharyngeal area as the summation with surrounding air-filled and osseous structures limits the evaluation of this region. Ultrasound has shown value if perforating injuries by plant material are present and can help to identify penetrating foreign bodies and assist in surgical interventions.

Assessment of Pharyngeal Function

Dysphagia is a nonspecific term and mainly describes abnormal swallowing. Common clinical signs include regurgitation, recurrent respiratory disease or weight loss. Dysphagia can result from functional or anatomic lesions, which can be intrinsic to the alimentary tract or extrinsic from adjacent structures causing compression of the alimentary tract. Dysphagia can involve any or all of the structures involved in swallowing, including the tongue, hyoid apparatus, soft palate, pharyngeal muscle, cranial esophageal sphincter, esophagus, and caudal esophageal sphincter. Various classifications of dysphagia have been made. Typically, dysphagia will be classified based on the location of the swallowing impairment as oropharyngeal, esophageal, or gastroesophageal.

Oropharyngeal dysphagia can occur in any of three different phases of swallowing: oral, pharyngeal, or cricopharyngeal. Dogs with disturbances in the oral phase of swallowing usually have difficulty with prehension of food and moving the bolus to the caudal aspect of the tongue. The main indications for radiography in cases of

suspected oropharyngeal dysfunction include screening for anatomic, mechanically obstructive lesions, particularly if there is a history of trauma or concern for a neoplastic lesion. In the early stages of the disease, oral neoplasms rarely cause swallowing disorders. When swallowing disorders are noted secondary to neoplasia, the disease process is typically very advanced.

In routine barium swallow studies, contrast medium may be noted in the dependent buccal fold, oral cavity, and valleculae. No contrast should be noted in the pharynx, cranial esophageal sphincter, and esophagus.

Pharyngeal phase dysphagia is associated with inadequate peristalsis, leading to retention of the contrast agent bolus in the oral cavity and reflux into the nasopharynx, oral cavity, and potentially the larynx.

With cricopharyngeal dysphagia, discoordination of the motor activity of the pharynx, cricopharyngeus muscle, and upper esophageal sphincter occurs. Cricopharyngeal achalasia refers to a lack of opening of the cricopharyngeal sphincter; radiographically, the passage of contrast agent is impeded and contrast agent can reflux into the nasopharynx, larynx, oropharynx, and piriform recesses.

Cricopharyngeal chalasia is a failure to close the cricopharyngeal sphincter. Radiographically, this is seen as a persistent passage of contrast agent between the pharynx and cranial esophageal sphincter. Additional reflux of contrast agent is typically noted, including into the piriform recesses. Pharyngeal and cricopharyngeal dysphagia show similar patterns of retention of contrast agent. If pharyngeal dysfunction is suspected, it is important to evaluate the swallowing of liquid and solid material.

Esophageal dysphagia causes a problem in transport of food through the body of the esophagus. Gastroesophageal dysphagia occurs secondary to a functional abnormality, which includes a motility disturbance or an obstructive process.

The Esophagus

The esophagus is a muscular tube that extends from the cricopharyngeus muscle at the level of the cricoid cartilage to the stomach. The largest aspect of the esophagus is located within the middle mediastinum. The normal esophagus is usually not visualized radiographically; occasionally a normal esophagus can be visualized due to small quantities of air present in the esophageal lumen secondary to swallowing of air. A normal esophagus might also be visualized if air is present in the mediastinum (pneumomediastinum). The normal esophagus may also be dilated during or immediately following general anesthesia; repeat radiographs can be necessary, with the patient awake, to exclude esophageal disease. The normal esophageal wall consists of four layers: mucosa, submucosa, muscularis, and serosa. In the dog, the entire musculature of the esophagus is striated. In the cat, the caudal third of the esophagus, caudal to the heart base, is smooth muscle. This causes obliquely directed folding of the overlying mucosa of the esophagus, resulting in a characteristic herringbone pattern noted during contrast imaging studies of the esophagus in cats.

The most common indications for radiography of the esophagus include a history of regurgitation and dysphagia, recurrent unexplained respiratory illness, ptyalism, gagging, change in attitude often associated with feeding, or cervical pain and swelling. The most common reasons for further imaging of the esophagus after survey radiographs include generalized dilation (megaesophagus), localized dilation, suspected esophagitis, esophageal foreign body or masses, and esophageal perforation. It is important to remember that failure to visualize the esophagus on plain radiographs does not exclude the presence of esophageal disease. An early sign of esophageal disease might include the retention of air in the esophagus noted on survey radiographs. This might warrant further evaluation of the esophagus, which can include an upper gastrointestinal tract radiography or endoscopy.

Upper Gastrointestinal Tract Radiography (Esophagram)

An exhaustive examination of the esophagus includes contrast radiographic examination as well as fluoroscopic evaluation of the motility of the esophagus. Contrast radiography of the esophagus requires no special preparation; however, plain radiographs should always be obtained prior to administration of contrast agent to outline abnormalities of the esophagus. It is important to include the entire esophagus in the study, from the pharyngeal area to the stomach.

The normal esophagus is collapsed after a primary peristaltic wave and contrast studies should therefore be performed with a reasonable amount of oral contrast agent to ensure adequate coating and distension of the esophagus for evaluation. Barium sulfate suspensions or paste are usually administered at a dosage of 2–6 mL/kg bodyweight. It is important to give a large enough bolus (usually 5–20 mL of contrast agent) to ensure complete swallowing. Smaller sized boluses may not stimulate a strong primary esophageal peristalsis sufficient to clear the contrast agent from the esophagus. Therefore, at least medium-sized fluid or solid boluses are recommended for evaluation of swallowing and the esophagus. The high-density, low-viscosity barium formulations designed for the stomach and small intestinal tract also coat the esophagus well. If, however, inadequate coating

of the esophagus results, barium paste should be used to enhance coating of the mucosa.

Double contrast esophagus studies are commonly performed in human patients but are rarely used in veterinary medicine. In some patients, where air is present in the dilated esophagus, it functions as an endogenous negative contrast agent and no additional contrast medium may be needed. If barium sulfate suspension is used for the esophagram, no contrast should be remaining in the esophagus in approximately 5 minutes; if barium paste is used, all contrast agent should be cleared from the esophagus by approximately 30 minutes. In general, in the normal esophagus, no contrast agent should be stored or remain after a contrast agent study has been performed.

In patients with suspected esophageal perforation, water-soluble contrast solutions should be used for evaluation of potential leakage from the esophagus. However, water-soluble iodine solution contrast agents should be used with great care for an esophagram, as ionic iodinated contrast agents are hypertonic and, when aspirated, will most likely cause severe pulmonary edema. If a bronchoesophageal fistula is suspected, nonionic iodinated contrast solutions should be used to reduce the risk of iatrogenic pulmonary edema. Water-soluble contrast agents for outlining the esophagus are usually administered at a dosage of 2–3 mL/kg bodyweight to achieve approximately 700 mg iodine per kg bodyweight and adequate distension of the esophagus. However, if no contrast leakage is identified, a repeat study with a higher density barium suspension can be performed to allow visualization of a smaller sized lesion that was potentially missed using a water-soluble contrast agent. It has been noted in studies in humans as well as experimentally in rats that no significant mediastinitis was identified post barium leakage through a very small esophageal defect, nor was a significant interference with subsequent radiographic evaluations noted. It has been recommended to warm up the barium solution to 40 °C when a perforation is suspected, as this decreases the viscosity of the barium sulfate solution without decreasing the radiopacity and increases the sensitivity of detecting smaller sites of leakage in the esophagus.

Generalized Esophageal Dilation (Megaesophagus)

Megaesophagus is a disorder caused by diminished esophageal tone and hypomotility, causing generalized dilation of the esophagus. Congenital and acquired forms of megaesophagus are recognized in the dog and cat. The underlying cause of congenital megaesophagus remains unknown, but inadequate development of the esophageal innervation or altered biochemical properties of the esophagus have been discussed.

Survey radiographs are often diagnostic for a dilated esophagus, when the esophagus contains food, water or air (Figure 48.3).

On lateral radiographs, the dilated esophagus is usually well demarcated dorsally by the longus colli muscle or summating within the thoracic vertebrae and ventrally summating with the dorsal aspect of the trachea, leaving the impression of a dorsally thickened trachea wall (the tracheal stripe sign; Figure 48.4). It is important not to confuse the tracheal stripe sign with pneumomediastinum, where the esophagus is circumferentially surrounded by air. In severe esophageal dilation, a ventral

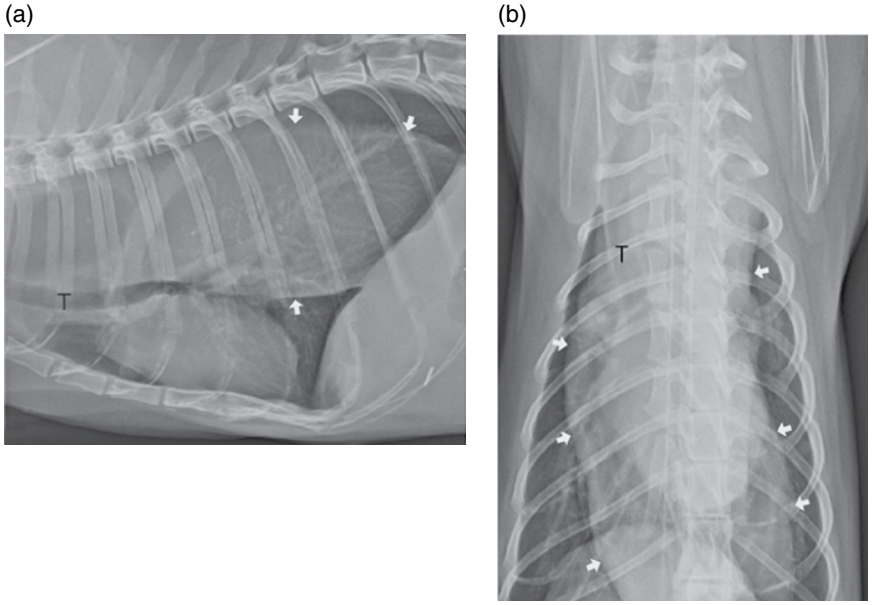


Figure 48.3 Severe generalized dilation of the esophagus with fluid and gas (megaesophagus) in a cat. Right lateral (a) and ventrodorsal (b) radiographs of the thorax demonstrating severe dilation of the esophagus (megaesophagus) resulting in ventral and right lateral displacement of the trachea (T) and ventral deviation of the cardiac silhouette.

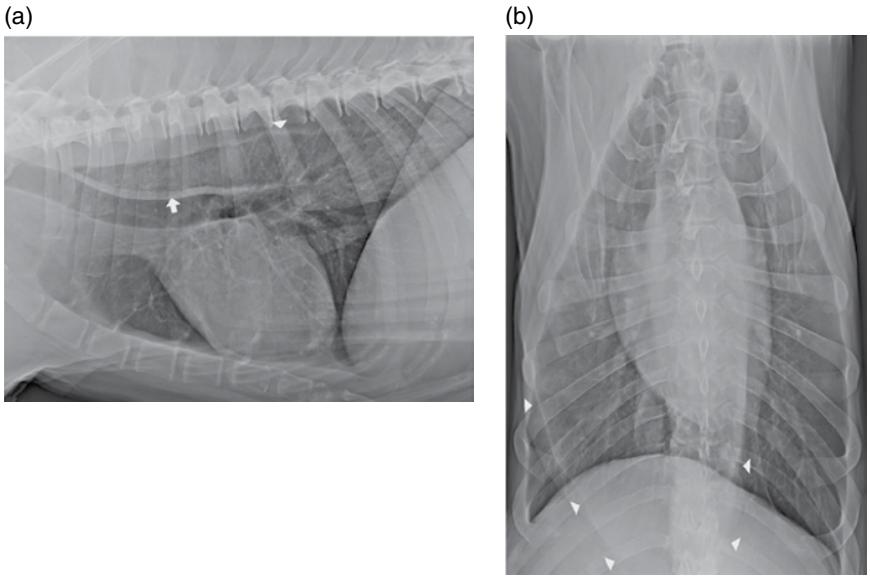


Figure 48.4 Moderate generalized dilation of the esophagus with gas in a dog. Left lateral (a) and dorsoventral (b) radiographs of the thorax. The ventral wall of the dilated esophagus is summating with the dorsal wall of the trachea resulting in a "tracheal stripe sign" (*arrow*) in the lateral radiograph. The borders of the dilated esophagus (*arrowheads*) show in the dorsoventral view a characteristic V-shape.

deviation of the trachea and cardiac silhouette may be noted. When the esophagus is fluid filled, a wide soft tissue attenuating area can be seen in the dorsal aspect of the thorax. In the VD or DV view of megaesophagus, the esophagus is usually located on or to the right of midline. A fluid- or gas-filled, dilated esophagus typically shows a V-shape narrowing from cranially to caudally on a VD or DV radiograph, with the narrowest area at the level of the esophageal hiatus at the diaphragm. A contrast esophagram is recommended if it is not possible to differentiate between generalized and focal esophageal dilation.

Vascular Ring Anomalies

Vascular ring anomalies are the most common reason for focal dilation of the esophagus in the cranial mediastinum. Other, less common causes for focal esophageal dilation include bronchoesophageal fistulae, neoplasia or strictures secondary to trauma of the esophagus. In addition to regurgitation, patients with vascular ring anomalies are often smaller than their littermates, have an overall low body condition and can have a history of regurgitation of solid food when weaning.

Vascular ring anomalies are developmental abnormalities of the primordial aortic arches resulting in a complete or partial circle of tissue around the trachea and the esophagus, causing compression of the encircled structures. Most commonly, a focal dilation of the esophagus cranial to the base of the heart is noted on imaging studies. Additionally, a marked focal leftward shift of the trachea is noted on DV or VD radiographs. A ventral deviation of the esophagus can be noted on lateral radiographs (Figure 48.5). In the dog, the persistent right aortic arch is the most commonly encountered vascular anomaly, reported in 95% of dogs with vascular ring anomaly. In patients with persistent right aortic arch, the aorta is formed by the right instead of the left fourth aortic arch. The left ligamentum arteriosum, connecting between the abnormally positioned aorta and the pulmonary artery, creates a vascular ring anomaly around the trachea and esophagus. Approximately one-third of these dogs also have an aberrant left subclavian artery, which, in combination with the persistent right aortic arch, can contribute to an additional partial ring formation, resulting in focal dilation of the esophagus.

In the cat, vascular ring anomalies occur less frequently than in the dog and reported vascular anomalies include a persistent right aortic arch with right or left ligamentum arteriosum, double aortic arch or aortic coarctation. If, in addition to the aforementioned imaging changes, a tracheal stenosis and/or malformation of the tracheal rings is present, a double aortic arch should be considered. Contrast-enhanced CT angiography will help to more accurately define and outline the vascular anomaly responsible for the focal dilation of the esophagus and can therefore help to improve surgical planning.

Esophageal Foreign Bodies

Esophageal foreign bodies occur commonly in dogs, but are less commonly noted in cats. Esophageal foreign bodies are most commonly found in the caudal esophagus and are often located between the heart base and the diaphragm. However, esophageal foreign bodies in the mid-mediastinum dorsal to the heart, in the cranial mediastinum cranial to the heart as well as just caudal of the pharynx have also been reported. Esophageal obstruction secondary to foreign bodies can lead to perforation (Figure 48.6).

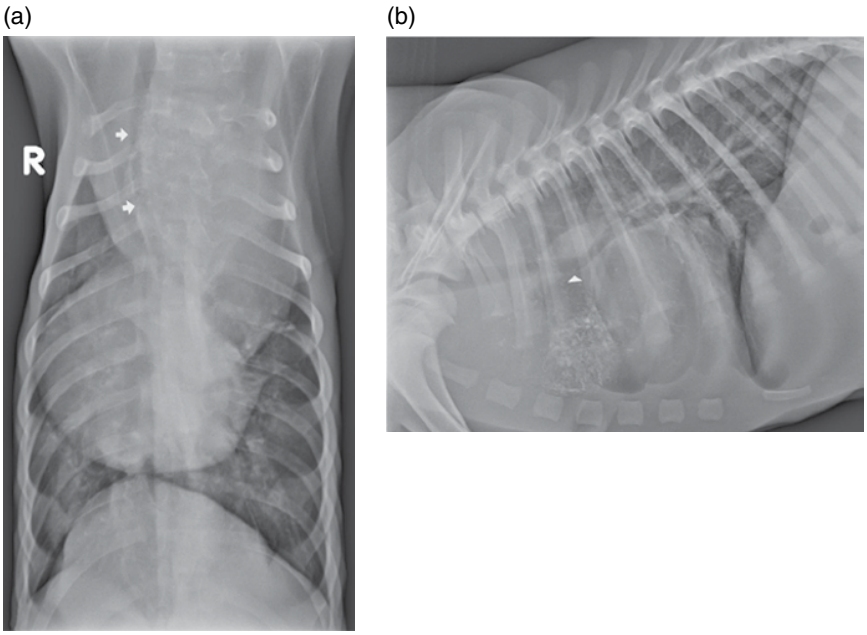


Figure 48.5 Dorsoventral (a) and right lateral (b) radiographs of the thorax of a young dog with a persistent right aortic arch and left ligamentum arteriosum confirmed at surgery. The esophagus cranial to the base of the heart is dilated (esophageal diverticulum), which is noticeable as a soft tissue attenuating structure within the cranial mediastinum, displacing the trachea (*arrows*) to the right and mildly ventrally (*arrowhead*). A small amount of mineral attenuating material is noted in the dilated aspect of the esophagus. Mild narrowing of the trachea is noted in the deviated segment.

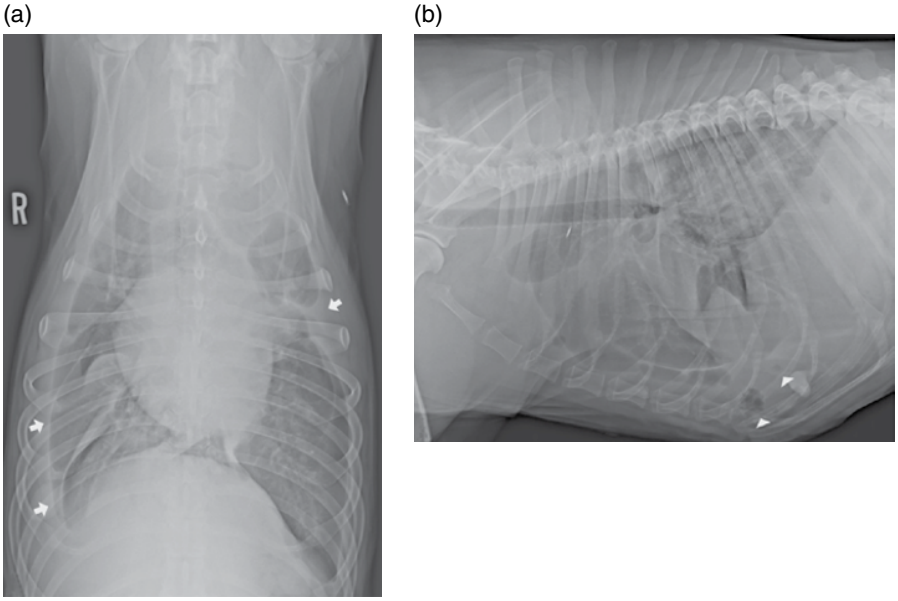


Figure 48.6 Esophageal perforation with secondary mediastinitis and pleuritis in a dog secondary to esophageal foreign body caused by swallowing a hoof dog treat. Dorsoventral (a) and right lateral (b) thoracic radiographs. Pleural fluid (*arrow*) and mediastinal fluid and gas (*arrowheads*) is present. The borders of the esophagus are indistinct.

Esophageal foreign bodies may be radiopaque and easily visualized (Figure 48.7) or soft tissue opacity and difficult to identify. Sometimes gas within the esophageal lumen might help in outlining the foreign body. A negative or positive contrast agent study of the esophagus might provide additional information. If perforation of the esophagus is suspected, small quantities of water-soluble contrast agent should be used to demonstrate the esophageal wall defect instead of barium sulfate suspension.



Figure 48.7 Esophageal foreign body. In the cranial cervical esophagus on a lateral radiograph of the neck of a dog a bone surrounded by gas is noted.

Esophagitis, Gastroesophageal Reflux

Common causes for esophagitis include gastroesophageal reflux, structural abnormalities of the hiatus of the esophagus (hiatal hernia), neoplasia, trauma, medication, and chronic vomiting. Esophagitis is difficult to diagnose on survey radiographs. On an esophagram, a caudally thickened and irregular esophagus might be noted. Radiographically, reflux esophagitis can be confirmed by filling the stomach with barium and pressing on the stomach. If reflux esophagitis is present, reflux of contrast agent into the esophagus is likely to be noted.

Esophageal Strictures

Esophageal strictures can occur secondary to severe erosive esophagitis, and are often associated with perianesthetic esophageal reflux or secondary to foreign body impaction, trauma or a surgery, where the esophagus was displaced and/or manipulated, such as during ventral cervical slot surgery. Plain contrast esophagram is usually diagnostic, revealing a segment of esophagus that persistently fails to dilate.

Esophageal Fistula

An esophageal fistula is an abnormal connection between the esophagus and trachea, bronchus, lung parenchyma or skin. Veterinary reports of esophageal fistulae are rare. Esophageal fistulae are very rarely reported in dogs and cats. The disease is occasionally reported in humans, especially children. The most commonly reported clinical signs include spontaneous coughing, coughing after drinking water, and recurrent chronic respiratory disease. The most commonly reported fistulae are congenital, but acquired fistulae secondary to injury of the esophagus, such as secondary to a foreign body, have been observed. The most commonly reported acquired fistulae are esophagobronchial, with less common reports of esophagotracheal and rarely esophagoaortic fistulae. As the clinical presentation of esophageal fistulae is similar to patients with aspiration pneumonia, it is crucially important to differentiate between the two conditions.

It is possible that the fistula opening can be identified during bronchoscopy or endoscopy of the esophagus; however, contrast agent swallowing studies using fluoroscopy are often more reliable for identification of the connection between the trachea, bronchus or lung and the esophagus. All images should be carefully evaluated for leakage of contrast agent outside the esophagus. If a fistula is suspected and not noted on an initial esophagram, it might be necessary to dilute the barium contrast medium (1:1) as dilution of the barium sulfate suspension decreases the viscosity and therefore allows visualization of smaller defects in the esophageal wall.

Additional imaging techniques, such as contrast-enhanced CT, might help to further define the precise location and size of a fistula. In humans, the use of air as a negative contrast agent to outline the esophagus has further helped to demonstrate the presence of the fistula.

Tumors of the Esophagus

Tumors of the esophagus are rare, likely accounting for less than 0.5% of the tumors reported in cancers in dogs. Similar epidemiologic studies in cats are currently lacking. Clinical signs of esophagus disease such as regurgitation are often only observed when the tumor has grown to such a size that it is causing obstruction of the esophagus.

In the dog, leiomyomas or leiomyosarcomas affecting the lower esophageal sphincter have been described (Figure 48.8). Aggressive neoplasms of the esophagus are extremely rare in dogs in areas not endemic for *Spirocerca lupi*. Extremely rarely, squamous cell carcinomas, neuroendocrine carcinoma or adenocarcinomas of the esophagus have been reported in the dog and cat.

Endoscopy of the esophagus may allow identification of esophageal masses. Similarly, contrast radiography will allow outlining of smaller masses. If the mass is large, it is likely to be noted on survey radiographs (see Figure 48.8). Additionally, tumors in the caudal esophagus might also be noted during an abdominal ultrasound exam, when the cardia of the stomach is evaluated.

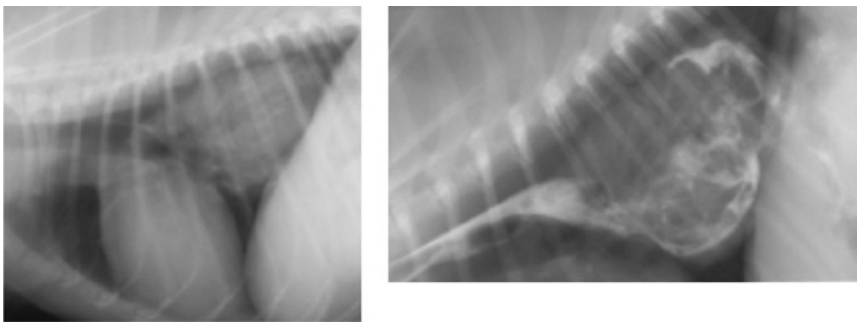


Figure 48.8 Neoplasia of the caudal esophagus. In the caudal mediastinum, a soft tissue attenuating mass is noted. On a barium esophagram, ventral displacement of the esophagus and an irregular contrast pattern are noted outlining a soft tissue attenuating structure. A small amount of contrast agent is noted in the stomach.

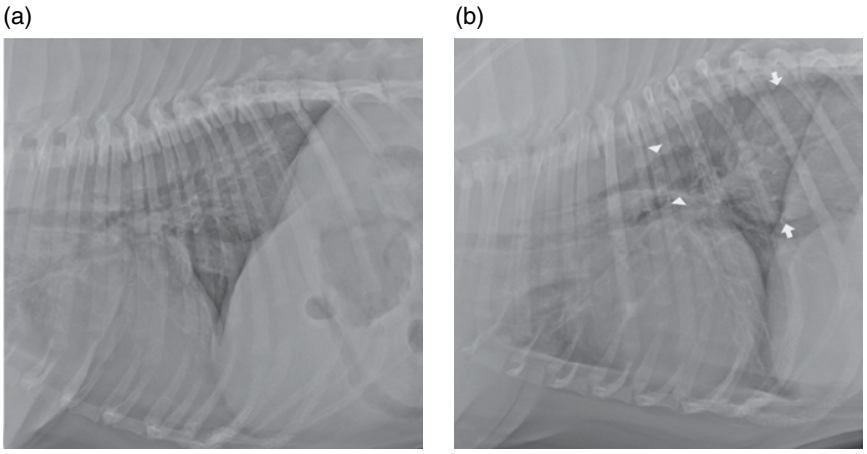


Figure 48.9 Sliding hiatal hernia (type 1 hiatal hernia) in a dog, which presented for thoracic radiographs to evaluate for the presence of pulmonary metastatic disease. (a) Right lateral radiograph. The stomach is in normal position but part of the stomach is summating cranially with the right diaphragmatic crus. (b) Left lateral radiograph. Part of the stomach is cranially positioned (*arrow*) and the esophagus is dilated (*arrowheads*).

Masses of the esophagus may lead to hypertrophic osteopathy, which might be noted on imaging studies before an esophagus lesion is identified.

Abnormalities of the Gastroesophageal Junction

Gastroesophageal Intussusception

Gastroesophageal intussusception is rare, and is caused by invagination of the stomach without or with other abdominal organs into the esophagus. This intussusception is only possible if a predisposing condition such as a megaesophagus, dilation of the esophageal sphincter or chronic vomiting is present.

Radiographically, a well-defined soft tissue mass is present in the caudal esophagus. Rugal folds might be seen within the soft tissue mass. Dilation of the more orad esophagus might be noted. The stomach or part of it might be absent on abdominal radiographs. Sonographically, no stomach or only part of the stomach might be identified in the abdomen. The cardia of the stomach might be severely dilated.

Hiatal Hernia

Diaphragmatic hernias are relatively common abnormalities. These hernias can involve the esophagus in hiatal hernias (Figure 48.9) and paraesophageal hernia, or the entry of stomach and abdominal viscera in peritoneopericardial hernias. Hiatal hernias may occur as transient or persistent hernias. Transient or sliding hernia is the most common form of hernia diagnosed in dogs and cats, where it is most frequently diagnosed in young animals. Occasionally, it is also noted in adult animals, in whom it is more likely to be an acquired form. The acquired form can occur secondary to trauma or severe upper respiratory disease. Commonly represented dog breeds include the English bulldog and SharPei. In cats, domestic shorthairs are more commonly affected. Animals with hiatal hernias may present with signs of regurgitation, hypersalivation, vomiting, and delayed growth. Sliding hernia may be difficult to diagnose due to its intermittent nature.

Radiographically, a dilated esophagus and abnormally cranial position of the stomach may be noted. In paraesophageal hernias, the gastroesophageal sphincter/junction remains in the correct position, but the fundus is displaced through the hiatus into the caudal esophagus.

The Stomach

The stomach is the most distensible organ of the digestive system, and plays an important role in the second phase of digestion. The stomach is positioned caudal of the liver and is fixed in position at the diaphragm and

duodenum. The stomach consists of four major anatomic divisions: the cardia, fundus, body, and pylorus. There are two sphincters, one each at the orad and aborad aspects of the stomach. The caudal esophageal sphincter extends into the cardia, while the pylorus is located at the junction between the stomach and duodenum. The pylorus is divided into the pyloric antrum and canal. The pylorus has an important gatekeeper function, only allowing smaller sized particles to exit the stomach into the small intestinal tract.

Radiographic Examination of the Stomach

In a survey radiographic study, the stomach is located predominantly to the left of midline with the cardia located slightly to the left of midline, ventral to the 11th and 12th thoracic vertebrae. The fundus is positioned to the left of midline and just caudal to the liver and diaphragm. The fundus is the only aspect of the stomach which can be in direct contact with the diaphragm. The antrum is usually not distinctly outlined and is located between the fundus and pyloroduodenal junction. The pylorus is located on or to the left of midline in the cat and on midline or to the right of midline in the dog. The gastric axis in the dog is usually perpendicular to the spine or parallel with the ribs. In the cat, it is usually more perpendicular to the spine. In a lateral radiograph, the pylorus is located approximately at the ventral aspect of the ninth rib.

Radiographic attenuation of the stomach is dependent on its content. The stomach usually contains both gas and fluid, but if the stomach is empty or only a small amount of fluid is present in the stomach, it may be difficult to visualize as it summates with the liver. The stomach has rugal folds, which are usually best seen on a contrast study or ultrasound evaluation. Rugal folds within the fundus of the stomach often create a mosaic pattern. In the body of the stomach, the rugal folds are more parallel and in the pylorus the number of rugal folds is reduced. Subjectively, rugal folds in the cat are less prominent than in the dog.

Obtaining multiple projections in various positions of the patient is important when evaluating the stomach radiographically. Changing the position of the stomach affects the position of the gas and fluid in the stomach.

In dorsal recumbency (VD view), gas is located in the gastric body and pyloric antrum and can be noted as a gas opacity structure summating with the stomach at the right and left side of midline. In ventral recumbency (DV view), the gas is present in the fundus of the stomach, which is then the most dorsal aspect of the stomach. In a DV view, a gas opacity structure is noted summating with the left cranial aspect of the stomach in the location of the fundus. In a right lateral recumbency view, the gas is located in the fundus region and the fluid is located in the gastric body/antrum. The fluid in the gastric body/antrum creates a round, circular, soft tissue attenuating area in the cranial abdomen, which is occasionally mistaken for a foreign body in the pylorus or a mass in the cranial abdomen. In the left lateral recumbent view, gas is present in the pyloric region, appearing as a gas opacity oval or triangle-shaped structure in the cranioventral aspect of the abdomen (Figure 48.10).

Ultrasound Examination of the Stomach

An ultrasound examination of the stomach helps evaluate the gastric mucosa and gastric content. If possible, patients should be fasted for 12 hours before an ultrasound examination is performed as food in the stomach might create artifacts. The stomach is positioned caudal to the liver, predominantly central to left of midline, and adjacent to the spleen. The cardia is located to the left of midline and can usually be seen as a thick bulge with a smooth mucosal outline at the border of the thoracic esophagus to fundus. The pylorus is located to the right or on midline in the dog and is usually on or slightly to the left of midline in the cat. The stomach wall thickness ranges from 3 to 5 mm in normal dogs and cats. The pyloric wall thickness in the cat is 3.8–5 mm, which is similar to established gastric wall thickness measurements of 3–5 mm. Under optimal conditions, five layers of the stomach and small intestine are visualized (Figure 48.11). The innermost hyperechoic layer corresponds to the luminal surface of the mucosa. The next hypoechoic layer is the mucosa, which is followed by another hyperechoic thin layer, the submucosa. The outer hypoechoic layer is the muscularis, which is adjacent to the outermost hyperechoic layer, the subserosa/serosal layer.

Gastrography

Indications for contrast studies of the stomach (gastrography) include vomiting, regurgitation, a history of foreign body consumption, chronic weight loss, bloating, and anorexia. Contraindications for performing gastrography include suspected gastric rupture, large amounts of ingesta or large amounts of fluid in the stomach. A potential contraindication could be a rigid stomach as overfilling of the stomach might cause vomiting, resulting in aspiration. Before a gastrography is performed, survey radiographs of the abdomen should be obtained. For all gastrography studies, 12 hours of fasting of the patient is recommended to reduce the risk of artifacts caused by food or other material in the stomach. Most of the study can be performed without sedation of the patient; however, if the patient is not sufficiently

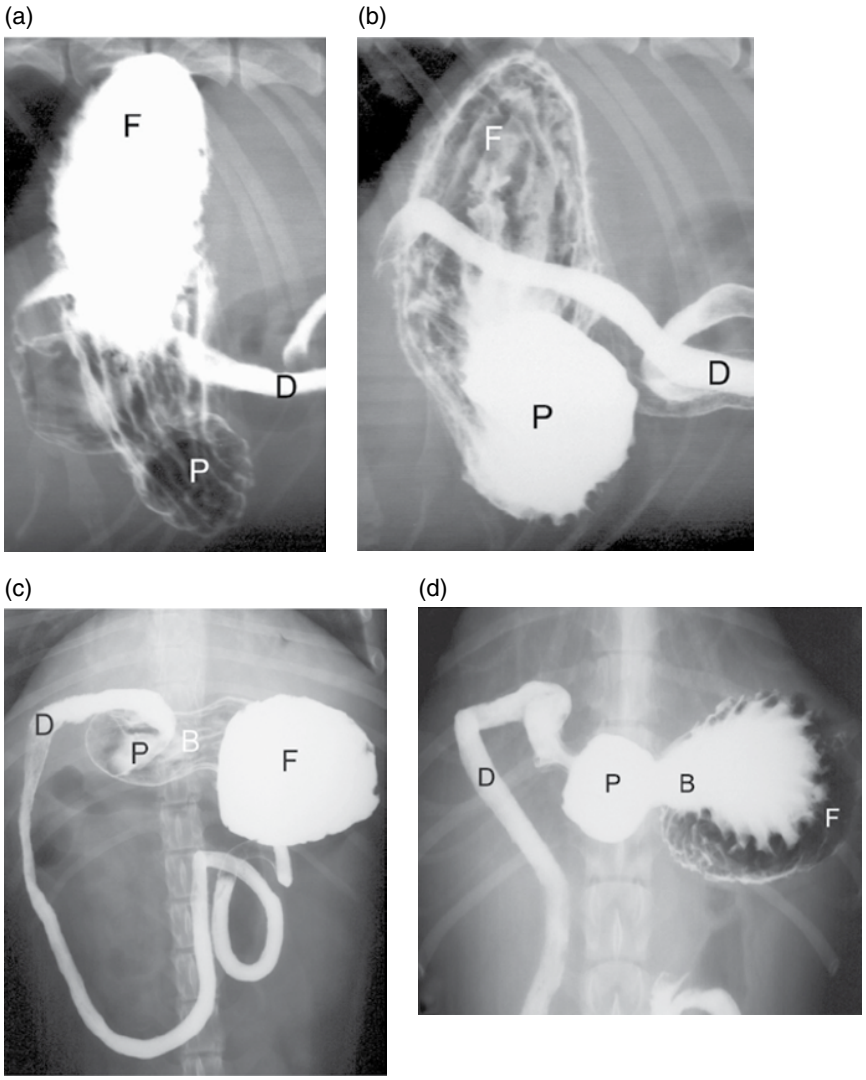


Figure 48.10 The movement of gastric content is dependent on the patient positioning. In a left lateral radiograph (a), fluid (barium contrast agent) is located in the fundus (F) of the stomach and the pylorus (P) is gas filled. In a right lateral radiograph (b), fluid is in the pylorus (P) and gas is in the fundus (F). In a ventrodorsal radiograph (c), fluid is in the fundus and gas is in the gastric body (b) and pyloric antrum. In a dorsoventral radiograph (d), gas is in the fundus and fluid is located in the gastric body (b) to pyloric area.

relaxed, mild sedation should be administered, ideally one which does not or only minimally affects gastrointestinal motility. Contrast studies of the stomach can be performed using negative contrast agents, positive contrast agents or as a double contrast study.

Negative contrast studies of the stomach are mainly performed to evaluate for the presence of a gastric foreign body or to evaluate the location of the stomach. Orogastric intubation is performed, followed by filling the stomach with room air at a dose of 6–12 mL/kg bodyweight, or filling the stomach until it is palpably distended. Alternatively, a carbonated beverage can be given into the buccal pouch (at least 30–60 mL) if the patient does not drink it voluntarily. After distension of the stomach is achieved, four views of the abdomen should be obtained. If a foreign body in the pyloric antrum is suspected, a horizontal beam view with the patient in left lateral recumbency might help to better outline the foreign body.

Positive contrast gastrography is performed by using either barium sulfate suspension or an iodinated contrast agent to outline the stomach. An iodinated contrast agent should be used if a perforation of the stomach is suspected or if surgery is planned immediately after the positive contrast agent study. Iodinated contrast agents provide less coating of the gastric wall compared to barium sulfate suspension. For large dogs, use 5–7 mL/kg bodyweight barium sulfate 30% weight to volume suspension and for small dogs or cats 8–12 mL/kg bodyweight barium sulfate suspension. In cats, the recommended barium sulfate suspension volume can range up to 20 mL/kg.

Orogastric intubation for application of the contrast agent is recommended to reduce the risk of aspiration. Otherwise, the contrast agent can be placed in the buccal pouch using a syringe, but if the patient struggles the procedure should be stopped and orogastric tube placement should be considered. If ionic iodinated contrast

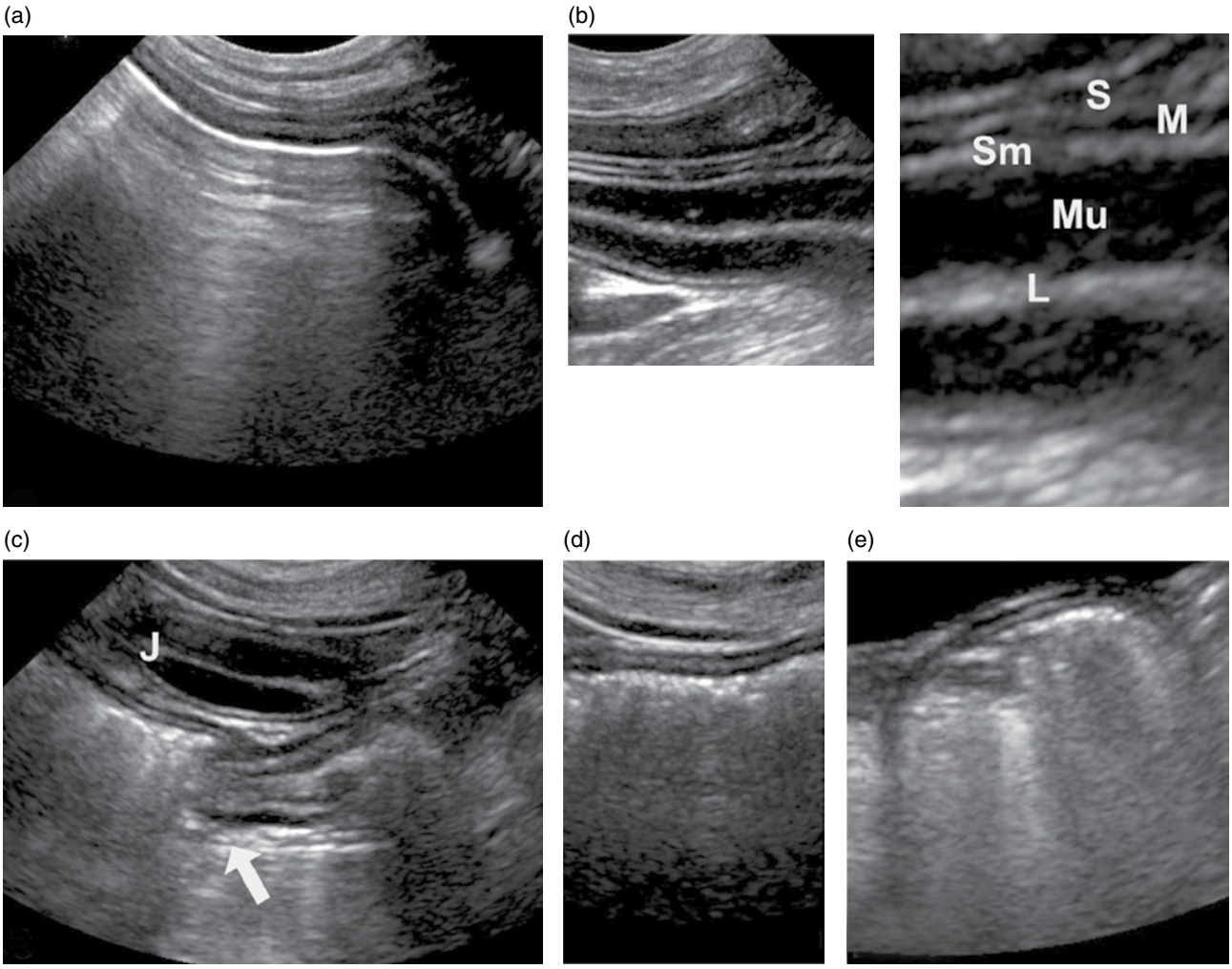


Figure 48.11 Normal gastrointestinal ultrasound images. Longitudinal ultrasound image of the stomach wall (a). Only the wall in the near field can be evaluated, as gas is present in the stomach causing reverberation artifacts and therefore limiting visualizing of the far wall. Longitudinal ultrasound image of the duodenum (b). The individual layers and lumen (L) are marked on a magnified image. Mu, mucosa; Sm, submucosa; M, muscularis; S, serosa. Longitudinal ultrasound image of the ileocolic junction (c) marked by an arrow. On the right side of the image is the ileum and on the left side is the ascending colon containing a small amount of gas. Between the ileocolic junction and the abdominal wall, a segment of jejunum (J) is noted. Longitudinal image of the ileum (d) and transverse image of the colon (e). The mucosa of the ileum is thinner when compared to the duodenum and jejunum. The colon wall is thinner and the individual wall layers are more similar in thickness.

agents are used, extreme caution is necessary to reduce the risk of aspiration as most ionic iodinated contrast agents designed for the gastrointestinal tract are hyperosmolar and draw in water, causing severe pulmonary edema when aspirated. Iodinated contrast agents are used at a dose of 2–3 mL/kg bodyweight. The iodinated contrast agent can also be diluted 1:4, but then the dose should be increased to 6–12 mL/kg bodyweight. Four views of the abdomen should be obtained to evaluate the stomach. A sufficient degree of distension of the stomach must be achieved to obtain a good-quality study.

The four views of the abdomen result in different appearances of the stomach due to the effect of gravity; the contrast agent will be positioned in the dependent aspect of the stomach and gas will be positioned in the nondependent aspect of the stomach similar to the distribution of water and gas in a four-view survey radiographic study. On the VD view, the barium sulfate suspension is located in the fundus region on the left and in the pyloric region in the right side of the abdomen. The body of the stomach is filled with air. In a DV view, the barium sulfate suspension is present in the body of the stomach and the fundus and pyloric area are gas filled. In a right lateral view, the barium sulfate suspension is located in the pyloric area and gas is noted in the body and fundus of the stomach. In a left lateral view, the

barium sulfate suspension is in the gastric fundus, while air fills the body and pyloric area of the stomach. Borders of the gastric wall to luminal contrast agent filling are normally distinct and well defined.

The diameter of the pylorus is usually approximately half that of the body of the stomach; if it is larger than that, disease of the pyloric canal may be present. The peristaltic wave normally runs from the fundus to the pylorus. During peristalsis, symmetric narrowing of the gastric fundus to pylorus wall may be noted.

Expected times for gastric emptying of contrast are quite variable. After administration of liquid barium sulfate suspension, emptying of the stomach should occur within the first 5–10 minutes, latest by 30 minutes. The stomach should be completely empty by a maximum of 2.5–3.5 hours in the dog and 15–60 minutes in the cat, if the barium was not mixed with food. Food material empties more slowly from the stomach and it can take up to 12 hours to observe a completely empty stomach. Emptying of the contrast agent from the stomach can also occur very rapidly if the stomach was empty and the dog fasted when the contrast study was started. Delayed gastric emptying can be noted in normal animals secondary to sedation, anesthesia, and anxiety. Delayed gastric emptying is frequently observed in anxious cats. Delayed gastric emptying can be noted in a wide range of diseases including gastritis, pancreatitis, neoplasia of the gastric or duodenum wall, and foreign bodies, to name a few.

Double contrast studies of the stomach are usually performed if a mucosal lesion (e.g., ulcer, gastritis, neoplasia) or presence of a foreign body is suspected. As this procedure can take more time than a simple gastrogram, sedation should be considered. Placement of an orogastric tube reduces the risk of aspiration of contrast agent and allows administration of air into the stomach. For a double contrast gastrography study, 1.5–3 mL/kg bodyweight barium 30% volume to weight suspension is given before 20 mL/kg air is added. Four radiographic views of the abdomen should be obtained. It is often helpful to gently roll the patient to achieve an even coating of the gastric wall before the four views are obtained.

Gastric Dilation

In gastric dilation, the stomach is distended without change in shape and position. This can be acute, secondary to aerophagia, gastritis, outflow obstruction, medical treatment, or chronic, secondary to a chronic obstructive process of the pylorus or proximal duodenum.

On a survey radiograph, a hugely dilated stomach with fluid and gas is noted (Figure 48.12). If the stomach is mainly fluid dilated, the radiographic diagnosis of gastric dilation may be more difficult as the stomach may appear as a soft tissue attenuating mass and can therefore not easily be distinguished from the liver. In these cases, caudal displacement of the colon and the location and shape of the soft tissue opacity might help to establish that the stomach is dilated. It is important to remember that not all patients with a gastric dilation have a mechanical obstruction. Additionally, gastric dilation may occur secondary to a mechanical obstruction of the duodenum, or secondary to pancreatitis.

The key to differentiation of gastric dilation from gastric dilation volvulus is the position of the pylorus. This is best determined by evaluating the right and left lateral recumbent views of the abdomen. In gastric dilation, the pylorus and duodenum in a right lateral recumbent view should be predominantly fluid filled, and in a left lateral recumbent view usually contain variable amounts of gas.

Gastric Dilation Volvulus

Gastric dilation volvulus is a frequently encountered, acute life-threatening disease in dogs. Gastric dilation volvulus rarely occurs in cats.

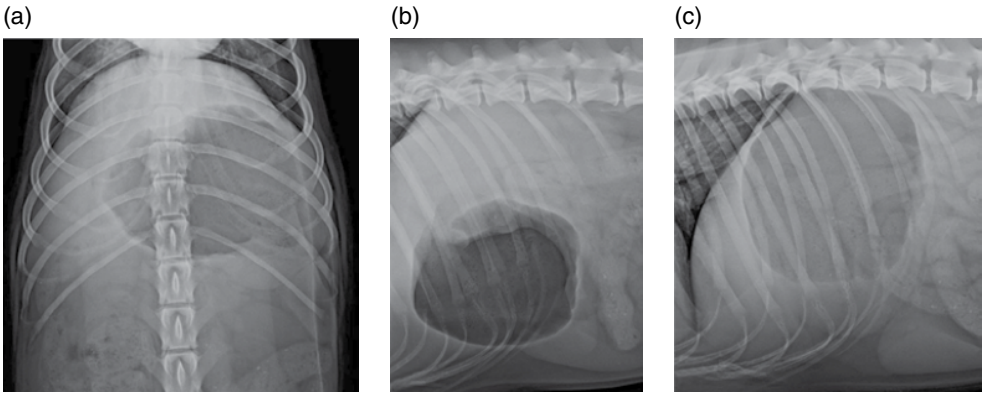


Figure 48.12 Gastric dilation. Ventrodorsal (a), left lateral (b), and right lateral (c) radiographs of the abdomen of a dog. Gas and fluid dilation of the stomach is noted. The stomach is in correct position. No compartmentalization is noted.

In gastric dilation volvulus, the stomach is usually abnormally distended, containing food, fluid and gas, and has an unusual shape and position (Figure 48.13). Often a rapid decision needs to be made on whether the stomach is rotated and dilated or only dilated. On abdominal radiographs, compartmentalization of the stomach is noted ("Smurf's head," "Popeye's arm"); if this happens, the stomach can appear to consist of two cavities, resulting from the dorsal and leftwards displacement of the gas-filled pylorus. The fundus tends to be ventrally and rightwards positioned, if a 360° rotation is not present. The right lateral radiographic view is often considered the most helpful view as it shows both abnormal gas filling and displacement of the pylorus and cranial duodenum (see Figure 48.13). In a normal right lateral view, the pylorus is typically fluid filled. In gastric dilation volvulus, however, gas is located in the pylorus and proximal duodenum.

The lack of gas distension of the stomach does not preclude the presence of gastric volvulus. If a previous gastric decompression has been performed, gastric volvulus might be present for days to weeks or might be seen at initial presentation. The radiographic principles mentioned before remain, with the exception of a lack of marked distension of the stomach.

The presence of gas in the gastric wall (pneumatosis) or peritoneal cavity (pneumoperitoneum) is a very strong indicator for gastric wall necrosis (Figure 48.14) if no prior treatment, such as gastric decompression, has been performed. However, it is important to remember that radiographs are not very sensitive for evaluation of gastric wall necrosis. Gas in the gastric wall might also be noted during an ultrasound exam and if gas is present, additional abdominal radiographs should be obtained, to evaluate the position of the stomach.

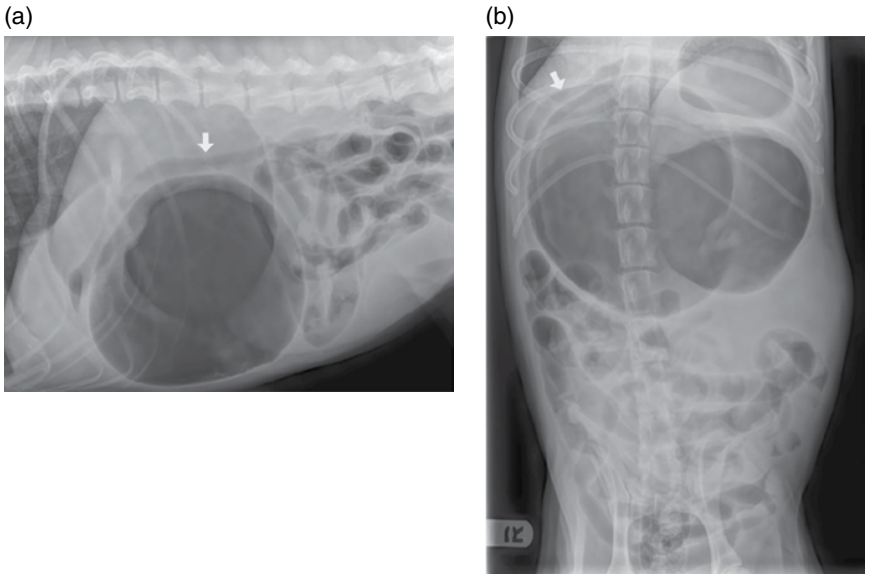


Figure 48.13 Gastric dilation volvulus. Right lateral (a) and VD (b) radiograph of the abdomen demonstrating a moderate gas distension of the stomach with compartmentalization of the stomach classic for gastric dilation volvulus. The duodenum is dorsally and laterally displaced (*arrow*).

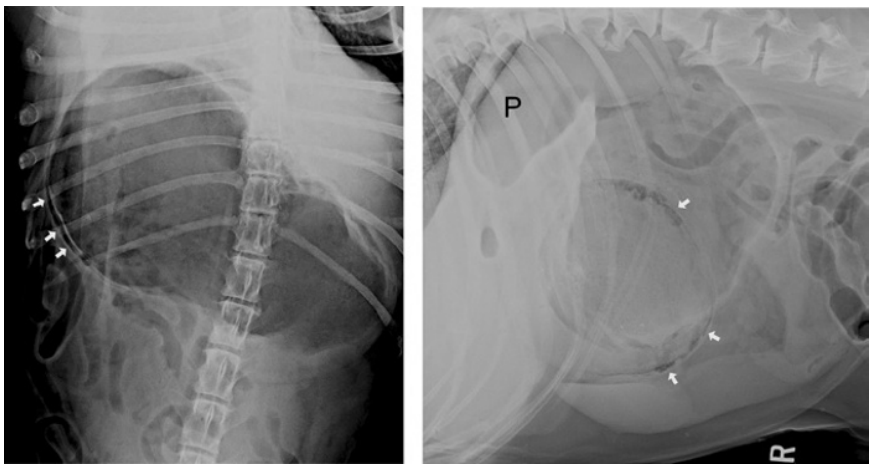


Figure 48.14 Gastric pneumatosis in a Doberman with gastric dilation volvulus. Ventrodorsal and lateral radiographs illustrating an abnormally positioned stomach. The pylorus (P) is dorsally displaced. Thin linear gas patterns are noted in the gastric wall consistent with gastric pneumatosis, which is highly suspicious for gastric wall necrosis secondary to the volvulus.

If gastric dilation volvulus is present, no further imaging is necessary and emergency procedures should be performed to decompress the stomach.

Chronic Gastric Outlet/Pyloric Obstruction

Chronic gastric outlet (pyloric) obstruction occurs relatively frequently secondary to either congenital or acquired pyloric stenosis or abnormal function of the pylorus. Pyloric obstruction is more frequently encountered in dogs than in cats. Radiographic recognition of gastric outlet obstruction often depends on the degree of distension and content of the stomach, and duration of the disease. Furthermore, positioning of the patient during radiography and frequency of vomiting affect the radiographic appearance of pyloric obstruction. Most frequently, the stomach is distended with gas and fluid, which can easily be noted on radiographs (Figure 48.15). It is important to remember that not all patients with a gastric dilation have a mechanical obstruction of the pylorus.

Gastric dilation may also occur secondary to mechanical obstruction of the duodenum or with concurrent pancreatitis. Left recumbent lateral views can help to decide if a duodenal obstructive lesion is present, as gas in the duodenum may be able to outline the cause of the obstruction. Additionally, in chronic obstructive gastropathy a "gravel sign" indicating retention of small mineral attenuating material particles in the stomach can sometimes be seen.

Contrast studies of the stomach or an ultrasound examination are often needed to establish the cause and site of outflow obstruction of the stomach. Contrast radiography of the stomach in cases of chronic obstructive gastropathy may reveal delayed gastric emptying, focal intraluminal contrast sparing areas in the pyloric antrum with incomplete filling and blunting of the pyloric canal. If contrast medium remains in the stomach 3–4 hours after administration, this usually indicates pyloric obstructive disease. Intraluminal filling defects in the pyloric antrum are often caused by thickened mucosal fold(s) extending into the lumen. The shape and radiographic appearance of the contrast agent filling of the pylorus have been described with various signs including the "beak," "tit," and "string" signs. Lack of filling or only partial filling of the pyloric canal has been described as the "beak" sign, where only a small amount of contrast agent extends in the form of a beak into the pyloric canal. The "tit" sign has been used when a small outpouching remains at the lesser curvature secondary to peristaltic waves. The "string" sign has been used when contrast agent extends through the pyloric canal but is concentrically narrowed secondary to circumferential thickening of the pylorus wall.

On an ultrasound exam, mucosal or muscular thickening of the pylorus wall may be noted and may help to differentiate between various etiologies of chronic outlet obstruction. In dogs with chronic pyloric hypertrophy, the hypertrophic muscularis may appear as a thick, hypoechoic layer (Figures 48.15 and 48.16). Sonographically, the measured thickness of the muscularis may help to categorize disease severity. The muscularis thickness in the pylorus is greater than 3 mm in mild to moderate hypertrophy and greater than 8 mm in severe chronic pyloric stenosis in dogs. Forceful, but ineffective, peristaltic contractions that fail to propel contents into the duodenum may be seen in some patients with gastric outflow obstruction.

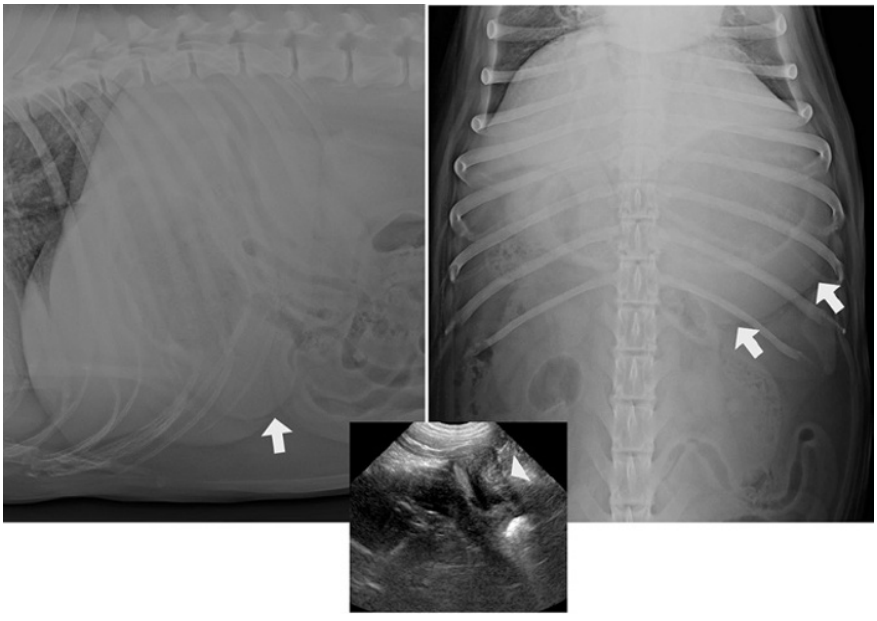


Figure 48.15 Ventrodorsal and left lateral radiographs of the abdomen of a vomiting dog. Moderate dilation of the stomach with fluid and gas is noted (*arrows*). The gastric wall appears subjectively thickened. An abdominal ultrasound exam revealed moderate thickening of the pylorus wall (*arrowhead*) with loss of wall layering.

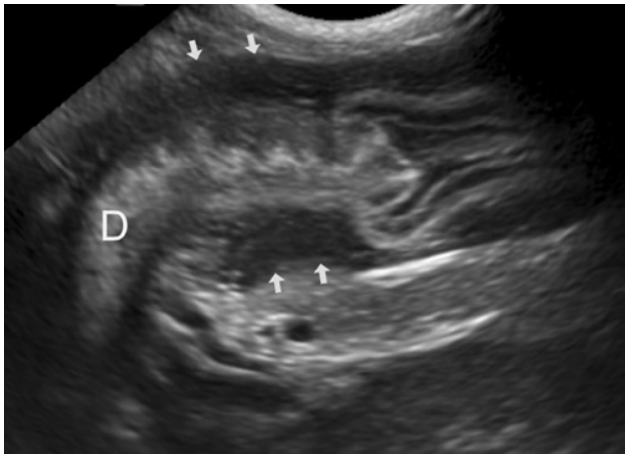


Figure 48.16 Longitudinal ultrasound image of the stomach of a dog with a history of chronic vomiting. Moderate thickening of the pylorus wall (*arrows*) with narrowing and irregularity of the luminal aspect is noted. D, duodenum.

Foreign Bodies

Gastrointestinal foreign bodies are a common diagnosis in dogs and cats presenting for emergency veterinary care (Figure 48.17). It can often be a challenge to diagnose gastrointestinal foreign bodies and decide if immediate surgery is indicated. Preferably, before an imaging study of the stomach is performed, the animal should be fasted for 12 hours. Accumulation of a small amount of fluid or gas in the stomach is normal even after fasting for 12 hours. Mineral or metal attenuating material in the stomach is easily recognized on survey radiographs. Mineral attenuating material in the stomach could be secondary to medical treatment of the patient, for instance with medications containing bismuth or kaolin, or this material could indicate delayed gastric emptying secondary to a chronic obstructive process involving the pylorus ("gravel sign"). Metal attenuating material in the stomach might not always cause obstructive signs, but might be toxic due to containing, for example, heavy metals such as zinc. Therefore, in patients with intravascular hemolysis, abdominal radiographs may be indicated to evaluate for the presence of metallic foreign objects. It is important to remember that aluminum is relatively radiolucent, unlike a lot of other metals, and is therefore difficult to detect on a survey radiograph.

Foreign bodies that are not mineral or metal attenuating can be challenging to detect. If foreign body ingestion is suspected, multiple views of the abdomen should be obtained. The gravity dependence of the fluid and gas in the stomach may help to outline a foreign body. If no foreign body is identified, contrast radiography, ultrasound or CT might provide more information. On a contrast radiographic study, foreign bodies are noted as a filling defect and this defect can be mobile within the stomach. However, if the object is large and/or the stomach is very empty, this object might not move much when changing the position of the stomach and might appear lodged in the stomach. Additionally, porous foreign bodies, such as cloth material or foam, may retain contrast agent and might be seen at the end of a contrast study, when most of the contrast agent has left the stomach.

On ultrasound, gastric foreign bodies are often hyperechoic with complete distal acoustic shadowing. If they contain gas, areas of incomplete distal acoustic shadowing can be noted. Additionally, they also may be recognized by their shape. Similar to radiography, foreign bodies usually move when repositioning the patient, but when the foreign body is large, it may show only minimal mobility within the stomach.

Gastrointestinal perforation is less frequently seen with foreign body ingestion, but has been reported when sharp objects such as wood sticks, skewers, needles (Figure 48.18) or multiple magnets are swallowed.

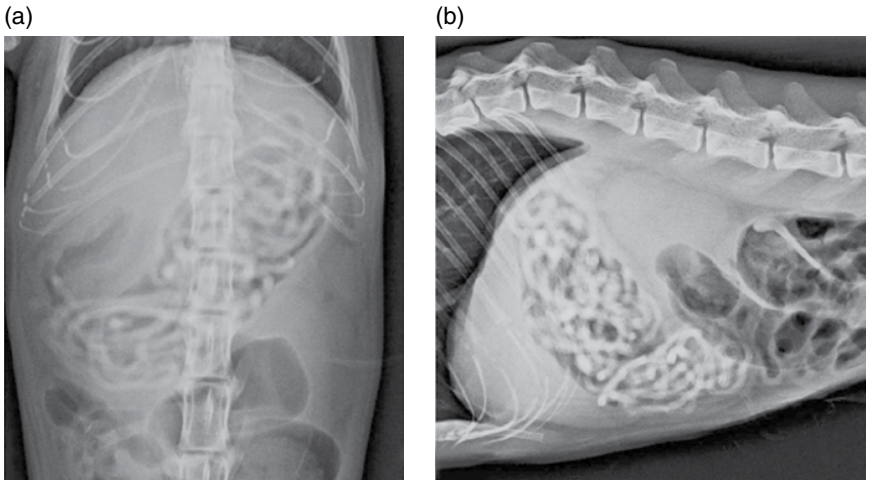


Figure 48.17 Multiple gastric foreign bodies are noted in the ventrodorsal and lateral radiograph of the abdomen of the cat. The foreign bodies represented multiple rubber hair bands ("scrunchies").



Figure 48.18 Longitudinal ultrasound image of a thin, hyperechoic, linear foreign body perforating from the pylorus area of the stomach (*arrowheads*) into the pancreas (P). The adjacent mesenteric fat is hyperechoic suggestive of secondary focal peritonitis. The foreign body was surgically removed and was a sewing needle.

Gastrointestinal perforation is suspected when peritoneal gas, with or without peritoneal fluid, is present either radio- or sonographically. Additionally, on ultrasound an increased echogenicity of the mesenteric fat can be noted. Occasionally gastrointestinal perforation secondary to a foreign body may not occur acutely or cause acute symptoms. Sometimes these foreign bodies lead to distant chronic inflammatory processes, which result in the occurrence of abscesses at unusual sites or radiolucencies or mass effects on a radiograph months to years later.

It should be remembered that more than one object could have been ingested and the search for foreign bodies should not be stopped at the stomach, but continued through the entire gastrointestinal tract.

Gastric Ulcers

Gastric ulcers might be seen on a contrast study of the stomach or ultrasound examination. In a gastrographic study, an outpouching of the gastric wall or defect with adjacent increased thickness of the gastric wall might be noted ("crater sign"). Additionally, the wall of the stomach adjacent to the ulcer might be rigid, which is best seen using fluoroscopy.

On an ultrasound exam, similar imaging features can be noted, including focal thickening of the gastric wall with a central area of decreased wall thickening ("crater"), loss of normal wall layering, decreased motility of the gastric wall, and retention of fluid in the stomach. Additionally, small focal areas of hyperechogenicity with reverberation artifacts suggesting microbubbles may be present in the central aspect of the ulcer.

Inflammatory Conditions of the Stomach and Duodenum

Imaging Features of Gastritis

On survey radiographs, large rugae may be noted; this may be most noticeable at the greater curvature of the stomach. On a contrast radiographic study, large rugae extending luminally and resulting in contrast-sparing areas are often present.

Sonographically, focal or circumferential wall thickening, loss of wall layering and, especially in chronic disease, a mass effect can be noted. Regional lymph node involvement may be present. Inflammatory disease of the stomach may appear similar to neoplastic or immune-mediated disease or uremic gastropathy on ultrasound (Figure 48.19).

Tumors of the Stomach

Primary gastric tumors are rare in the dog and cat and account in the dog for less than 1% of all malignancies. Benign (e.g., polyps, adenomas) and malignant (e.g., adenocarcinoma, lymphosarcoma, fibrosarcoma, leiomyosarcoma, gastrointestinal stromal tumor) neoplasias have been described. In the dog adenocarcinoma and in the cat lymphoma are the most frequently diagnosed gastric tumors. Most of the gastric tumors are epithelial in origin and most frequently affect the distal two-thirds of the stomach. Benign masses such as polyps are more commonly seen in the pyloric antrum and are often unnoticed until an imaging exam or endoscopy is performed. Gastric tumors can cause a pyloric outflow obstruction or affect normal gastric motility. Gastric adenocarcinomas in dogs can also present with ulceration of the gastric wall.

Radiographic Features of Gastric Tumors

Survey radiographs are often not sufficient to diagnose gastric wall tumors, even when all four views of the abdomen are obtained. On survey radiography, focal areas of gastric wall thickening, loss of normal rugal folds, and masses protruding into the lumen might be noted. Pyloric outflow obstruction might be noted, which can be characterized by a fluid-distended stomach and/or mass effect in the pyloric area. Usually survey radiographs need to be followed by contrast radiography, ultrasound or, when available, CT to further evaluate the stomach and stage the disease.

On a contrast radiographic study, intraluminal masses typically cause signs such as a filling defect in the contrast medium, abnormal appearance of the rugae, focal unusual distension of the gastric wall, a lack of peristalsis or delayed gastric emptying.

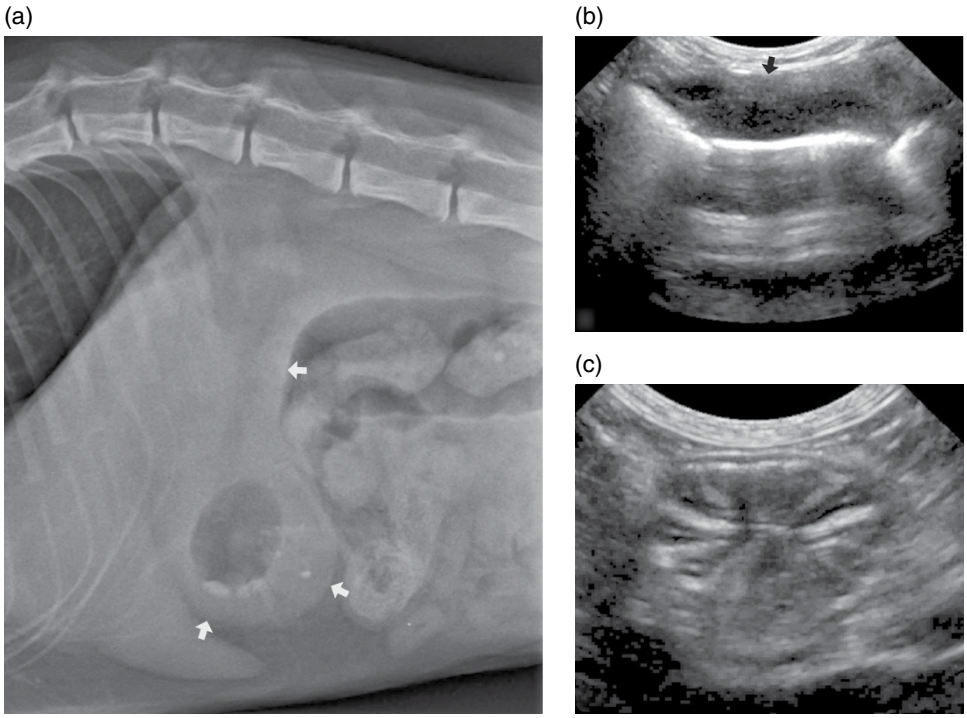


Figure 48.19 Eosinophilic gastritis in a cat. Lateral radiograph (a) of the cranial abdomen is suggestive of a moderate thickening of the gastric wall, which was confirmed on an ultrasound exam (b) of the stomach. On the longitudinal ultrasound image, moderate to severe thickening of the gastric wall with loss of wall layering and reduced echogenicity is noted. Part of the fundus of the stomach shows a normal wall architecture as illustrated in the ultrasound image (c).

Ultrasound Features of Gastric Tumors

An ultrasound examination of the stomach can be useful in diagnostic assessment for gastric neoplasia. However, ultrasound examination of the stomach may be limited by the presence of gas. Repositioning of the patient and thus moving the gas will improve evaluation of the gastric wall. The sensitivity of detection of gastric wall masses using ultrasound has been reported to range between approximately 50% and 80% and is dependent on the experience of the operator. The presence of fluid in the stomach, which also can be administered prior to the ultrasound examination, may reduce the presence of air artifacts and therefore enhance the visualization of gastric wall pathology.

Ultrasound examinations of gastric wall tumors often demonstrate a variety of features, including loss of gastric wall layering, masses arising from certain wall layers, presence of cavitations, asymmetric or symmetric thickening of the wall, and the presence of peritoneal fluid (Figure 48.20). Extension of the mass through the serosal surface may be noted, most commonly seen with carcinoma. Additionally, the involvement of regional lymph nodes, liver, spleen, and intestine can be evaluated for staging the disease. Ultrasound has been used to attempt to differentiate between various gastric neoplasms, but poor correlation with histology was noted. Ultrasound-guided fine needle aspirates may be helpful to accurately diagnose a gastric neoplasm.



Figure 48.20 Longitudinal ultrasound image of the stomach of a cat. A large, eccentric gastric wall thickening with loss of normal wall architecture and distortion of the wall is noted. Peritoneal fluid is present. This was most concerning for neoplasia. Fine needle aspirates confirmed a gastric carcinoma.

Computed Tomographic Features of Gastric Tumors

Computed tomography and magnetic resonance tomography are commonly used in human patients to stage gastric tumors, but currently no similar studies are available in veterinary patients. Computed tomography can be

helpful to evaluate the extent of the gastric lesion and stage disease. On CT images, a thickened gastric wall, loss of wall layering, and contrast enhancement of the wall might be seen. Additionally, enlargement and contrast enhancement of regional lymph nodes can be noted. However, the CT criteria for gastric neoplasia might also be seen in other benign disease such as gastritis.

Gastrointestinal Bleeding

A variety of diseases can result in gastrointestinal bleeding. If the bleeding is caused by an ulceration or mass, contrast radiography and ultrasound may identify the site of the bleeding. However, if minimal wall alteration is present, contrast radiography and ultrasound might not identify the cause of bleeding.

Small Intestine

The small intestine consists of three segments: the duodenum, jejunum, and ileum. The segments of the small intestine in the dog and cat do not have characteristic mucosal folds. The long mesentery of the small intestines provides only a limited fixation of the small intestine.

Radiographic Examination of the Small Intestine

The descending duodenum shows the most consistent positioning of the small intestinal segments and is located in the right craniolateral abdomen, running parallel to the abdominal wall from just ventral to the right kidney to the level of the 4th–5th lumbar vertebrae, where it turns medially. The ascending duodenum runs from the caudal duodenal flexure cranially and towards midline. The jejunum is the largest portion of the small intestine and is relatively evenly distributed throughout the abdomen, from caudal to the stomach to cranial to the urinary bladder. If the dog is very deep chested and the gastrointestinal tract very empty, loops of small intestine might be noted adjacent to the dorsal aspect of the diaphragm. In obese animals, the small intestine is often located more centrally in the abdomen due to displacement by peritoneal fat.

In the cat, a large falciform fat pad may lead to caudal displacement of the small intestine. The aborad portion of the ileum might be visualized at the ileocecocolic junction, which lies in a VD view right of midline at the level of the second lumbar vertebra and in a lateral view ventral of the approximately fourth lumbar vertebra. The jejunum and ileum are otherwise indistinguishable radiographically. The duodenum can be minimally wider than the jejunum and ileum.

Usually the small intestinal segments are of very similar width and little variation in diameter is present. The normal small intestinal diameter in the dog is usually less than 1.4 times the height of the midportion of the fifth lumbar vertebral body or less than twice the width of the 12th rib. In the cat, the normal small intestinal diameter should be less than 12 mm. In the cat, the small intestinal tract might have a more "string of pearls" appearance, when compared to the dog. It is critical to differentiate the small intestine from the large intestine when decisions about an increased small intestinal diameter are made.

If an animal has not eaten, the small intestines contain a mixture of fluid and gas. In the dog, typically up to two-thirds of the small intestinal loops are gas filled and in the cat usually very little gas is present in the small intestine. Gas usually redistributes through the intestinal tract relative to the position of the animal. In the left lateral view, gas is often present in the duodenum as it is located dorsally and on the right. However, positional radiographs are less valuable for the redistribution of gas in the small intestine compared to the stomach. The small intestine can also contain small mineral or metal attenuation structures depending on the diet, or if an animal is an indiscriminate eater or is receiving medication. The visualization of medications in the intestinal tract is dependent on their size and attenuation. Some medications contain mineral to metal opaque material; examples include calcium carbonate, iodinated compounds, iron-containing preparations, potassium, and aluminum.

Gentle compression techniques using a wooden spatula or spoon while obtaining abdominal radiographs can be helpful to further evaluate segments of small intestine, by reducing the summation from other abdominal structures.

Ultrasound Examination of the Small Intestine

Similar to radiography, the descending duodenum is the most consistently positioned section of the small intestine and can therefore easily be followed using ultrasound. The duodenum can typically be visualized extending from the pylorus along the medial aspect of the right abdominal wall caudally. After the caudal duodenal flexure, the ascending duodenum can be followed medially, but its aborad aspect cannot be differentiated from the jejunum. The jejunum is usually relatively evenly distributed throughout the abdomen.

Throughout the duodenum and jejunum, the mucosa is normally the thickest layer (Figure 48.21). The other layers of the small intestinal wall are similar in thickness and thinner than the mucosa.



Figure 48.21 Longitudinal ultrasound image of the descending duodenum. The mucosa is the thickest layer of the duodenum wall. A hyperechoic area extending towards the serosal surface of the wall is noted. This is only noted on one side of the wall and consistent with a Peyer's patch and should not be confused with an ulcer or perforation.

The total wall thickness is thinner in smaller dogs than in large-sized dogs, ranging from 2.9–4.7 mm in small dogs, 3.0–5.5 mm in medium-sized dogs to 3.1–5.7 mm in large-sized dogs, respectively. In cats, the small intestinal wall usually ranges between 2 and 3 mm. Similar to contrast radiography, care must be taken that, in the descending duodenum, Peyer's patches (see Figure 48.21) are not misinterpreted as duodenal ulcers.

The mean number of peristaltic contractions noted in the stomach and proximal duodenum is 4–5 contractions per minute. In the midabdominal small intestinal tract, 1–3 contractions per minute are expected.

Contrast Radiography of the Small Intestine

Ultrasound has often replaced the need for contrast radiographic studies as these studies of the small intestinal tract are often laborious and time-consuming. However, if ultrasound is not available, contrast radiography is helpful to evaluate luminal diameter, wall thickness, mucosal surface, luminal content, and position of the intestinal tract. This is especially helpful in patients in which the abdominal serosal detail is decreased, due to their young age, emaciation, or a disease process. Furthermore, contrast radiography can provide additional information for evaluating intestinal transit times.

Before an upper gastrointestinal contrast study is performed, orthogonal survey radiographs of the abdomen should be done. If dilation of the intestine is present, suggesting ileus, a contrast study might be contraindicated. If the ileus is functional, the contrast agent will usually move very slowly through the intestinal tract and if a mechanical ileus (due to an obstructing foreign body, for instance) is present, the time required to complete a thorough contrast radiographic study may inappropriately delay surgery. If, based on radiographs, an intestinal perforation is suspected, the patient should be referred to surgery. However, if an intestinal perforation is suspected and on survey radiographs no signs of perforation such as peritoneal gas are noted, a contrast radiographic study may provide useful additional information. Usually intestinal contrast studies are performed using barium sulfate suspension; however, if a perforation is suspected, an iodinated contrast agent may be preferred.

It is preferable that the patient is fasted before an intestinal contrast imaging study is performed. Sedation can affect the transit time of the contrast agent, and if necessary the effect of sedation must be considered. In dogs, acepromazine has shown minimal effects on intestinal motility, while providing a reasonable level of sedation. In cats, a combination of diazepam and ketamine shows a similarly low effect on intestinal motility while providing an acceptable level of sedation, and is preferable to acepromazine.

To perform a contrast study, the barium sulfate suspension or iodinated contrast agent is administered either through an orogastric tube or orally using a syringe. Orogastric tubing is preferred as it reduces the risk of aspiration. It is important to remember that if an ionic iodinated contrast agent is used, aspiration can lead to fatal pulmonary edema and therefore great care should be taken if these agents are used, especially in patients with a known history of swallowing problems or being prone to aspiration. The recommended volume of barium sulfate suspension is 8–12 mL/kg bodyweight for small or medium-sized dogs, 5–7 mL/kg for large-sized dogs, and 12–20 mL/kg for cats. Radiographs should be obtained at regular intervals. As mentioned earlier, for the stomach all four views of the abdomen should be obtained. However, for the small intestinal tract, orthogonal views are often sufficient. Usually radiographs at 0, 15, and 30 minutes and one, two, and three hours post contrast agent administration are obtained, until the contrast agent has reached the colon. Barium sulfate contrast agent can usually be seen in the duodenum within 15 minutes and in the jejunum within 30 minutes. After 90–120 minutes, it is common to see contrast at the level of the ileocecocolic junction. After 3–5 hours, it is common to see the contrast agent within the ileum and colon. Usually, in the dog using barium, the transit time for the small intestine ranges from two to four hours and emptying of the small intestine is typically noted around five hours post administration. In the cat, the transit of barium is faster and ranges from one to two hours.

If an iodinated contrast agent is used, it is usually given in a dose of 2–3 mL/kg bodyweight or approximately 700 mg iodine/kg bodyweight. Iodinated contrast agents can be diluted 1:1. They have a faster transit time through

the intestinal tract, and reach the colon in approximately half the time when compared with barium sulfate contrast agents. As the iodinated contrast agents transit more rapidly through the gastrointestinal tract, radiographic views should be obtained more frequently, usually every 10–30 minutes. As mentioned earlier, barium sulfate is inert and not metabolized by the gastrointestinal tract; however, iodinated contrast agents are absorbed by the mucosa of the intestinal tract and therefore the luminal contrast rapidly declines over time, making diagnosis of an intestinal lesion more difficult.

In the normal duodenum of the dog, small indentations of the contrast agent ("pseudoulceration") might be seen in the antimesenteric border of the wall. This is normal, and results from the presence of Peyer's patches. In the cat, a strong beading of the small intestine ("string of pearls" appearance) might be noted (Figure 48.22).

Barium-impregnated polyethylene spheres (BIPS) have been used in the past, but are now rarely used. Their main indications are in the evaluation of transit time of the gastrointestinal tract; however, their transit times were variable and as no coating of the intestinal wall is achieved, the indications for the use of BIPS are limited.



Figure 48.22 Upper gastrointestinal contrast radiographic study of a cat. Strong beading of the small intestine is noted ("string of pearls" appearance; *white arrow*). This is normal in the cat.

Inflammatory Disorders of the Small Intestine

Inflammatory bowel disease is a broad term encompassing all disease resulting in an inflammatory process of the intestinal wall. On survey radiographs, usually no abnormality is noted. It is important to remember that on survey radiographs, an increase in thickness of the small intestinal wall is difficult to impossible to assess as the presence of fluid and mucus within the intestinal tract can mimic intestinal wall thickening in loops of intestine with normal wall thickness. On contrast radiographic studies, a rapid transit of barium contrast agent might be noted. Additionally, the mucosal surface might be irregular and there might be a loss of normal fimbriation of the mucosa. Enteritis may be generalized or only involve segments of the small intestinal tract. Usually no ileus is present.

Ultrasound Features of Inflammatory Disease of the Small Intestine

The most common ultrasound finding noted in inflammatory disease is an increase in wall thickness with persistently preserved normal wall architecture. It is important to note that this is a nonspecific finding. Additionally, in enteritis the intestinal wall can be normal. It is reported that in dogs, duodenum wall measurements up to 6 mm and jejunum wall thickness measurements up to 7 mm may be normal.

In inflammatory disease, thickening of the intestinal wall can be local or generalized and as this is similarly noted in patients with intestinal neoplasia, it can be challenging to differentiate patients with neoplastic from patients with inflammatory disease using imaging alone. As an example, in feline patients with gastrointestinal eosinophilic sclerosing fibroplasia, focal, mixed echogenic masses with central hyperechoic areas and loss of wall layering have been described. These central hyperechoic areas within the masses were suspected to correspond to the areas of fibrosis noted on histopathology. These masses distort the normal intestinal wall architecture, which is frequently described with neoplastic intestinal disease. Another inflammatory example that can feature focal nonsymmetric thickening of the intestinal wall with altered or loss of normal wall layering is mast cell disease. In most animals with inflammatory intestinal disease, when increased wall thickness of the intestines is noted, the wall layering remains preserved and the thickening tends to be symmetric and circumferential.

Sonographically, in some patients it can be noted that only individual layers are affected and increased in thickness or altered in echogenicity. In cats, an increase in the muscularis layer thickness has been reported with chronic enteritis, but again, this finding is nonspecific as

Table 48.1 Common imaging findings assessed using ultrasound, contrast radiography or computed tomography in benign versus malignant intestinal wall thickening

Benign	Malignant
Symmetric	Asymmetric
Circumferential	Eccentric
Mild to moderate	Moderate to severe
Usually segmental or diffuse	Usually focal
	Frequently abrupt transition
Usually normal lumen width	Often focally narrowed intestinal lumen
Preserved wall layering	Lost wall layering
No or mildly enlarged lymph nodes	Moderately to severely enlarged lymph nodes

it has also been seen in normal patients or patients with neoplastic disease.

Hyperechoic lines within the mucosa which are perpendicular to the luminal surface have been associated with lacteal dilation in patients with protein-losing enteropathy and lymphangiectasia. In most of these patients, wall layering of the intestine is persistently preserved. Rarely, these hyperechoic lines have been noted in patients with neoplasia.

In some patients with inflammatory bowel disease, a mild increase in size of the jejunal lymph nodes might be noted (up to 10 mm in diameter; normal up to 5 mm in diameter). A more severe enlargement of jejunal lymph nodes is more suggestive of a neoplastic than an inflammatory process (Table 48.1).

Small Intestinal Obstruction (Mechanical Ileus)

Radiographic findings in small intestinal obstruction are dependent on the extent (incomplete or complete), location, and duration of obstruction. Small intestinal obstruction can occur secondary to foreign material, intestinal neoplasia or a mass causing compression of the intestinal lumen. Mineral or metal attenuating foreign bodies are radiographically easily detected but non-mineralized and nonmetallic foreign bodies within the intestinal lumen or masses of the small intestinal tract can be challenging to detect. Care should also be taken that mineralizations in the mesenteric fat (mesenteric fat necrosis, "Bates bodies") summating with loops of intestine are not confused with an intestinal foreign body (Figure 48.23). Bates bodies are usually an incidental finding and are more frequently seen in cats than in dogs.

Radiographic findings with mechanical intestinal obstruction include intestinal distension, visible foreign material, and stacking of small intestinal loops. Ambiguous radiographs may require additional imaging or repeat radiographs for optimum assessment. The most common sign utilized to diagnose mechanical obstruction is the presence of variations in the appearance of segments of small intestine (Figure 48.24). Typically, more orad loops are dilated and aborad to the obstruction there is a normal-sized population of small intestinal loops.

Various methods to assess the small intestinal diameter have been suggested, including comparison of the largest small intestinal diameter with the shortest height of the fifth lumbar vertebral body. A ratio of less than 1.6 is considered the upper limit of normal small intestinal diameter in dogs. If the values are below 1.6 an obstructive process is very unlikely. The higher the ratio,

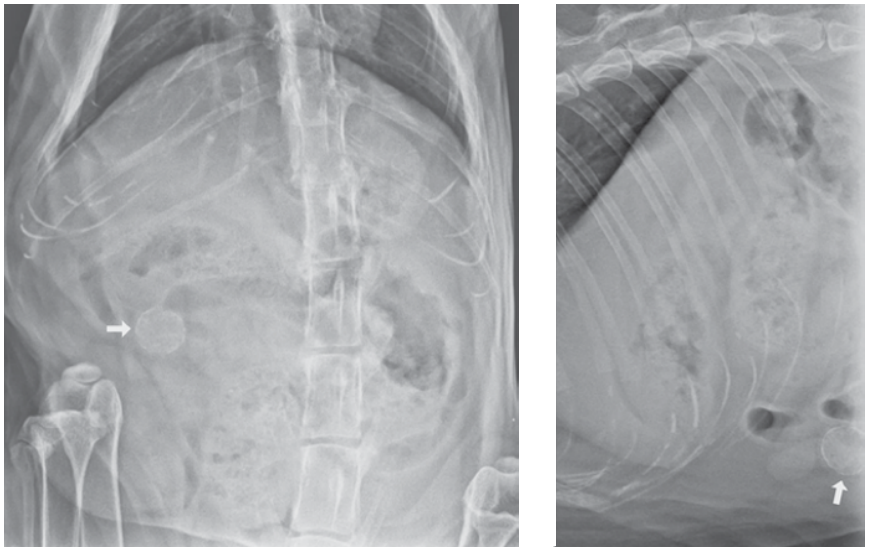


Figure 48.23 Focal calcified peritoneal body ("Bates body"). Dorsoventral and lateral radiograph of the cranial abdomen in a cat, which underwent thoracic radiographs for evaluation of the cardiopulmonary structures. In the midventral abdomen, a mineral attenuating round structure is noted, which is summating with loops of small intestine and should not be confused with an intraluminal foreign body. There is no small intestinal dilation.

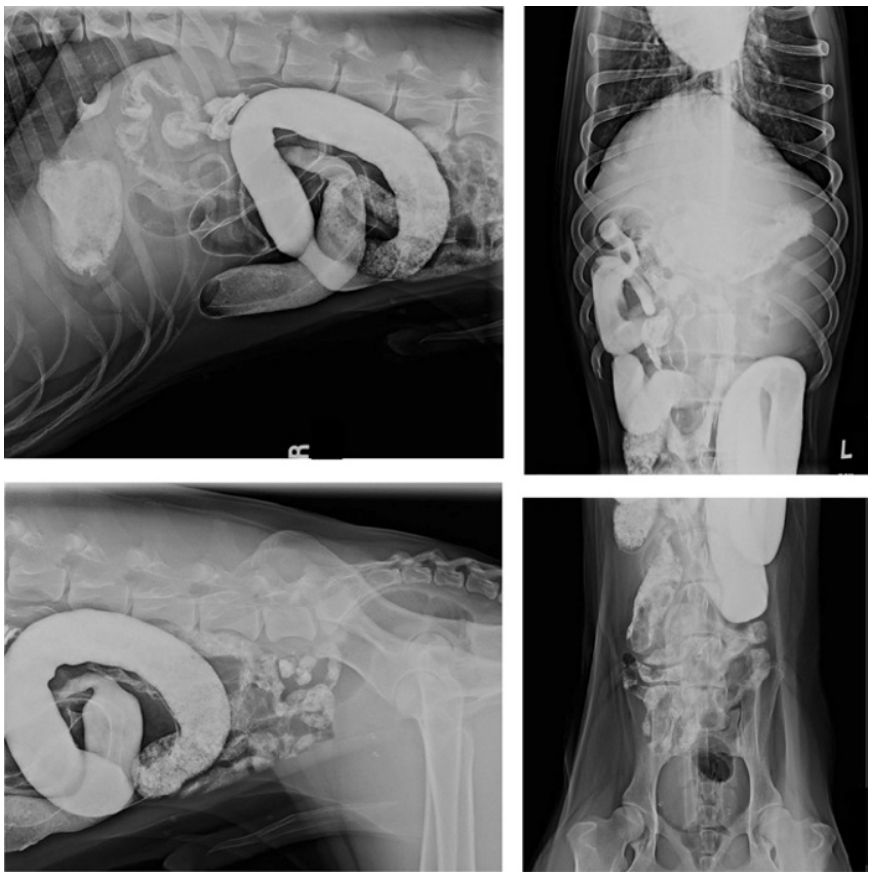


Figure 48.24 Small intestinal mechanical ileus. Lateral and VD radiographs of the abdomen post upper gastrointestinal barium study illustrate a severe dilation of a midabdominal segment of jejunum. On one end of the dilated jejunum, a curved radiolucent area is noted. In surgery, a hoof foreign body and 30 cm of devitalized jejunum were removed.

the more likely a mechanical obstruction is present. Another evaluation technique compares the largest small intestinal diameter with the width of the 12th rib, with two times the width of the 12th rib considered the upper normal limit. In the cat, the small intestinal diameter should not be greater than 1.2 cm. Another measurement technique described in cats calculates a ratio of the maximum width of a loop of small intestine, measured from outer to outer wall, divided by the dorsoventral height of the cranial endplate of the second lumbar vertebra with both measured on a lateral radiograph of the abdomen. Ratios lower than 2.0 were more likely associated with a nonobstructive intestinal process and with ratios larger than 3.0, the increased small intestinal diameter was more than 70% likely to be associated with an obstructive intestinal process (Table 48.2).

Single measurements should not be used as the sole criterion for diagnosis of mechanical obstruction; other radiographic findings and the history of the patient should be evaluated when considering the differential diagnoses. If the radiographic findings are equivocal and repeat radiographs are obtained, the presence of radiopaque foreign material in a similar location over a 24–48-hour period should increase the suspicion of mechanical ileus.

Table 48.2 Useful guidelines for evaluating the normal small intestinal diameter

Measurement	"Rule of thumb"
Compared to shortest height of the 2nd or 5th lumbar vertebra	Less than 1.6 times
Compared to width of the 12th rib	Less than 2 times
Compared to other normal small intestinal loops	Less than 2 times
Small intestinal diameter	In the cat less than 1.2 cm

Small Intestinal Foreign Body

Radiographically, radiopaque foreign bodies are the easiest to identify. Foreign bodies containing air, especially when creating a characteristic pattern such as in peach pits, walnuts, or corncobs, can easily be identified radiographically. If the foreign body leads to a complete obstruction of the small intestine, an orad dilation of the small intestine with normal intestinal diameter distal to the obstruction is typically noted. However, if the obstruction is incomplete or long-standing, minimal or no small intestinal dilation might be present.

In an ultrasound examination of the small intestine, foreign material in the intestinal tract often appears hyperechoic with strong distal complete acoustic shadowing. These shadowing structures often do not move with peristalsis and fluid distension of the small intestine orad to the lesion is often observed. Foreign bodies may have a distinct shape and surface, which allows differentiation of them from food material.

Linear Foreign Body

Linear foreign bodies cause plication of the small intestine and are usually the result of swallowing a linear object and fixation of part of the foreign material orally or in the stomach. In the cat, linear foreign bodies are often fixated around the caudal aspect of the tongue. In the dog, most linear foreign bodies are restrained by material in the stomach.

Classic radiographic features of linear foreign body obstruction include plication or "bunching" of the small intestine and the presence of intestinal intraluminal gas with an abnormal angular or tear drop shape (Figure 48.25). Perforation of the small intestine can occur, and in addition to bunching of the small intestines, a reduced serosal detail and free peritoneal gas may be seen (Figure 48.26).

Sonographically, an abnormal tortuous path of the small intestine, often the duodenum, with a central hyperechoic, linear structure might be noted. Additionally, an object with strong distal shadowing might be seen in the pylorus of the stomach.

Intussusception

Intestinal intussusception can be gastroduondenal, jejunojejunal (Figure 48.27), ileocolic, cecocolic, and colonocolic.

Radiographically, severely dilated loops of intestine might be noted. Sometimes a soft tissue attenuation mass with orad gas in a convex shape is seen.

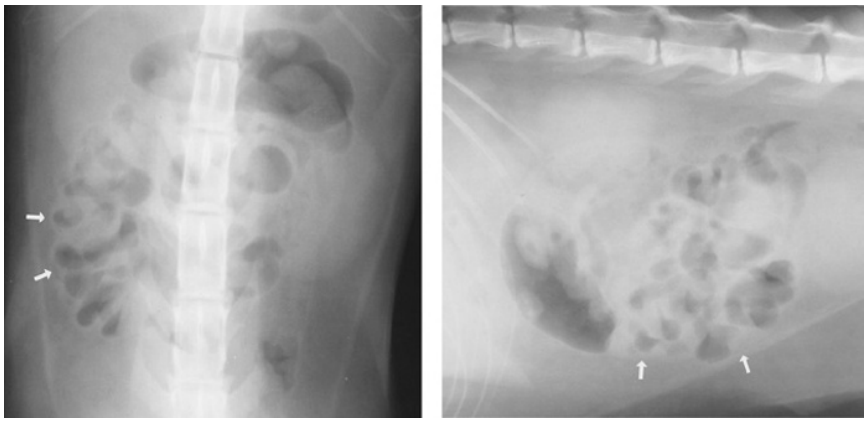


Figure 48.25 Linear foreign body. Ventrodorsal and lateral radiographs of the abdomen of a cat illustrating multiple bunched-up loops of small intestine. On cross-section, the luminal gas of the bunched-up small intestinal loops has an abnormal tear drop shape. Both findings are classic for linear foreign body.

(a) (b)

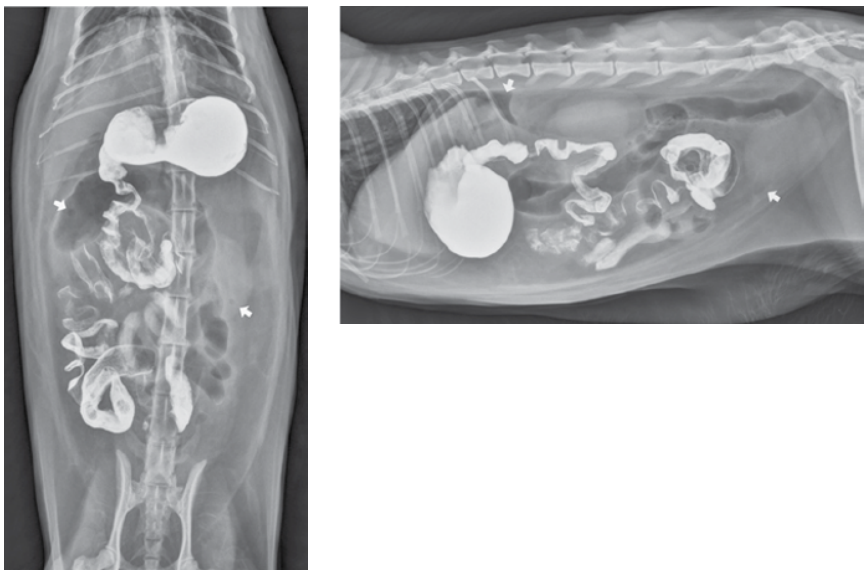


Figure 48.26 Linear foreign body with perforation. Ventrodorsal (a) and lateral (b) radiographs of the abdomen post upper gastrointestinal barium contrast study demonstrate bunched-up loops of small intestine, some with a tear drop shape of the luminal gas. The reduced serosal detail and peritoneal gas (*arrows*) are consistent with perforation.

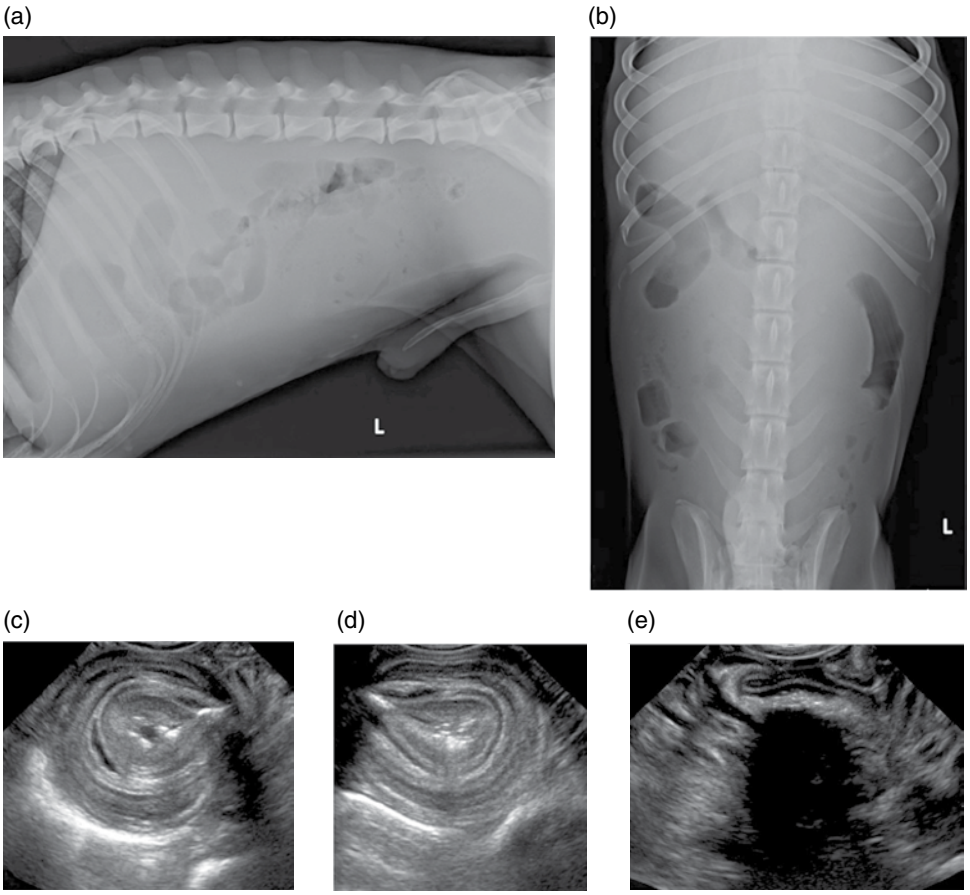


Figure 48.27 Jejunojejunal intussusception. Lateral (a) and ventrodorsal (b) radiographs of a thin dog. A reduced serosal detail is present. Gas-dilated loops of small intestine are noted in the cranial abdomen. In the caudal abdomen, a soft tissue attenuating mass effect with very small, irregular shaped loops of small intestine is noted. Transverse (c,d) ultrasound images revealed a series of hypoechoic and hyperechoic concentric rings with a small amount of central fluid and gas consistent with an intussusception. Additionally, in one segment of jejunum, hyperechoic distal shadowing material (e) consistent with foreign material is present.

Ultrasound may reveal a series of hyperechoic and hypoechoic concentric rings with a central hyperechoic area on transverse images ("target" or "onion ring" sign). On longitudinal ultrasound images, a similar pattern of hyperechoic and hypoechoic lines may be noted, in addition to circumferential inward folding of the intestinal wall at the site of the intussusception.

Tumors of the Small Intestine

Intestinal tumors account for approximately 3–10% of the tumors in cats and dogs. Approximately 75% of feline intestinal tumors are caused by lymphoma, compared to approximately 30% of intestinal tumors in the dog. In dogs, adenocarcinoma, lymphoma, and tumors of smooth muscle origin are most frequently seen.

If the intestinal neoplasm is small in size and does not cause obstructive disease, abdominal radiographs are often normal. If the intestinal mass is large or causes obstructive disease, radiographic signs consistent with mechanical ileus are noted. On contrast radiographic studies, circumferential narrowing of the lumen of the small intestine might be present.

Ultrasonographic findings in intestinal tumors vary widely and include focal or diffuse intestinal wall thickening, loss of normal wall layering, increased thickness of the wall layers, altered echogenicity (Figure 48.28), and loss of peristalsis. However, minimal sonographic or no sonographic changes of the intestinal wall have also been noted in lymphoma. Involvement of regional lymph nodes may be present, characterized by increased size, altered shape, and echogenicity. These observations may increase the suspicion for intestinal neoplasia, and help stage disease.

Intestinal Adhesions

There is limited information about the imaging of adhesions in veterinary patients. If intestinal adhesions lead to mechanical ileus, dilated loops of small intestine may be noted. Radiographically, stacking of loops of small intestine, which do not change position with repositioning

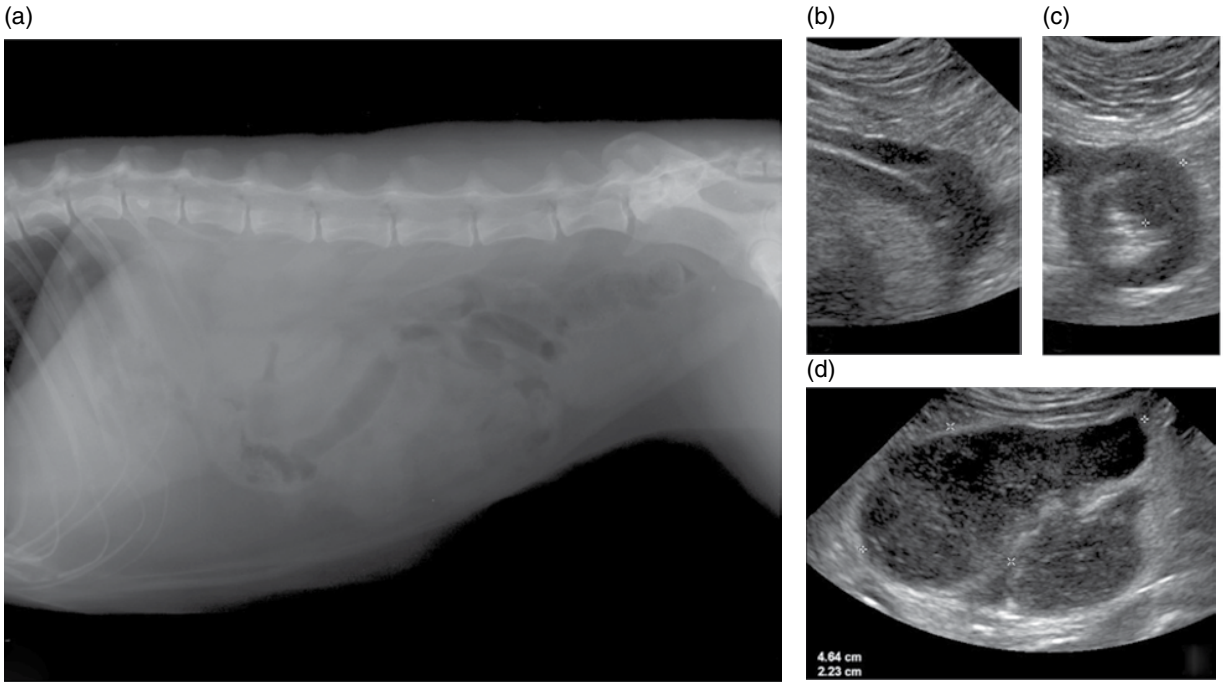


Figure 48.28 Intestinal lymphoma. Lateral radiograph (a) of the abdomen of a cat. In the midabdomen, a soft tissue attenuating mass effect is noted and segments of small intestine are dorsally displaced. On longitudinal (b) and transverse (c) images of the jejunum, a focal, eccentric wall thickening with loss of wall architecture and reduced echogenicity is noted. The jejunal lymph nodes (d) are severely enlarged and heterogeneously hypoechoic. The severe lymphadenopathy in combination with the jejunal wall changes is highly suspicious for neoplasia such as lymphoma, which was confirmed with cytologic samples obtained with ultrasound guidance.

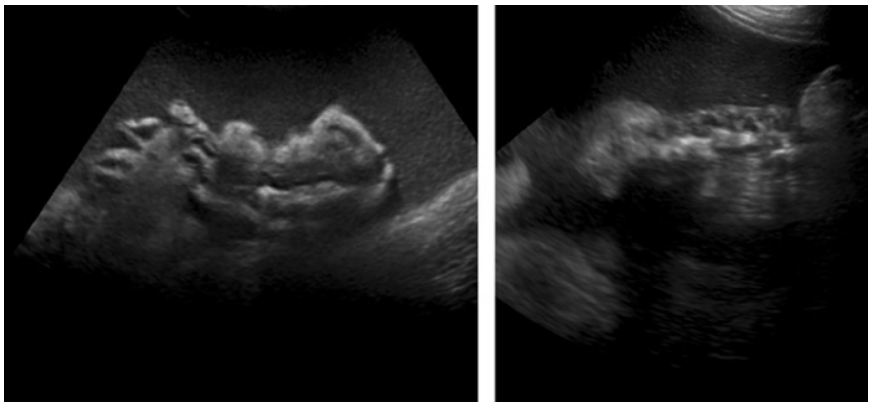


Figure 48.29 Longitudinal ultrasound images demonstrating severely corrugated loops of jejunum with peripheral hyperechoic tissue. A large amount of echogenic peritoneal fluid is present. The patient had a severe peritonitis secondary to perforating gunshot wound of the abdomen.

of the patient or repeat radiographs, may be present. In human patients, the lack of peritoneal fat between the loops of small intestine and abdominal wall has been described as a potential indicator for adhesions. On ultrasound, corrugation of small intestinal loops or lack of mobility of loops in the abdomen may be noted (Figure 48.29). Additionally, hyperechoic strands of tissue connecting segments of small intestine with each other or the abdominal wall may be present.

Intestinal Herniation

Intestinal herniation can occur through a defect in the mesentery, abdominal or body wall, perineum or diaphragm. The position of the small intestine is usually easily assessed using orthogonal radiographs. If there is a loss of serosal detail such as in young or emaciated patients or when peritoneal fluid is present, contrast radiography or ultrasound may be required to evaluate the position of the small intestine.

Small Intestinal Volvulus and/or Torsion

Small intestinal volvulus and/or torsion are rare in dogs and have seldom been described in cats. In cases of intestinal volvulus, the intestines rotate around the mesenteric axis, causing vascular compromise. Rotation along the long axis of the intestine is termed *torsion*.

Both intestinal volvulus and torsion can occur concurrently. The most commonly involved segment of small intestine in an intestinal volvulus of the dog is the jejunum. Radiographic findings in the early phases of this disease are vague and nonspecific. It is not uncommon that radiographs are normal. In the later phases of disease, generalized dilation of the intestines (paralytic ileus) may be noted; sometimes a circular position of the intestines might be present.

Paralytic (Functional) Ileus

Paralytic or functional ileus is a dysfunction of the musculature of the gastrointestinal tract resulting in dysmotility due to a variety of causes (neurologic, metabolic, vascular impairment, toxic).

Establishing a radiographic diagnosis of functional intestinal ileus can be challenging. The most common radiographic finding is a diffusely dilated small intestinal tract. Focal dilation of the small intestinal tract is more commonly noted with mechanical obstruction but there is likely a commonality between these two diseases.

A barium contrast radiographic study can be performed and a diffuse dilation of the intestinal tract may be noted; however, the lack of motility might result in incomplete transport of the barium through the intestinal tract and therefore in an incomplete evaluation of the intestinal tract, or leave the false impression of obstruction. Ultrasound might provide more information as it allows evaluation for the presence of intestinal peristalsis in addition to identifying intraluminal or intramural lesions. Sonographically amotile and stiff intestinal walls may be noted.

Intestinal Ulceration/Perforation

Survey radiographs can be normal in intestinal ulceration and perforation. However, in perforation, frequently either peritoneal free gas and/or fluid can be seen. Ulcerative disease of the intestinal tract is most commonly seen in the duodenum. As the normal Peyer's patches present in the duodenum can appear as focal areas of thickening ("pseudoulcers") on ultrasonographic and contrast radiographic studies, care must be taken to not confuse this normal finding with disease. In a contrast radiographic study in ulcerative disease, focal thickening of the intestinal wall with variable outpouchings can be noted. If perforation has occurred, contrast leakage into the peritoneal cavity may be present.

On ultrasound examination of patients with ulceration, regional thickening of the intestinal wall with small hyperechoic speckles representing gas in the intestinal wall may be present. If perforation of the intestinal wall is present, these hyerechoic speckles can be traced through the intestinal wall into the surrounding mesenteric fat and peritoneal cavity. Additional ultrasonographic findings noted with intestinal perforation can include adjacent hyperechoic (bright) mesenteric fat, peritoneal fluid, reduced gastrointestinal motility, corrugation of the intestinal tract, and regional lymphadenopathy.

Postoperative Appearance of the Stomach and Small Intestine

The most common reasons for obtaining postoperative radiographs include the evaluation of feeding tube placement (gastric, gastrojejunal, etc.) or if the patient is not improving as expected post surgery. Postoperative imaging studies are also used to determine a baseline appearance, which may result in easier detection of postoperative complications. The evaluation of postoperative imaging studies can be challenging and it is crucially important to be familiar with the anatomic and physiologic changes that occur during as well as postoperatively and be familiar with the surgical technique used.

Radiography is often used as a first technique to evaluate for the extent of peritoneal gas and fluid, position of the stomach and intestines as well as the presence and position of surgical devices including drains and tubes. As noted previously, functional ileus of the stomach and intestines occurs commonly post surgery and can result in vomiting, diarrhea or constipation. Radiography, ultrasound, and CT can all be used to evaluate for the presence of free peritoneal gas. Radiography is currently the most commonly used technique, but a small volume of free abdominal gas can be difficult to recognize on conventional radiographs made with a vertically directed X-ray beam because the gas bubbles are small and irregular in shape and may be misinterpreted as bowel gas unless they are located in a region where gastrointestinal structures are normally not located. Radiographs can be obtained with a horizontal X-ray beam, with the patient either in dorsal recumbency, so that the gas accumulates beneath the abdominal wall, or in lateral recumbency, so that the gas rises to the highest aspect of the abdomen and can usually be found under the abdominal wall in the craniodorsal abdomen. Most of the peritoneal gas is absorbed in 3–7 days, but it has been reported that peritoneal gas might be noted on radiographs for up to 25 days post surgery. Ultrasound is a highly sensitive technique to evaluate for the presence of peritoneal gas, but in studies in human patients, it has been noted that the ability to detect gas is highly operator dependent.

Peritoneal fluid can be noted on radiographs for up to 1–2 weeks, especially if the fluid is proteinaceous such as serum, blood, and lymph, which are absorbed more slowly. Solutions containing water and electrolytes are absorbed more rapidly by the peritoneal membrane and

might not be visualized after 24 hours on abdominal radiographs.

Depending on the surgical intervention, radiographic changes may or may not be present. Usually no changes are noted if a partial gastrectomy or gastric biopsies have been performed. Additionally, no displacement of the stomach would be expected with these procedures. If a gastropexy was performed to reduce the risk of a gastric dilation volvulus in the future, or to inhibit cranial movement of the stomach, it is expected that the pylorus will be near the right lateroventral abdominal wall. Commonly, the pyloric antrum will be displaced caudoventrally and will be noted caudal to the last rib. If an enterotomy or intestinal biopsy has been performed, usually no radiographic changes are expected. Radiographic changes are only expected if the surgery has led to adhesions or if an extensive intestinal resection has been performed.

Ultrasound can aid in visualizing the gastropexy or enterotomy site to evaluate healing of the suture site and for the presence of adhesions. The most common ultrasound features noted are alterations or loss of wall layering. An increase in wall thickness is commonly noted at the site of the gastropexy or enterotomy. An increased echogenicity of the mesenteric fat adjacent to the surgical site and variable amounts of peritoneal fluid containing hyperechoic particles may be noted. It is expected that the increased echogenicity of the mesenteric fat and the peritoneal fluid resolves in the majority of cases within approximately 10 days post surgery.

Large Intestine

The large intestine consists of the cecum, colon, and rectum. The cecum is a S-shaped blind-ending tube located usually in the right cranial abdomen at the junction of the ileum and colon. The colon is divided into three distinct anatomic areas: the ascending, transverse, and descending colon. The colon is attached by a short mesentery, which gives the colon a semifixed position in the abdomen. The ascending colon continues from the ileum at the ileocecocolic junction and runs in a cranial direction. The ascending colon is usually positioned caudal to the stomach and is frequently noted to the right of midline; the ascending colon continues into the transverse colon. The transverse colon is located caudal of the stomach and runs from right to left in the abdomen. The descending colon continues from the transverse colon and runs caudally along the left lateral aspect of the abdomen. Once the descending colon enters the pelvic canal, it is called the rectum, which continues to the anus.

Radiographic Examination of the Large Intestine

The cecum is located to the right of midline on ventrodorsal and centrally in the abdomen on lateral radiographic views. In the dog, usually a characteristic gas pattern of the cecum is noted (corkscrew- or C- or S-shaped appearance). In the cat, the cecum is not commonly seen. The colon is usually localized by its content. The ascending colon can be identified when filled with gas or fecal matter in the right cranial abdomen. The transverse colon can be noted caudal to the stomach and can be displaced caudally with enlargement of the stomach or pancreas. The descending colon is usually located left of midline, but if filled with a large amount of fecal matter and the patient has been held in a right lateral position, the descending colon may also be seen to the right of midline in normal patients. The rectum is the most caudal extension of the descending colon, starting at the pelvic canal and ending at the anus.

Radiographic evaluation of the colon includes evaluation of the content as well as the size of the colon. Most of the feces should be seen in the colon with only a small quantity present in the rectum. The normal diameter of the colon can be quite variable and depends on defecation habits and time since last defecation. However, radiographically, the normal colon diameter should be less than the length of the fifth or seventh lumbar vertebral body. The seventh lumbar vertebra is often more variable in length than the fifth and therefore using the fifth lumbar vertebra might be a more reliable tool in the decision-making process. Additionally, the colon diameter should be less than three times the diameter of the small intestine.

Ultrasound Examination of the Large Intestine

The ileocecocolic junction is usually noted in the right cranial abdomen, but it can be quite mobile. Orad to the ileocecocolic junction, the terminal portion of the ileum can be noted, which can easily be followed orad. The ileum has a distinct appearance, characterized by a prominent submucosal layer and often folded appearance of the luminal mucosa (see Figure 48.11). Adjacent to the ileum, the cecum can be seen, which is a blind-ending sac on one side and can be followed to the ileocecocolic junction on the other side. The cecum is often difficult to examine using ultrasound, especially in the dog, where the presence of gas in its lumen may limit its evaluation. In the cat, the cecum usually does not contain gas and therefore it is easier to evaluate. The cecal wall tends to be more hypoechoic than the colon wall and has an irregular luminal mucosal surface. From the ileocecocolic junction, the ascending colon can be followed cranially into the transverse colon, which then can

be followed caudally into the descending colon. The descending colon can also be seen caudally in the abdomen, dorsal to the urinary bladder. Ultrasonographic assessment of the rectum is limited due to its location within the pelvic canal and therefore it is not accessible with ultrasound. The cranial aspect of the rectum may be visualized by tilting the ultrasound probe caudally from cranioventral to the pelvic floor. Positioning the ultrasound probe from caudal in the anus area and tilting it cranially can visualize the caudal aspect of the rectum.

Due to the typically hyperechoic content (fecal material and gas) in the colon, the colon wall close to the ultrasound probe may be the only aspect of the wall that is easily seen. The colon wall has a characteristic ultrasound appearance and is usually hyperechoic relative to the small intestine. All five layers of the colon wall are of equal thickness and are thinner than in the small intestine (see Figure 48.11). The colon wall in the dog and cat is usually very thin and only measures 1–2 mm in thickness, rarely exceeding 3 mm in normal dogs. If the colon is very empty, luminal folding of the colon wall can be noted and the wall might subjectively appear thickened. It is a common finding that no peristalsis is noted in the colon.

Barium Examination of the Large Intestine

Indications for performing a contrast study of the colon include evaluation of the position and appearance of the colon, the presence of strictures, suspected intussusception, masses associated with the colon, congenital abnormalities, or colitis. Patient preparation should include fasting for 24 hours if no preexisting clinical contraindication is present. If only positional information of the colon is needed, a pneumocolonography might provide sufficient information. It is important to remember that an upper gastrointestinal contrast radiographic study is often insufficient for evaluation of the colon as the colon is incompletely distended with contrast material and as fecal material often creates intraluminal contrast filling defects, which can be misinterpreted as mural or intraluminal lesions. Therefore, if a contrast study is performed to evaluate the colon wall, a more extensive preparation of the patient is required to ensure that the colon is empty.

Patient preparation should include a laxative 24 hours prior to cleansing enemas of the colon. For the contrast radiographic procedure, sedation or anesthesia is preferred as it limits straining by the patient. Barium enemas are best performed by placing a soft-tipped catheter with an inflatable cuff within the anal sphincter. The cuff should be gently expanded to avoid overextension of the rectum or anal sphincter. In unsedated patients, expansion of the cuff or placement of a catheter into the rectum might not be tolerated. Barium sulfate suspension (5%) at 7–14 mL/kg bodyweight should be slowly infused (over 5–7 min) to allow contrast to extend to the ileocolic junction. If available, fluoroscopy can be used to monitor the advancement of the contrast agent within the colon and especially to ensure that contrast is not infused beyond the ileocolic junction. Once the contrast agent is infused, the catheter should be closed off and the patient should be gently rolled to allow for uniform coating of the colon. Ventrodorsal and right lateral radiographic views should be obtained and additional views should be added as needed to fully evaluate the colon.

Double contrast radiography of the colon (double contrast colonogram) can be performed by slowly and carefully insufflating air into the colon after a barium enema has been performed. Double contrast colonography can improve evaluation of colon wall lesions, help identify strictures, and improve evaluation of the ileocecocolic junction.

The mucosal surface of the colon should be smooth, continuous, and well defined when the colon is filled with barium contrast agent. In the colon of the dog, small lymph follicles can be found and this might present radiographically as small focal areas of thickening of the colon wall or spicules similar to very small ulcers. These areas should become less apparent once the large intestine is distended. In the cat, the largest aggregate of lymph follicles can be noted in the ileal area and apex of the cecum; however, this is usually not discernible on radiographs.

Pneumocolonography

The most common reason pneumocolonography is performed is to gain positional information about the colon, allowing differentiation between small and large intestines. Pneumocolonography provides a quick, safe, and easy way to outline the entire colon but provides only limited information about involvement of the mucosa, wall thickness and areas of the colon which cannot be distended. In cases where a wall lesion is suspected, a barium enema should be performed. Pneumocolonography is most easily performed by using either a soft-tipped catheter or catheter-tipped syringe placed within the anal sphincter. In general, 1–3 mL of air/kg bodyweight should result in sufficient filling of the colon. It is important to ensure that the entire colon, including the cecum, is filled and distended with air. It is important to close off the catheter or syringe once the colon is insufflated to ensure that the air does not escape. Ventrodorsal and right lateral radiographic views should be obtained and additional views should be added as needed to fully evaluate the colon.

Computed Tomography of the Large Intestine

Computed tomography can be an excellent technique for evaluating the large intestine. Similarly to radiography, contrast is often needed to distend the colon and evaluate all aspects of the intestinal wall. When the colon is empty and the intestinal walls are collapsed, intestinal wall lesions are very difficult or impossible to identify. Additionally, if large amounts of fecal matter are present in the colon, artifacts created by this might limit visualization of the colon wall. Therefore, similar to radiography, optimal patient preparation, including cleansing enemas, should be performed before a contrast CT study of the abdomen is performed to evaluate the colon. The normal anatomy of the colon and regional lymph nodes is easily evaluated using CT and the ability to perform dorsal and sagittal reconstructions of the CT images helps to gain a better three-dimensional understanding of normal anatomy or pathologies. The colon wall is thin and measures 1–2 mm in thickness.

Virtual endoscopy using CT images can be performed. However, currently its use and clinical value are limited as CT does not allow assessment of the color of the colon wall or to obtain biopsies at the same time and evaluation of the wall is limited (Figure 48.30).

Inflammatory Disorders of the Large Intestine

In the acute phase of colitis there may be no abnormality present on survey or contrast radiographic studies. Infrequently, in cases of mild colitis, contrast radiographic studies show a mild thickening of the intestinal wall. Small areas of focal thickening, consistent with ulceration, may be noted. In more severe forms of colitis, more extensive thickening of the colon wall with larger areas of ulceration may be noted on contrast radiographic studies. With increasing disease severity, spasm of the colon might be present. With chronic colitis, decreased width, shortening and enlargement of the colon have all been described.

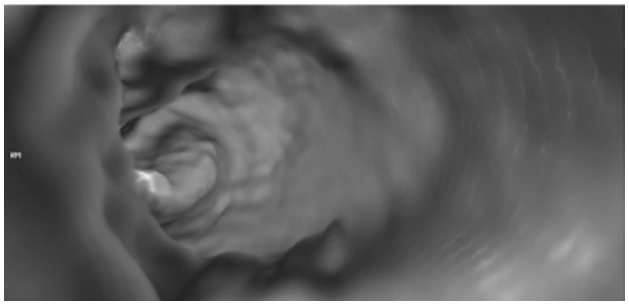


Figure 48.30 Virtual colonoscopy. Three-dimensional reconstruction virtual colonoscopy image of a normal colon. Several colonic folds are visible.

On ultrasound examination, increased thickness of the colon wall with loss of wall layering and decrease of echogenicity of the colon wall may be noted. Mild regional lymph node enlargement may be present.

Typhlitis can be challenging to diagnose clinically as well as via imaging techniques. In mild to moderate typhlitis, no radiographic changes are often noted; in severe typhlitis on contrast radiographic studies, similar changes as seen in colitis can be noted. On ultrasound, thickening of the cecum wall with a decrease of echogenicity of the wall layers might be noted (Figure 48.31).

Tumors of the Large Intestine

Tumors of the large intestine account in dogs for more than 60% of the gastrointestinal tumors diagnosed; however, it is important to remember that the prevalence of gastrointestinal neoplasms in dogs is still only 3–10% of all tumors diagnosed. Some benign tumors, especially when polypoid, might not require extensive imaging. Survey radiographs are often negative and do not provide additional information. Contrast radiography using a barium enema or double contrast colonography may allow localization of the colon wall thickening. However, colonography only allows limited evaluation of regional lymph nodes and other abdominal organs, such as the liver. Therefore, if a malignant lesion is suspected, contrast-enhanced CT or ultrasound (Figure 48.32) are preferred. These techniques allow not only visualization of the colon wall mass, but also staging of regional lymph nodes, the peritoneum, and parenchymatous organs. If a colon wall mass is suspected, CT may be preferred over ultrasound, as lesions within the pelvic canal show only limited accessibility using ultrasound due to the lack of penetration of the ultrasound wave through the osseous structures of the pelvic canal.

Megacolon

Megacolon is a broad descriptive term indicating enlargement of the colon, which can be due to lack of innervation or abnormal innervation of the colon wall, mechanical obstruction (e.g. malunited pelvic fractures, neoplasia, rectal stricture) or dietary or psychogenic causes. Idiopathic megacolon is the most common reason reported in the cat for enlargement of the colon. Patients with megacolon often have a history of constipation, painful or difficult defecation or tenesmus.

Classic radiographic findings in dogs and cats include a marked increase in the diameter of the colon (Figure 48.33). If the colon measures more than 1.5 times the length of the fifth or seventh lumbar vertebra, or more than three times the diameter of the small intestine, this is suggestive of a megacolon.

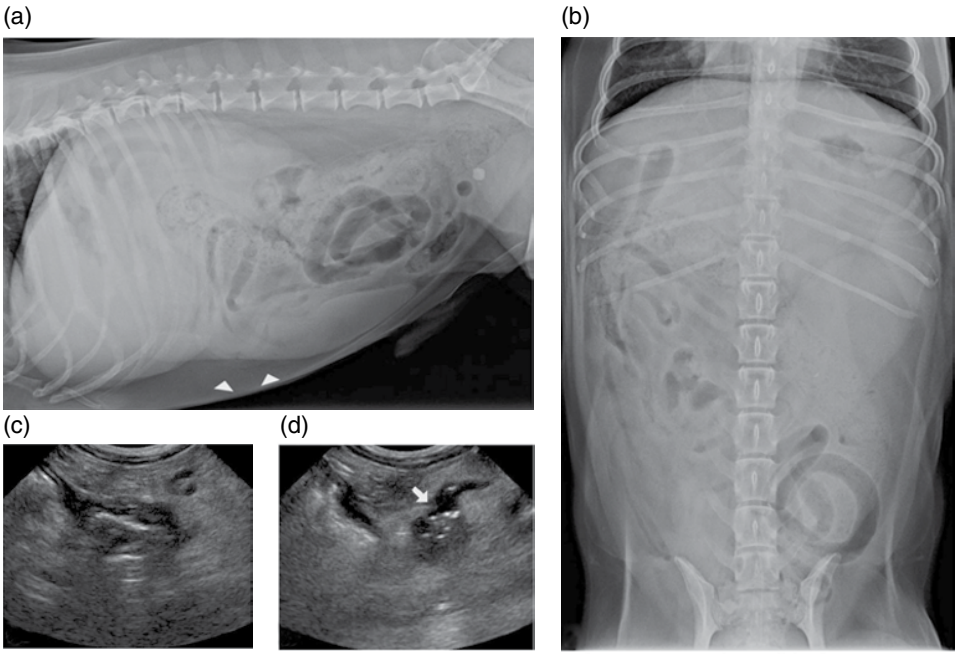


Figure 48.31 Cecal perforation secondary to typhlitis. Right lateral (a) and ventrodorsal (b) radiographs of the abdomen demonstrated a loss of serosal detail and a small amount of peritoneal free gas. The origin of the gas was not identified on radiographs; however, an intestinal perforation was suspected. A urinary bladder stone was noted. Longitudinal ultrasound images of the cecum (c) and ileocecocolic area (d) illustrating thickening of the cecum wall with loss of wall layering and decrease in echogenicity. A small amount of peritoneal fluid with hyperechoic specular reflectors, characteristic of gas, is noted adjacent to the cecum. In surgery, a perforation of the cecum was noted. The cecum was removed and histopathology confirmed typhlitis.

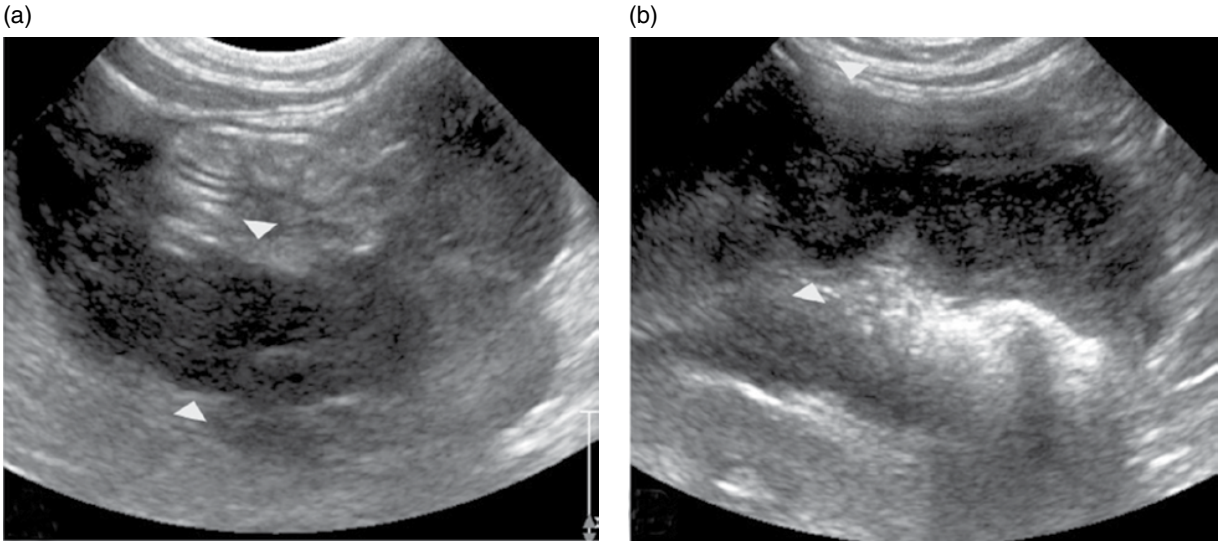


Figure 48.32 Lymphoma of the colon wall in a cat. Transverse (a) and longitudinal (b) ultrasound images of the descending colon. The colon wall is severely thickened (*arrowheads*) with a loss of wall layering and a decrease in echogenicity.

Megacolon Secondary to Abnormal Innervation or Smooth Muscle Function

Several diseases such as cauda equina syndrome, sacral spinal cord deformity in Manx cats (sacrococcygeal agenesis), aganglionosis or hypoganglionosis of the colon wall can lead to megacolon.

Radiographically, patients with abnormal innervation or smooth muscle functional abnormality of the colon wall may present with various degrees of enlargement of the colon (Figure 48.34). With aganglionosis or hypoganglionosis of the colon, a severe dilation of the colon is noted. This dilation often abruptly narrows towards the

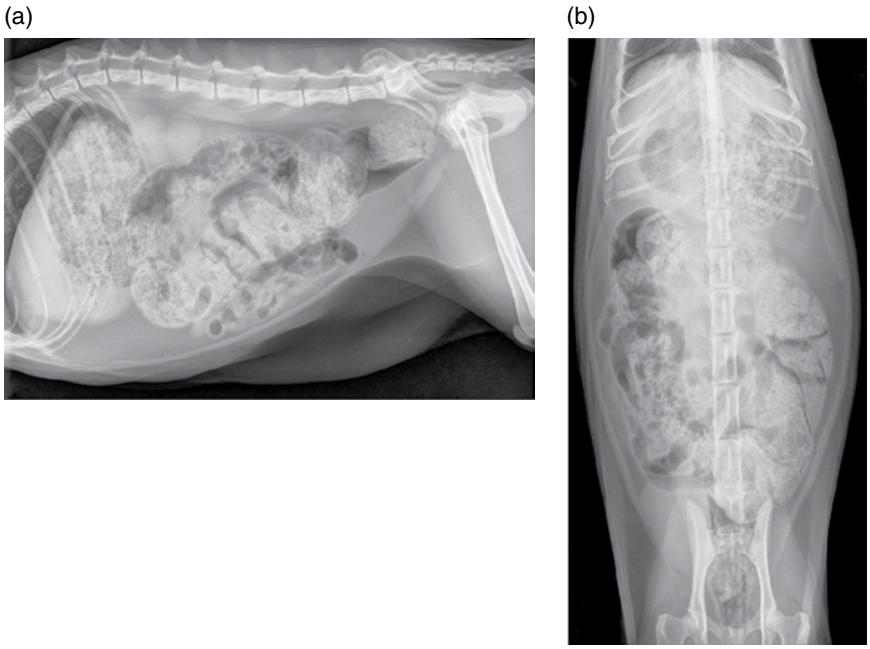


Figure 48.33 Megacolon in an obstipated cat. Right lateral (a) and ventrodorsal (b) radiographs illustrating a severely enlarged colon. The fecal material is mineral attenuating and large desiccated fecal balls, which cannot be emptied, are noted in the descending colon to rectum.

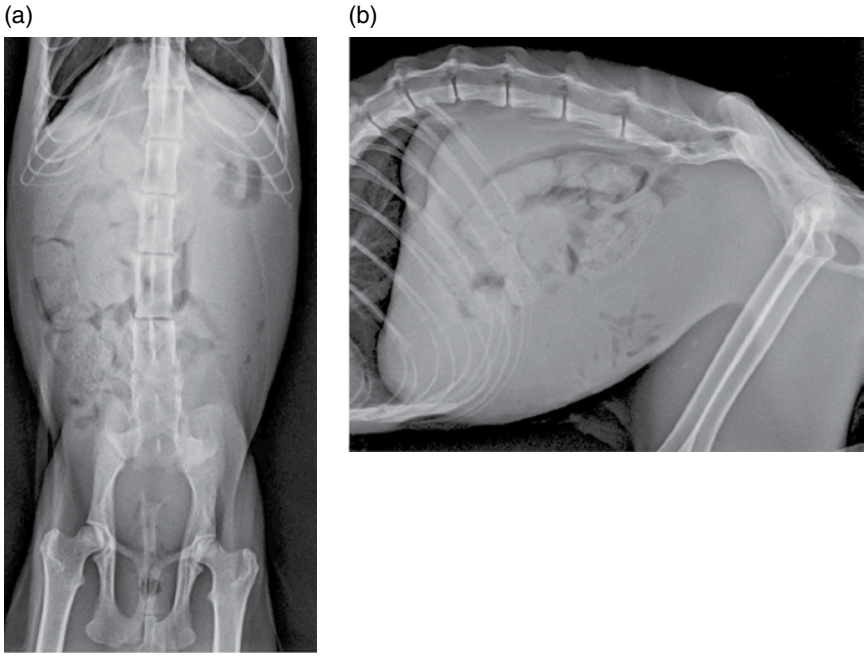


Figure 48.34 Lumbosacral malformation in a Manx cat with secondary megacolon. Ventrodorsal (a) and lateral (b) radiographs of the abdomen illustrating a fusion of the last lumbar vertebra and sacrum. The colon is filled with fecal matter and dilated. A reduced serosal detail is noted in the abdomen. The cat is emaciated.

rectum and anus, as these segments of the intestinal tract are frequently not involved in the disease process (Figure 48.35).

Large Intestinal Mechanical Obstruction

Large intestinal mechanical obstruction can lead to megacolon. Radiographically, in contrast to patients who have a lack of nerve or muscle function of the colon wall, dilation of the colon and rectum can be noted. In these cases, the osseous and soft tissue structures of the pelvis and lumbosacral spine should be carefully evaluated for the presence of pathologies causing obstruction of the large intestine. Radiopaque foreign material such as stones (Figure 48.36) or metallic objects can easily be identified on survey radiographs. Once a foreign object has made it through the small intestinal tract into the colon, it is usually expected that it will pass unhindered through the colon.

In dogs with prostatic enlargement or neoplasia, with or without secondary sublumbar lymphadenopathy, a

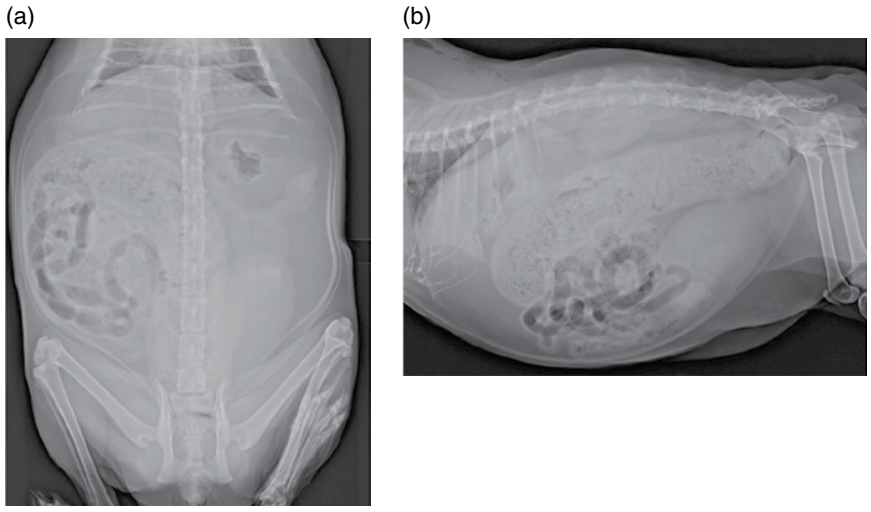


Figure 48.35 Severe megacolon in a Manx cat. Ventrodorsal (a) and lateral (b) radiographs of the abdomen illustrating severe distension of the colon with fecal matter. The colon narrows abruptly towards the rectum. A small amount of urinary bladder sediment is noted. A small amount of subcutaneous emphysema from a subcutaneous fluid injection is present.

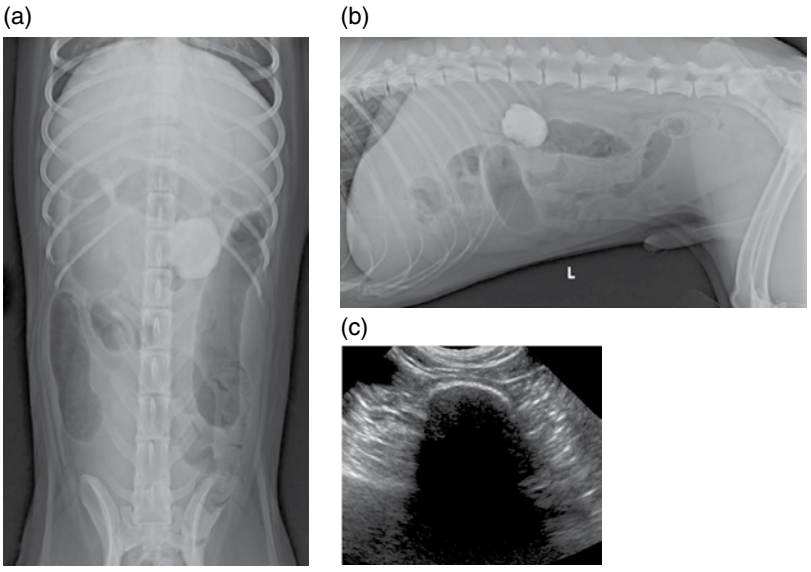


Figure 48.36 Stone in colon. Ventrodorsal (a) and left lateral (b) radiographs of the abdomen of a dog. A mineral attenuating structure (stone) is noted summating with a gas-filled loop of intestine on the lateral radiograph. On the VD radiograph, the stone is summating with the descending colon. The small intestines are in part fluid filled and in part gas dilated, which was concerning for a mechanical ileus. Transverse ultrasound image (c) illustrating a hyperechoic, distally shadowing structure representing the stone within the colon. No small intestinal obstructive disease was noted.

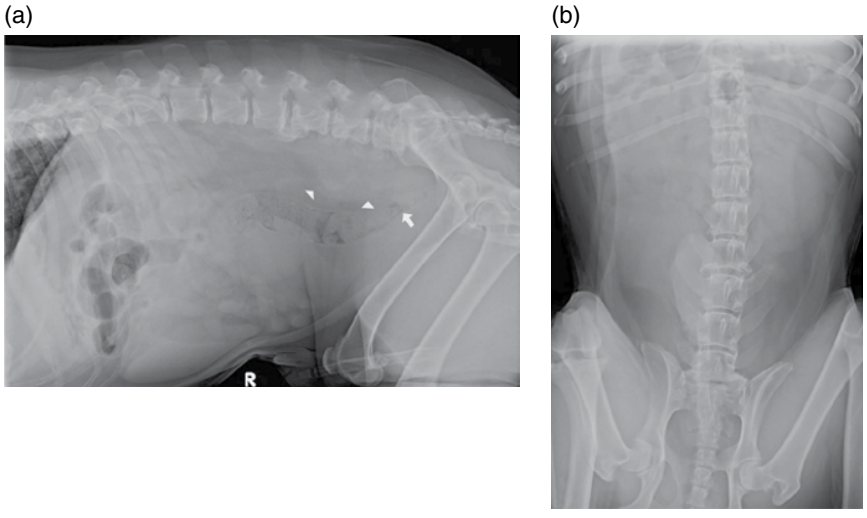


Figure 48.37 Severe sublumbar lymphadenopathy secondary to prostate neoplasia. Right lateral radiograph of the abdomen illustrating ventral displacement and compression of the descending colon (*arrowheads*) secondary to severe sublumbar lymph node enlargement due to prostate neoplasia and metastases to the lymph nodes.

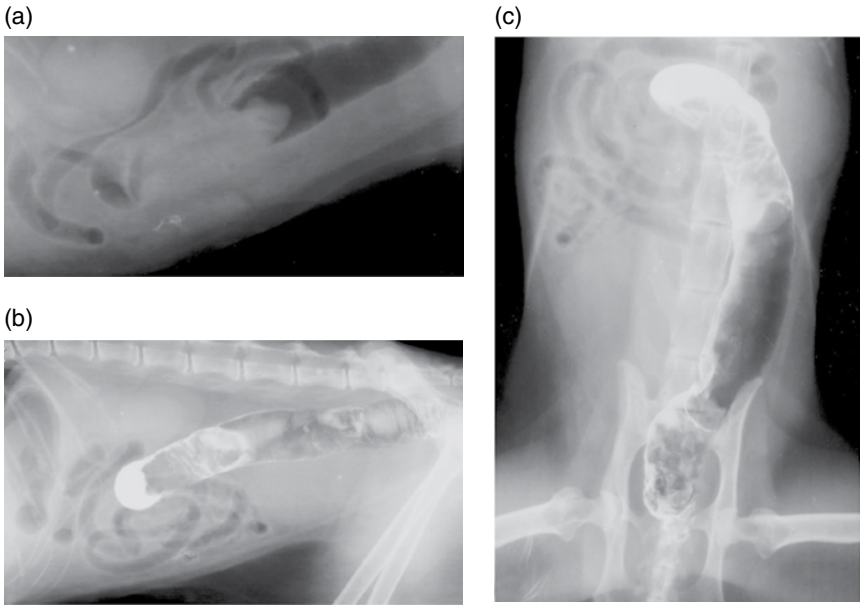


Figure 48.38 Colonocolic intussusception. On survey radiographs (a), a soft tissue attenuating mass with rounded borders is noted in the cranial aspect of the descending colon. After a barium enema was performed (b,c), a contrast-sparing filling defect is noted in the colon. This study was followed by an upper gastrointestinal contrast study to evaluate the position of the ileum. A colonocolic intussusception was confirmed at surgery.

dorsal displacement and compression of the colon is commonly noted. Additionally, if sublumbar lymphadenopathy is present, the descending colon ventral to the caudal lumbar to cranial sacral spine is ventrally displaced (Figure 48.37).

Cecal or Colonic Intussusception

The most common intussusceptions seen in the colon are ileocolic, cecocolic, and colonocolic. The intussusception might be seen as a soft tissue attenuating mass with round borders within the colon on survey radiographs, especially when the colon is gas filled (Figure 48.38).

In ileocolic intussusception, the cecum and ascending colon are not filled with gas, whereas in normal dogs some degree of gas filling is normally seen in the cecum. In cecocolic intussusception, the cecum can be seen as a radiolucent filling defect in the colon on a barium enema. The ileocolic junction and ileum are persistently normally seen (Figure 48.39).

Colonic Torsion and Volvulus

Colonic torsion and volvulus is a rare disease that has a high mortality, similar to gastric and small intestinal torsion and volvulus. A moderately to severely distended colon can be noted and the colon can be abnormally positioned. Frequently the colon is displaced cranially (Figure 48.40). However, radiographic findings in colonic torsion or volvulus may also be nonspecific and early exploration might be necessary to correctly diagnose and correct a colonic torsion or volvulus.



Figure 48.39 Cecocolic intussusception (cecal inversion) in a dog. Ventrodorsal radiograph post barium enema demonstrating an irregular-shaped radiolucent filling defect in the ascending colon, which is representing the cecum intussuscepted into the colon. The ileum and ileocolic junction are normal and contrast filled. No normal positioned cecum is identified.

Congenital Abnormalities of the Colon

A variety of congenital abnormalities have been described for the colon in the dog and cat including a short colon, atresia ani or rectum, double colon, diverticula, and fistula.

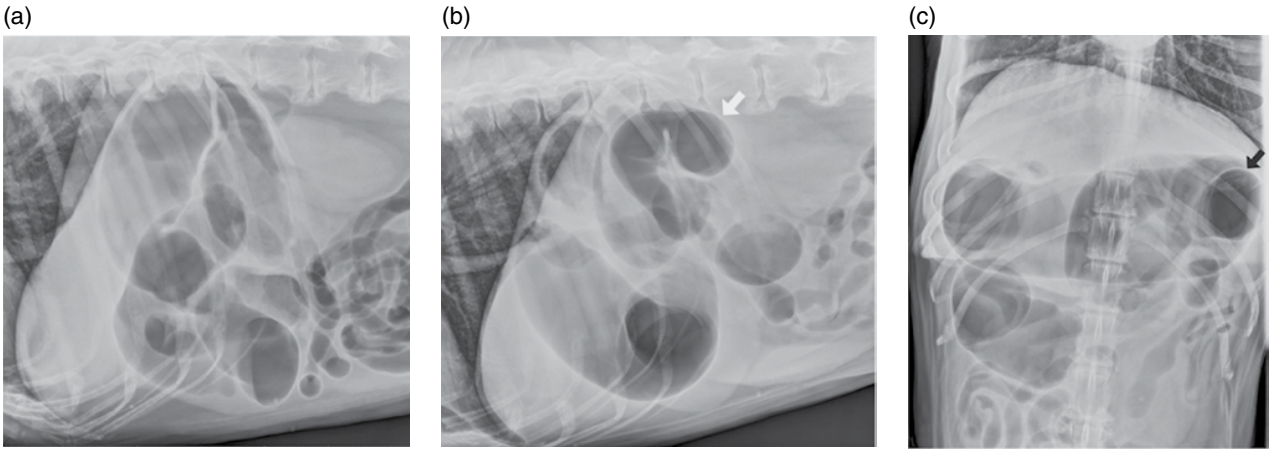


Figure 48.40 Colon torsion. Left lateral (a), right lateral (b), and ventrodorsal (c) radiographs of the abdomen of a dog. The colon is severely gas distended and cranially displaced. The cecum is dorsally and left laterally displaced (*arrows*). Most of the small intestinal segments are gas filled.

In patients with a short colon, the ileocecocolic junction is often positioned left lateral of midline at the cranial aspect of the descending colon. The clinical importance of this finding is unclear. Most congenital colon abnormalities require a contrast-enhanced study, either using radiography or CT, to fully evaluate the extent of the lesion. Especially when fistulae are present, a combination of an iodine enema and the use of intravenous iodinated contrast agents using CT might provide the best anatomic information. In diverticulae, a herniation of the mucosal layer through the muscular wall occurs. If a diverticulum is present in the rectum, it might be confused with sacculation on physical examination. Rarely, a diverticulum can rupture, which can lead to a significant retroperitonitis and peritonitis, which can be recognized radiographically by free peritoneal and retroperitoneal gas.

Displacement of the Colon

The most common displacement of the colon and/or rectum is into the perianal area, which occurs secondary to weakening or rupture of the pelvic diaphragm (perineal hernia). In addition to the displacement of the colon and/or rectum, retroflexion of the urinary bladder can occur, which causes obstruction of the urethra. On radiographs, usually a soft tissue attenuating mass can be seen in the perianal area usually ventral and lateral to the tail. This is often best seen on lateral radiographs. On ventrodorsal radiographs, lateral or caudal deviation of fecal matter in the colon and rectum may be noted. Sometimes a sigmoid shape of the colon and rectum can be seen.

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49

Gastrointestinal Endoscopy

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Gastrointestinal endoscopy is an attractive diagnostic tool for many gastrointestinal disease cases presenting to companion animal practitioners. This technique can allow direct visualization of the gastrointestinal mucosa in the esophagus, stomach, upper part of the small intestine, colon, and distal ileum. While some of these procedures are straightforward, entry into the upper part of the small intestine and the distal ileum can be quite challenging in some patients.

Endoscopy is often viewed as a much less invasive method of obtaining gastrointestinal mucosal biopsy samples than can be achieved with either exploratory laparotomy/celiotomy or laparoscopy-assisted full-thickness biopsies. While endoscopic biopsy has an advantage of lower risk and less perioperative morbidity, the quality of endoscopic biopsy samples is often found wanting. This is particularly the case with the use of smaller endoscopes with very narrow biopsy channels that limit the size of the biopsy instruments that can be passed.

With refurbished flexible endoscopy systems becoming more readily available on the market, and at reasonable prices, there is increasing utilization of these instruments and procedures in generalist practices. Competence in flexible gastrointestinal endoscopy requires meaningful amounts of hands-on practice, and guidance from an experienced operator in a hands-on training environment is the best way to achieve competence in a short period of time. The purpose of this chapter is to provide an overview of flexible endoscopic equipment types, correct handling and manipulation of the endoscope, methods for obtaining biopsies, a general overview of the steps for several endoscopic procedures, and the use of flexible endoscopy for some minimally invasive therapeutic procedures such as feeding tube placement and foreign body retrieval.

Endoscopy Equipment Options

All visual light endoscopes operate by channeling light from an external source, via fiberoptic light guides, to the area of interest. This light then illuminates the area being examined, and an image is formed. The actual mechanism leading to image formation is typically from one of two options: either the use of additional fiberoptic elements to return the light via an objective lens at the operating end of the scope (these are commonly called fiberscopes), or via direct capture of a digital image using an imaging chip at the distal, patient end of the instrument (videoendoscopes) (Figure 49.1). Fiberscopes represent an older technology, and are usually cheaper than equivalent-sized videoendoscopes, but they do have significant shortcomings. Fiberscopes are more affected by fiber breakage, as the image depends on light successfully traveling in both directions. The image is often quite dim, as there are more light losses involved with transit along the length of the scope and back. The generation of medical records with these endoscopes is also more difficult, requiring an accessory camera attached to the eyepiece, representing another potential point of failure. While fiberscopes were long the mainstay of flexible endoscopy in veterinary medicine, videoendoscopes are preferable due to superior image quality, greater ease of use, and greater ease of generation for permanent medical records.

Endoscopes used for gastrointestinal procedures should feature four-way tip deflection, allowing the deviation of the tip left or right of center and up or down. Tip deviation is defined relative to the midline of the control handle, with the control cluster in the operating hand. Some smaller scopes, designed for airway examination rather than gastrointestinal endoscopy, have only up and down deflection controls while left to right turns are made by turning the entire endoscope.

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Figure 49.1 A typical flexible videoendoscopy "tower" as used for most gastrointestinal endoscopic procedures in companion animal medicine. In this particular system, the light generator and image processor are in the same unit, with separate vacuum pump and image printer. In other systems the light source and image-processing functions may be separate components. Note the large monitor and scope rack at the top of the tower. While the scope rack is a safe place to rest the scope during the procedure, it is not recommended to transport the scope (particularly longer and heavier colonoscopes) on this rack when moving the tower.

Flexible endoscopes are available in a variety of sizes, with variations in both diameter and length. Greater diameter endoscopes will typically have larger working channels, allowing the use of larger biopsy instruments, snares or foreign body retrieval devices. Larger diameter endoscopes also have greater intrinsic stiffness, which can be both beneficial (passing through restrictions such as the antrum and pylorus is easier with a stiffer endoscope) and a complicating factor (it is difficult to make very tight turns in very small animals). Generally, a flexible endoscope of around 7–9 mm diameter overall, and working length of 120–150 cm, will be adequate for gastrointestinal procedures in most companion animal practices. This length may be limiting, however, for full upper gastrointestinal examinations or colonoscopy in very large-breed dogs.

Bronchoscopes are not recommended for gastrointestinal endoscopy, as simultaneous up/down and left/right tip deflections are important for successful navigation of the upper gastrointestinal tract; it is almost impossible to achieve this when the endoscope has already made several turns to reach the gastric antrum and pylorus.

Most operators hold the control cluster in the left hand while holding and advancing the body of the endoscope with the right hand. Operators with large hands may be able to manipulate the control wheels using the fingers and thumb of the left hand, while operators with small hands will need to operate the control wheels with the right hand while supporting the control cluster with the left hand. The tension control levers (Figure 49.2) are very useful for operators who must alternate between right hand control manipulations and endoscope advancement. With very long endoscopes, longer than those typically used in companion animal practice, two operators may be necessary to control endoscope advancement and tip deflection separately.

Record Keeping for Endoscopy Procedures

Endoscopic examination findings are a critical part of the medical record in patients undergoing these procedures. Generation of a report will typically involve image capture from the endoscope and a written report detailing findings and observations. Image captures should contain sufficient information to identify the patient, along with the date of examination.

The actual content of the written component of the report will obviously vary depending upon the area being examined. The World Small Animal Veterinary Association (WSAVA) has produced template documents encapsulating the essentials for endoscopy reports for upper and lower gastrointestinal tract endoscopy procedures; these files are available to download from www.wsava.org/guidelines/gastrointestinal-guidelines. These forms include a section for recording the other documentation modalities used, but the guidelines do not make any particular recommendations regarding the best choice of image capture modality.

Image capture systems are very variable, and all have strengths and weaknesses. For quite some time, the use of video printers, which capture images from the processing unit and print to photographic paper, was the standard method. While some systems and practices continue to use these printers, the specific printer technology used (dye sublimation) is rarely used in

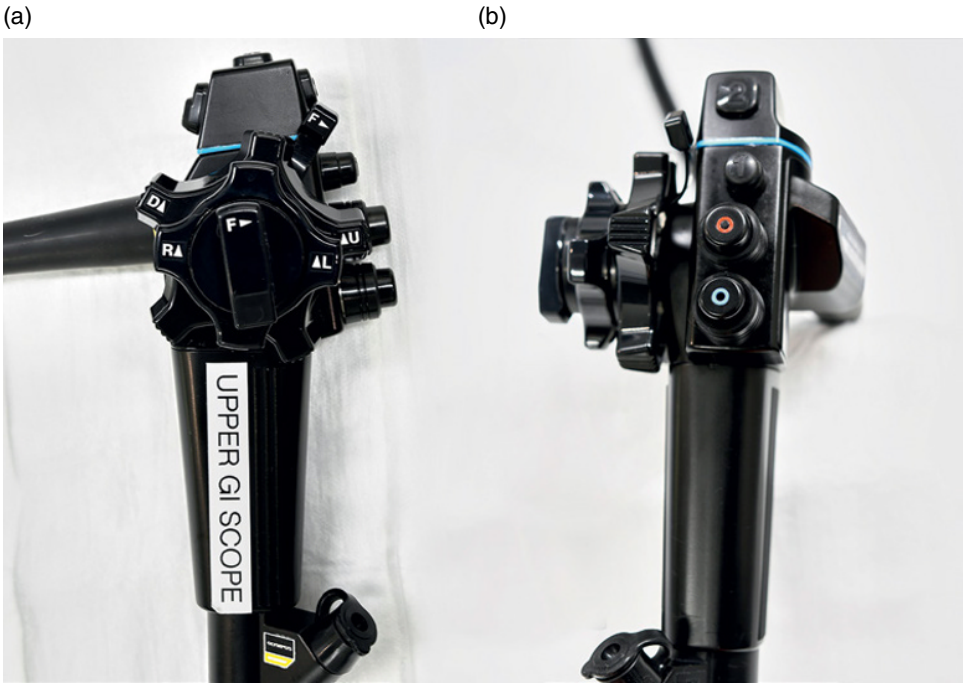


Figure 49.2 Control cluster of a typical flexible videoendoscope, in this case a gastroduodenoscope. (a) The control wheels, labeled U^ D^ and L^ R^, control tip deflection up/down and left/right, respectively. The direction of tip deflection is in reference to the center line and upper surface of the control cluster. Outside the U-D wheel, and in the center of the L-R wheel are a lever and wheel, respectively, marked F>; these are tension controls (labeling indicates the direction to give greater freedom of movement) that can be used to reduce tip deviation freedom. (b) A selection of buttons on this particular endoscope pause video capture and trigger still image capture; these are not present in this position in all endoscopes of this type. Below the two image capture buttons, a press button with a red outer rim operates suction. The bottom button, with a blue rim and small hole in the center, is a combined air/water insufflation control. Placing the operator's finger over the central hole without depressing the button will cause air insufflation, while pressing down the button causes water to be delivered from the end of the scope, washing across the distal lens. While other endoscopes from other manufacturers may have different colored or shaped buttons, the positioning of vacuum above air/water insufflation is standard across all manufacturers. Below the control buttons, a black rubber cuff is apparent; this is the seal for the working channel.

commercially available printers, thus these printers and their disposables (ink ribbons, specific papers) are expensive and increasingly difficult to source. These printer systems are hard to recommend for integration into modern veterinary practice workflows.

At the opposite extreme from the traditional dye sublimation printer, some modern endoscopy systems are able to record digital video or digital still image captures from the endoscope in real time, and then export the resulting files to either a hospital-wide DICOM system or directly into a hospital electronic record system. These capabilities are very useful for streamlining record management in busy practices, and also provide the ability to show captures to clients and generate multiple copies that can be saved to removable media or transferred digitally via email. The specific hospital management systems and DICOM products that endoscopy systems can interface with vary by manufacturer, and should be considered if a practice is planning to purchase a newer system. Aftermarket image capture and DICOM export hardware are also available from some vendors, again these systems can require significant configuration and software support, which should be clarified during the purchasing process.

A final option that is commonly used with refurbished but older endoscopy systems is to attach some form of recording device (commonly a CD or DVD recorder) to a video output from the endoscope processor. In some cases, it is possible to configure these systems to trigger capture using either a foot pedal or the capture button on the endoscope, but again as technology progresses and changes, this is becoming increasingly difficult. The simplest, but most risky, option is to simply collect and record all video from the video output and record it as a continuous stream. If doing this, it is important to consider the length and size of the recording, as many upper and lower gastrointestinal tract endoscopy procedures will last for 1.5 hours or more. Use of CD/DVD recorder systems also requires the endoscope operator or assisting technical staff to remember to start and stop recording, and finalize the recording to allow burning the final disk. The disks themselves have variable, and often short,

useful lives after burning, and may not survive for the duration necessary to meet legal requirements for record keeping in some localities.

Given the combination of workflow advantages, archivability, and integration with other hospital systems, systems that can achieve digital capture and archiving are generally the best option currently available, and will have the greatest future proofing.

Endoscope Handling

General Manipulations

The endoscope is a fragile instrument and needs to be handled carefully and appropriately to avoid damage to the scope and minimize risk to the patient. Gastrointestinal endoscopy requires an adequate plane of anesthesia. Mouth blocks or gags should be used to keep the mouth open while carrying out upper gastrointestinal tract endoscopy. These both make entry of the endoscope into the upper gastrointestinal tract easier, and provide a degree of protection against the endoscope body being bitten if patient anesthesia is inadequate.

Operation of the endoscope relies on fine control wires that extend from the control cluster to the tip of the scope, while light transmission and image formation rely on the fine fiberoptic strands within the scope body. Both of these components can be damaged if placed under excess stress. To minimize stress on the endoscope components, it is best to make fine adjustments of the operating tip that allow general visualization of a target area, while larger deviations and turns are made by turning the whole endoscope body rather than applying significant strain to the endoscope tip. A fine adjustment is made using the control wheels, the scope is advanced and turned using the entire scope body, then additional adjustments are made to gradually bring the endoscope into the desired position.

Visualization of some areas of the gastrointestinal tract, particularly the gastric cardia and aboral surface of the esophageal sphincter, requires more stressful maneuvers. Visualization of the cardia and lower oesophageal sphincter usually requires a "J-maneuver" where the tip of the endoscope is placed into maximal upwards deflection (Figure 49.3). This position is particularly stressful on the mechanical components of the endoscope, and should only be used for as long as needed to adequately visualize the anatomy in this region.

Passage of the endoscope through the pylorus into the proximal duodenum is mildly stressful on the endoscope, as in many dogs it requires a simultaneous downwards and right tip deflection while pushing against some resistance. Once the pylorus has been traversed, however, there is little to no stress applied to the endoscope as it is advanced along the duodenum.



Figure 49.3 Maximal upwards flexion of a flexible videoendoscope, necessary for visualization of the gastric cardia, aboral surface of the lower esophageal sphincter, and distal rectal lumen. This position is highly stressful on the endoscope control structures and fiberoptic elements, and should be held for as short a period as possible. Do not introduce the endoscope into a lumen (for instance, in an attempt to visualize the distal palate or rectum) while holding the endoscope in this position, as the additional compression on the distal end of the endoscope can cause severe damage.

The endoscope tip and body should be lubricated with a water-based lubricant before introduction into the gastrointestinal tract. In the initial stages of the upper gastrointestinal examination, particularly with smaller dogs and cats, there is a risk that the endoscope may slip out of the esophagus and, if not being held by the operator, the tip may fall and hit the floor or other hard surfaces, risking damage to the imaging system or the fiberoptics. This can be particularly problematic for operators with smaller hands who need to take their right hand off the endoscope body to make tip deflections. Having an assistant hold and advance the endoscope body independently from the main operator can minimize the risk of scope dislodgment and damage.

Biopsy Instruments and Working Channel Use

The biopsy and vacuum channel of the endoscope are lined with a thin, rubberized material to allow adequate flexibility while keeping the fiberoptics, control wires, and imaging electronics sealed against water ingress. Damage to the inner lining of the biopsy/vacuum channel can result in scope flooding and costly repairs, as the entire endoscope must be disassembled to repair and replace these parts.

It is imperative that biopsy instruments and retrieval snares/baskets are held closed or within their protective outer sheath when passing through the endoscope. Open biopsy jaws or exteriorized retrieval instruments can puncture or otherwise damage the internal lining of the endoscope.

Occasionally, it is necessary to biopsy lesions that require significant tip deflection for adequate visualization. A mass on the aboral surface of the esophageal sphincter, for instance, will require a J-maneuver for adequate visualization (see earlier). Attempting to pass a biopsy instrument through the endoscope while it is in this position is risky as the instrument is directly pushing against the channel lining. It is less risky to retract the endoscope slightly to allow the tip to relax, pass the instrument until it is visualized leaving the endoscope and within the gastric lumen, then return to the maximally flexed position to obtain the biopsy. Obtaining an adequate biopsy from masses in this region can be quite difficult, as the severe turns of the endoscope restrict the ability of the biopsy instrument to move within the channel.

After a biopsy is obtained, the biopsy instrument should be kept completely closed until it has been entirely removed from the biopsy channel. Foreign bodies are retracted with the retrieval instrument until they are close to the operating end of the endoscope, then removed by retracting the entire endoscope.

Endoscope Cleaning and Maintenance

Care and maintenance of endoscopes require attention to detail, care with handling of the instrument, and the use of appropriate cleaning products and equipment. These are expensive and fragile pieces of equipment, and repair costs are high. Generally speaking, it will be best for only one or two specific individuals (practitioner or technician) to be tasked with cleaning and maintenance of flexible endoscopes to ensure consistency of handling and adequate knowledge of the necessary steps. While some general observations are given here, manufacturer's guidelines should be followed. This is particularly important with respect to cleaning fluid selection, as different manufacturers use differing materials in their endoscopes that may be damaged by inappropriate cleaning solution use.

Endoscopes must be thoroughly and effectively cleaned, on both external surfaces and within the biopsy/vacuum and air/water channels, after use and before storage. On completion of an examination, it is good practice to suction plain or distilled water (not saline) through the endoscope to clear material that may have lodged within the working channel. The exterior body of the endoscope should be wiped down with water-moistened wet gauze or toweling to remove grossly contaminating material.

Complete cleaning of the endoscope requires several steps and use of different cleaning products to achieve both physical cleaning and sterilization.

The first step of cleaning is typically achieved with an enzymatic detergent solution. The endoscope is soaked in this solution, then the outer surfaces gently wiped down. The detergent solution is also pumped through the biopsy and air/water channels using a manifold (Figure 49.4) that attaches in place of the removable buttons. If manually cleaning the endoscope, these channels are then further cleaned by passing specific cleaning brushes.

After lower level cleaning with the enzymatic/detergent solution, higher level sterilization can be achieved using specific sterilization fluids. These fluids are often corrosive and toxic, and can produce toxic fumes. The operator cleaning and sterilizing the endoscope must wear adequate personal protective equipment, including facemask and eye protection. After exposure to the sterilization solution is complete, the endoscope is thoroughly rinsed with sterile water, both externally and through the internal channels. The sterilization solutions

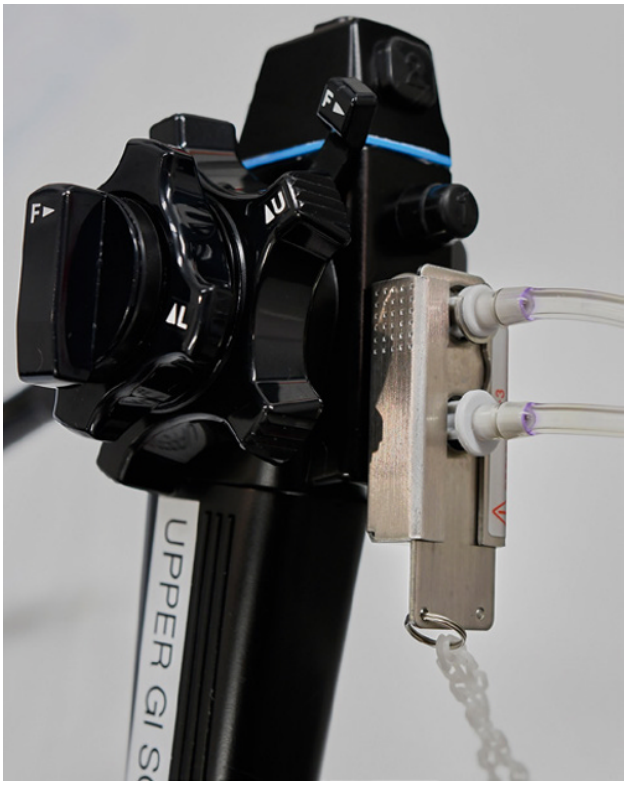


Figure 49.4 Attachment of a specialized manifold in place of the air/water and vacuum buttons allows administration of cleaning and sterilizing solutions to the inner working channels of the endoscope.

are irritating to mucosal tissue, so it is important to ensure that residues of the cleaning solution have been removed before use on a patient.

Endoscopes should be stored dry, following effective cleaning (Figure 49.5). If space is available, they can be stored in specially constructed rack systems in a dedicated cabinet. Other items unrelated to endoscopy should not be stored in the same cabinet to minimize the risk of endoscope damage. If a dedicated cabinet is not used, the cleaned and dried endoscope should be stored in the original shipping/packing case to provide adequate protection. Obviously, if transporting endoscopes in the field or between hospital sites, they are best carried in their specific transport case.

Effective complete cleaning and sterilization of an endoscope can be quite time-consuming. In practices that carry out several procedures in a day, investment in an automated scope cleaning and reprocessing system can be cost-effective, freeing up technician resources for other tasks. These systems can automatically carry out both the low-and high-level cleaning steps, final rinsing of the endoscope and pressure testing without further manual input, typically in less than one hour. These systems may also generate a record for each endoscope of cleaning solution exposure times and pressure test results, and monitor the age and use of the cleaning solutions. An additional advantage is that the operator is protected from the cleaning and sterilization fluids during endoscope reprocessing.



Figure 49.5 Clean and dry flexible endoscopes stored in a dedicated storage cabinet. An effective and sturdy retention system should be used to minimize the risk of endoscopes being dropped and damaged.

Endoscopic Terminology

Endoscopic evaluation of the gastrointestinal tract provides an opportunity to assess the gross appearance of the gastrointestinal mucosa. Findings with gastrointestinal endoscopy therefore are usually descriptions of the mucosa and attempt to define the ways, if any, in which the mucosa differs from normal. Standardization of the language used to describe endoscopy findings is useful to maintain consistency in interpretations and comparison across patients. The terms recommended for the description of the mucosa, most of which are also incorporated into the WSAVA recommended reporting forms for gastrointestinal endoscopy procedures, are summarized in Table 49.1 and discussed in greater detail below.

Friability

Friability refers to the susceptibility of the mucosa to superficial damage and hemorrhage on contact with either the endoscope tip/body or biopsy instruments.

Table 49.1 Terminology used for the description of endoscopically visualizable abnormalities of the gastrointestinal mucosa

Parameter	Definition
Normal mucosa	No macroscopic lesions are observed
Friability	Occurrence and degree of bleeding on contact of the endoscope or biopsy instrument with the mucosal surface
Granularity	Perceptible alterations in the visible texture of the mucosa
Erosion(s)	The presence of superficial linear to patchy mucosal defects, usually with bleeding present
Hyperemia	Subjective perception of the redness (pale to markedly reddened) of the mucosa
Lymphatic dilation*	The presence and degree of white foci (punctate to diffuse) within the mucosa
Mass present	Detection of abnormal tissue protruding into the intestinal lumen

Source: Modified from Slovak et al. (2015). Reproduced with permission of Elsevier.

* Lymphatic dilation is assessed and scored only in the small intestine.

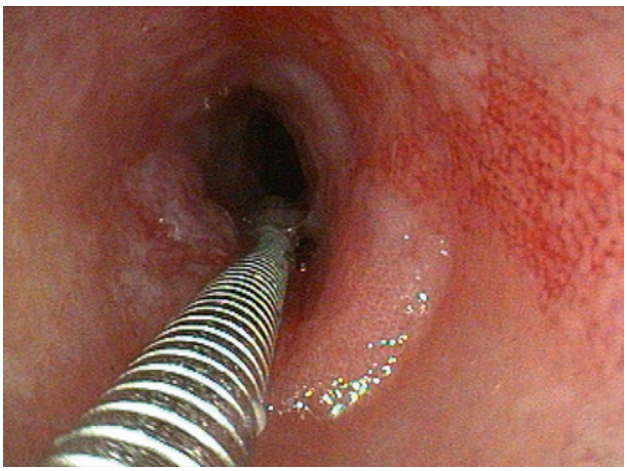


Figure 49.6 Increased friability and iatrogenic mucosal compromise of the small intestinal mucosa. There is noticeable "stripping" of the superficial mucosa visible to the right of the image; the stripped mucosa is visible piled close to the right side of the endoscopic biopsy forceps. This degree of mucosal damage from contact with the endoscope is abnormal, even within the small intestine.



Figure 49.7 Increased mucosal granularity in the small intestine. The endoscope is approaching the end of the descending duodenum, the caudal duodenal flexure is visible in the distance. Note also the sporadic areas of lymphatic blebbing, particularly in the lower right quadrant of the mucosa. This patient was diagnosed with mild to moderate lymphoplasmacytic duodenal inflammatory disease.

The natural friability of the mucosa varies with the anatomy of the gastrointestinal tract, and this must be considered in the context of the examination findings. The esophageal and gastric mucosae, for instance, are robust and the normal mucosa should show little to no change or damage from contact with the endoscope. This is particularly true of the esophagus, antral mucosa, and pylorus. Compared to the stomach, the small intestinal mucosa is more fragile, and even normal patients will show some degree of superficial mucosal damage following contact with the endoscope, but there should not be grossly visible "stripping" of the mucosa from the submucosa, and any bleeding following contact should be minor (Figure 49.6). The large intestinal mucosa is more robust than the small intestine, but is not as resistant to impact damage as the gastric mucosa, thus contact with a colonoscope will usually produce some visible change in the mucosa, but this is less pronounced than in the small intestine.

Granularity

Granularity refers to the visual texture of the mucosa. Again, the normal texture of the mucosa varies across the gastrointestinal tract. In the small intestine, both increased and decreased granularity may be observed, while villus blunting due to infiltration or mucosal denudation may result in an abnormally smooth appearance of the small intestinal wall, or a "cobble stone" appearance caused by a patchy distribution of blunted villi. Mucosal thickening and swelling secondary to cellular infiltration or lymphatic drainage disorders can lead to an increase in granularity and a perceptible "piling" of mucosa into more prominent folds that do not dissipate with insufflation (Figure 49.7).

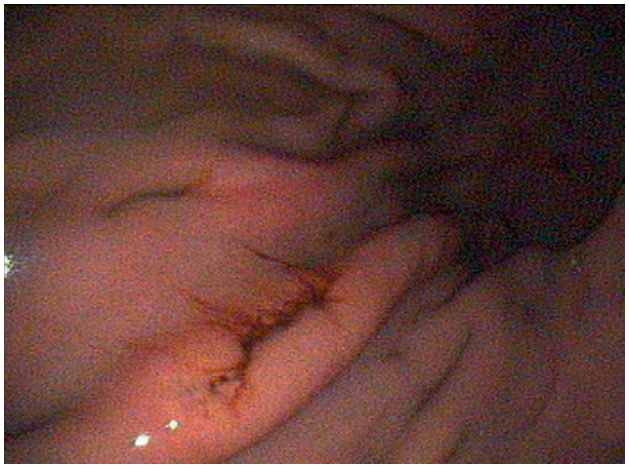
Erosion(s)

Erosion(s) are preexisting, generally superficial, linear to irregularly shaped mucosal defects, often marked by mild intra- or submucosal hemorrhage. These must be distinguished from lesions due to abnormalities in friability. Erosions represent an area of change in the gastrointestinal mucosa, but there should still be mucosa present (Figure 49.8). Visible loss of the mucosa with crater formation and visible submucosa is more consistent with ulceration than erosion. Erosions likely progress to ulceration in some individuals; animals with nonsteroidal antiinflammatory drug (NSAID)-induced gastritis, for instance, commonly show numerous erosions. Many erosions are linear or elongated oval shapes, oriented along the longitudinal axis of the intestinal tract, likely due to damage resulting from the passage of ingesta over the diseased mucosa.

Lymphatic Dilation

Lymphatic vessels are usually only visible in the small intestinal mucosa, and become more prominent in deeper parts of the small intestine, such as the jejunum. Lymphatic visibility is greater in the small intestine due to the role of the intestinal lymphatics in fat absorption,

(a)



(b)

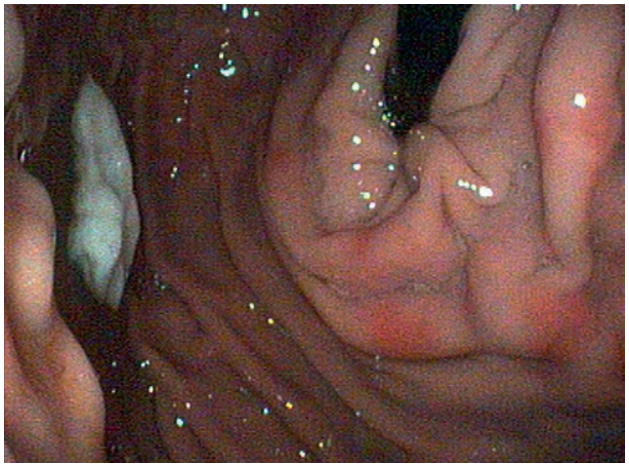


Figure 49.8 Erosions in the gastric mucosa. In the lower left of image (a), a larger erosive lesion is visible; just above this the mucosa is hyperemic and shows very superficial erosion. Note that the erosions follow the longitudinal direction of the rugae. In (b) several superficial erosions without hemorrhage are visible surrounding the lower esophageal sphincter and in the gastric cardia. This patient's histologic diagnosis was of multifocal, chronic erosive gastritis, likely secondary to chronic NSAID usage.

resulting in the presence of milky white lymph within the lacteals. Visible lymphatics within the villi are not necessarily abnormal, particularly when the lymphatics are obviously consistent in appearance and form well-circumscribed linear structures within each villus. This is a normal finding, and is more readily visible in animals that have had shorter fasting periods before the procedure. The use of milk or ice cream mixed with polyethylene glycol solutions for colonoscopy preparation (see later) is often associated with a dramatic increase in visibility of the lacteals, even in normal dogs. This should not be overinterpreted in patients having both upper and lower gastrointestinal (GI) tract procedures.

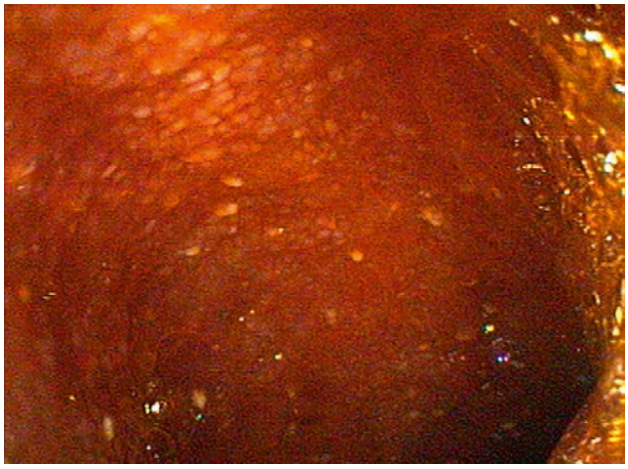


Figure 49.9 Diffuse lymphatic drainage abnormality in a dog with marked protein-losing enteropathy. Note the presence of markedly engorged lacteals within the villi in the upper left quadrant of the image, and scattered throughout.

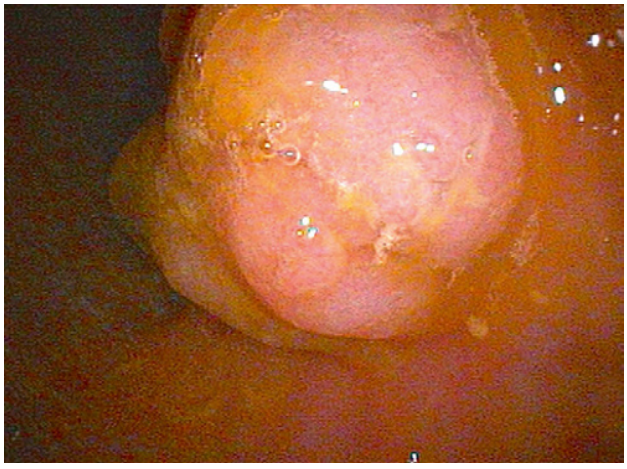


Figure 49.10 Luminal mass effect, a benign rectal polyp in a dog. The mucosa shows a "cauliflower" appearance but is not ulcerated. Histopathology was consistent with a chronic inflammatory process.

Abnormal lymphatic drainage is associated with "blebbing" and diffuse spread of lymph into the villi and the submucosa. There may be solitary punctate lesions spread diffusely throughout the small intestine, or larger areas of contiguous leakage may be perceived (Figure 49.9).

Mass Effects

Abnormal tissue entering the lumen of the gastrointestinal tract may arise from the mucosa or the submucosal layers. Mucosal masses are usually readily identified due to the obviously dysplastic appearance of the epithelium (Figure 49.10). In some cases, the mucosa will be eroded

and ulcerated, and will bleed easily (i.e., highly friable) on contact with the endoscope. Submucosal masses are recognized in areas where the lumen shows obvious architectural distortion that does not resolve with insufflation. Submucosal masses are relatively easy to recognize endoscopically, but the diagnostic yield from endoscopic biopsy of these lesions is poor. Full-thickness biopsy is usually required for accurate diagnostic assessment of submucosal or mural masses.

Hyperemia

The color of the intestinal mucosa can be assessed, and perceptible alterations from normal (again, bearing in mind that the mucosal coloration varies along the gastrointestinal tract) may be noticeable during an examination. While superficially attractive as a readily perceivable abnormality, hyperemia is actually a poor indicator of abnormalities within the mucosa. Many variables influence mucosal redness, including the hemodynamic state of the patient, circulating red blood cell mass, local changes in perfusion, and the overall color balance of the imaging system being used. Some, but by no means all, endoscopy imaging systems can have their color balance (white balance) calibrated against a white background material, which will improve the ability of the operator to define changes in redness on that specific system, but not all systems are readily calibrated, and calibration must be carried out regularly. Due to these shortcomings, diffuse hyperemia and other changes in mucosal coloration are not usually considered useful diagnostic findings during gastrointestinal endoscopy.

Upper Gastrointestinal Endoscopy Procedures

Esophagoscopy

Indications

Common indications for esophagoscopy in companion animals include assessment of patients with dysphagia, regurgitation, poor appetite, and hematemesis. Esophagoscopy is also frequently useful in the diagnosis and management of esophageal foreign bodies, strictures, and diverticulae. The esophagus is also, obviously, traversed in the process of all other upper gastrointestinal examinations and should be thoroughly examined during these procedures.

Patient Positioning

As esophagoscopy is commonly performed during other upper gastrointestinal tract procedures, the patient is typically placed in left lateral recumbence (the positioning of choice for gastroduodenoscopy). If the planned procedure is only involving the esophagus (foreign body removal or stricture ballooning, for example), sternal or right lateral positioning can be used, but there are no specific advantages of these positions over left lateral recumbence.

Equipment Choice

Both flexible and rigid endoscopes may have some utility in examination of the esophagus, but in most patients there is insufficient working length with rigid endoscopes to examine the entire esophagus. Flexible endoscopes with four-way tip deflection and a working channel are preferable, particularly if removal of a foreign body using flexible retrieval instruments is anticipated. Four-way tip deflection gives the operator a greater ability to manipulate the positions of grasping forceps or basket snares. Air and water insufflation is important, particularly for adequate examination of the cranial esophagus.

General Technique and Landmarks

The neck is extended dorsally, and the endoscope passed dorsally over the endotracheal tube to the retropharynx. Gentle pressure against the retropharynx will result in the passage of the endoscope through the upper esophageal sphincter and into the cervical esophagus.

The cervical esophagus is usually flacid and collapsed. After passage through the upper esophageal sphincter, air is insufflated to visualize the esophageal lumen. Once fully insufflated, passage of the endoscope is usually straightforward. Landmarks during the examination are the thoracic inlet (where the esophagus changes direction slightly), heart base (where there is a slight narrowing of the esophageal lumen; usually the wall will show motion due to cardiac movement), and the lower esophageal sphincter. The three landmark locations also represent areas of esophageal narrowing, and are the most common sites to encounter obstructing foreign bodies.

Ideally, as much of the esophageal lumen as possible should be visualized before advancing the endoscope over large distances. In regurgitating patients, look closely for wall defects or outpouchings that may represent esophageal diverticula, or areas of esophageal lumen that do not insufflate fully (indicating possible strictures).

Normal Findings

The cervical esophagus is normally flacid and collapsed on entry. Insufflation reveals longitudinal mucosal folds, which are flattened by air insufflation. Within the thoracic cavity, the esophagus is usually flaccid and shows a patent lumen without need for further insufflation. The normal esophagus will drape over the large vessels in a

normal animal; visualization of a strong pulsatile motion from these vessels is not necessarily suggestive of a megaesophagus.

The esophageal wall in dogs is usually smooth, or very slightly corrugated, on full insufflation. The cat has a series of mucosal folds in the distal third of the esophagus that give the normal esophageal lumen a "herring bone" appearance in this species.

The lower esophageal sphincter is readily visualized in most animals, assuming that there are no impeding foreign bodies. The lower esophageal sphincter is usually closed on examination, but a relaxed and open sphincter is not necessarily abnormal. Often, a small amount of stable white foam (aerated saliva) is adherent on the distal esophageal mucosa, which is also normal.

Potential Abnormalities Observed in Esophagoscopy Procedures

Esophagitis

Esophageal inflammation is a common finding in dogs with gastrointestinal disease, particularly if there is gastroesophageal reflux or chronic vomiting. Changes in the esophageal mucosa with esophagitis are highly variable, and often do not correlate closely with the perceived clinical severity of signs. The most common changes seen with esophagitis are increased granularity of the esophageal mucosa, hyperemia or erythema, and mucosal erosions. Often, these changes are most pronounced in the distal esophagus, particularly if they are secondary to gastroesophageal reflux (Figure 49.11).

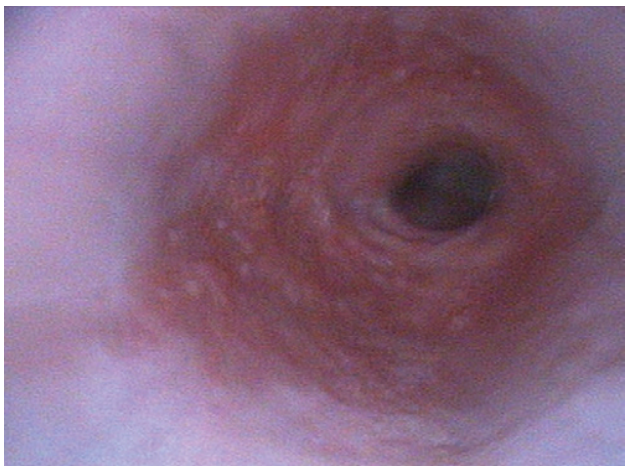


Figure 49.11 Esophagitis, likely due to recurrent gastroesophageal reflux, in a canine patient. There is increased granularity and hyperemia of the distal esophageal mucosa, and the lower esophageal sphincter is dilated. Some mild erosions are also visible in the more proximal aspect of the esophageal mucosa, particularly to the left of the image.

In humans, chronic gastroesophageal reflux can lead to squamous differentiation of the distal esophageal mucosa, which is considered a preneoplastic change. Similar changes are occasionally seen in dogs with chronic gastroesophageal reflux, but the potential for neoplastic transformation is unknown.

While a relaxed, partially dilated lower esophageal sphincter is not necessarily an abnormal finding in dogs and cats, the prolapse of gastric mucosa into the esophageal lumen is abnormal. This may occur as a result of severe, chronic reflux esophagitis, hiatal hernias, or be due to the presence of mass lesions on or just below the lower esophageal sphincter (see Gastric Tumors, later).

Esophageal Foreign Bodies

Esophageal foreign bodies are a significant medical emergency, and delays in detection and definitive treatment should be avoided as much as possible. Large obstructing foreign bodies, such as bones, swallowed chew toys, etc., are readily visualized. Common locations for foreign body entrapment are at the thoracic inlet, cranial to the heart base, and cranial to the lower esophageal sphincter, with the lower esophageal location being the most common. Sharp, more linear objects such as needles, fish hooks, etc. may lodge at any point in the esophageal lumen, but again are most commonly encountered at the thoracic inlet and cranial to the lower esophageal sphincter. Sharp linear foreign bodies often accumulate additional material such as hair, grass, and food fragments that can complicate assessment and removal.

Before endoscopy to assess and possibly attempt removal of an esophageal foreign body, it is important to have recent (ideally same day) thoracic radiographs with at least two orthogonal views. These should be carefully assessed for evidence of preexisting esophageal perforation (pneumomediastinum, mediastinitis, pneumo- or pyothorax), as these indicate a need for earlier surgical intervention. In addition, it is important to document that the foreign body is still present, and apparently within the lumen, before proceeding to esophagoscopy. Strategies for foreign body removal are discussed further later.

Esophageal Diverticulae

Esophageal diverticulae are outpouchings of the esophageal mucosa through defects in the mural musculature. On endoscopic examination, these lesions may appear as obvious outpouchings of the mucosa, they may look like an additional lumen, or they may appear to be large accumulations of hair and/or fermenting food material entrapped within the diverticulum. Large diverticulae are usually detected on plain radiographic examination of the thorax as part of the work-up for esophageal disease.

Esophageal Neoplasia

Primary esophageal neoplasia is uncommon to rare in both dogs and cats, with cats most frequently diagnosed. Squamous cell carcinoma is occasionally diagnosed within the thoracic esophagus, visualized as an eroded, proliferative mass in the distal esophagus. This diagnosis is most commonly made in elderly cats, and carries a poor to grave prognosis. Preendoscopy work-up including plain and contrast-enhanced esophograms will often reveal the soft tissue mass, which may initially be mistaken for a foreign body.

Gastroscopy

Indications

Common indications for gastroscopy include assessment of recurrent vomiting, poor appetite, weight loss (assuming other significant co-morbidities have been ruled out), hematemesis (particularly if "coffee ground" vomiting is present), and attempts at removal of gastric foreign bodies. Gastroscopic technique is also used for some minimally invasive feeding tube placements (percutaneous endoscopic gastrostomy [PEG] and percutaneous endoscopic gastrostomy-jejunostomy [PEG-J]; see later). The stomach must be traversed as part of the approach to the small intestine for duodenoscopy, and should be assessed thoroughly, including the collection of biopsies from each area of the stomach, in any patient being worked up for possible inflammatory disease of the gastrointestinal tract.

Patient Positioning

For most procedures involving gastroscopy, the patient should be placed in left lateral recumbence. As the pylorus is in the right side of the abdominal cavity in both dogs and cats, left lateral recumbence will position the antrum and pylorus dorsally, thus allowing gas to fill these parts of the stomach. This is important for clear visualization of a number of significant landmarks, and greatly simplifies the process of transiting the antrum, through the pylorus to the small intestine. Left lateral recumbence will also typically cause foreign bodies that are obstructing the pylorus to fall into the gastric body under the influence of gravity. There is much greater room to maneuver and less complex scope deviations necessary to retrieve foreign bodies from the gastric body than from within the antrum

One exception from the typical left lateral placement for gastroscopy is made when the patient is having a minimally invasive feeding assistance device placed, such as a PEG or PEG-J tube. These devices are placed through the greater curvature of the stomach, exiting at the left paranephric fossa, and thus placing the patient in right lateral recumbence is necessary to improve visualization of this region of the gastric wall. If the sole reason for the gastroscopic procedure is PEG/PEG-J tube placement, the entire process is carried out in right lateral recumbence. If the feeding device is to be placed at the end of a diagnostic upper gastrointestinal examination, it is best to start in left lateral recumbence and then reposition the patient after completion of the examination.

Equipment Choice

Gastroscopy requires the use of a flexible endoscope with four-way tip deflection. If the primary reason for the procedure is foreign body retrieval from the stomach, a relatively large endoscope (7–9 mm diameter) can be useful even in cats and very small dogs. For full visualization of all areas of the stomach and potential entry into the duodenum via the pylorus, a smaller endoscope might be advantageous with very small patients (for instance, a 5–6 mm pediatric gastroscope), but with care even a 7–9 mm endoscope can be advanced through the pylorus of many smaller dogs and larger cats.

General Technique and Landmarks

Landmarks for visualization during gastroscopy include the greater and lesser curvatures of the stomach, the cardia and aboral surface of the lower esophageal sphincter, the incisura angularis, antrum, and pyloric sphincter. All these areas and structures are readily accessible to examination in the majority of veterinary patients, assuming careful and thorough technique is applied.

The stomach is entered via the lower esophageal sphincter, which is straightforward with gentle application of pressure in the vast majority of veterinary patients. One notable exception to this would be dogs with severe megaesophagus, for any reason, where the dilated and flaccid esophagus drapes into the thoracic cavity, resulting in outpouchings that tend to capture the endoscope, and significant elevation changes are necessary to reach the lower esophageal sphincter.

After entering the stomach via the lower esophageal sphincter, a reduction in resistance to passage is felt. At this point, with the working end of the endoscope just entering into the cardia of the stomach, air insufflation is started to moderately inflate the gastric lumen. During insufflation, the gastric rugae should be closely observed for areas that are not flattening out or show marked apparent changes in rugal fold directions, as these can indicate areas of wall infiltration and pathology. Directly ahead of the endoscope from this position will be the greater curvature of the stomach and the gastric body. From this position, left and right deviations of the endoscope can be used to get a general overview of the gastric lumen.

Rightwards deviation of the endoscope tip will provide a view of the greater curvature descending to the antral

wall. Usually, the pyloric sphincter and inner antral lumen are not visible from the lower esophageal sphincter, but the incisura angularis is easily identified and is an important landmark for further manipulations. Leftwards deviation of the endoscope tip from the lower esophageal sphincter reveals the oral aspect of the fundus and greater curvature, but the cardia is not visible from this position.

The endoscope tip is advanced into the gastric lumen following insufflation, and the endoscope placed into a J shape by maximal upwards deviation using the control wheels. This will typically provide a view back towards the face of the incisura and into the antrum, and should allow visualization of the pyloric area. Applying rotational torque to the endoscope will provide a view of the cardia and the lower esophageal sphincter. The visualization of the endoscope body entering via the lower esophageal sphincter provides obvious confirmation that the cardia and lower esophageal sphincter are being visualized.

Relaxing the strain on the upwards deviation control and gently pushing the endoscope forwards will typically result in the body of the endoscope contacting the greater curvature of the stomach, and minor torqueing of the endoscope towards the right (relative to the control cluster) will usually result in a view along the greater curvature into the antral lumen towards the pylorus. Gentle forwards pressure is then applied to enter the antrum and approach the pyloric sphincter.

Entry into the antrum and visualization of the pyloric sphincter can become very difficult if the gastric body is aggressively insufflated. Introducing more and more air is tempting as it allows a larger field of view, but the resulting compression of the antrum, and greater distance of greater curvature wall that must be traversed, make entry to the antrum much more challenging. This is particularly true with very large dogs, where the entire 120–150 cm working length of the endoscopes commonly used in veterinary practice will be taken up by transit of the esophagus and around the greater curvature.

After visualization of all areas of the stomach, the endoscope may then be advanced to and through the pylorus to enter the duodenum if duodenoscopy is planned. This technique is discussed in greater depth later.

Normal Findings

The mucosa of the gastric body is generally light pink to red, and prominent rugal folds are apparent on first entry to the stomach and early in the insufflation process. The majority of the rugae run longitudinally around the greater curvature of the stomach, which can be a useful guide for orientation. Rugae should disappear as the stomach becomes distended during insufflation, but prolonged periods of aggressive insufflation should be avoided due to the risk of respiratory and circulatory compromise, and the greater difficulty of continued examination. The mucosa should be smooth in appearance. The mucosa within the antrum is a lighter color than in the main gastric body, and rugae are either absent or greatly reduced. Patchy erythematous regions, particularly on the greater curvature, are normal. The pylorus is usually not directly visible on first entry to the antrum, but instead is surrounded by a number of mucosal folds in the distal antrum. Careful observation will usually allow visualization of small amounts of bile reflux or transient opening of the pylorus.

Fluid, residual food particles, and foreign bodies will tend to pool in the left fundus when the patient is in left lateral recumbence. In normal animals, there will be scant fluid or mucus present, while those with gastrointestinal disease can exhibit large pools of fluid, mucus, and food particles. Excessive fluid will obscure visualization of the gastric mucosa in this region, and may camouflage foreign bodies. Ideally, as much fluid as possible should be suctioned from the fundus during the examination. This will improve visualization, and also decreases the risk of vomiting or regurgitation and aspiration on recovery.

Potential Abnormalities Observed in Gastroscopy Procedures

Gastritis

Gastritis is commonly encountered during gastroscopy. Gross changes that may be visible include marked reddening of the mucosa, thickening of the mucosa, increased prominence and extent of mucosal erythema, and thickening of the rugae resulting in slower and less complete flattening of the rugae during insufflation. While any or all of these changes should increase suspicion for the presence of gastritis, it is important to remember that some patients may show histologic evidence of gastric inflammation with relatively mild to nonexistent grossly visible changes. Biopsy collection is crucial to allow accurate assessment. In many animals with gastritis, the gastric mucosa is perceptibly "easier" to biopsy, requiring less avulsion force to remove tissue. Biopsy sites from animals with gastritis will often bleed more freely. As greater volumes of bleeding can be seen in animals with gastric inflammation, it is wise to biopsy the stomach at the end of the gastroduodenoscopy procedure otherwise bleeding can result in obstruction of the view.

Gastric Ulceration

Common causes of gastric ulceration include inappropriate or prolonged NSAID use and local neoplastic processes (particularly gastric carcinoma). Ulceration can also be seen due to paraneoplastic effects from mast cell

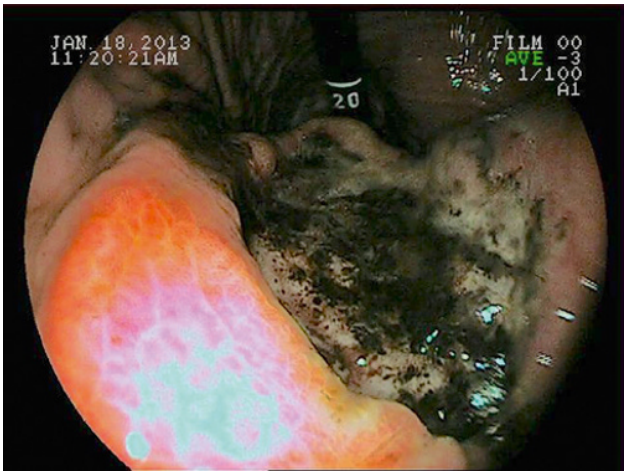


Figure 49.12 Severe ulceration on the wall of the gastric lesser curvature in a canine patient presenting with severe recurrent vomiting. In the lower left quadrant of the image, close to the endoscope, the upper edge of the incisura angularis is visible and is also dramatically abnormal. This patient was diagnosed with mucinous gastric carcinoma via endoscopic biopsy.

neoplasms and gastrinomas. Paraneoplastic ulceration secondary to severe and persistent gastric hyperacidity is often profound and severe.

Ulceration is usually seen in the secretory compartment of the stomach. The incisura angularis is also very commonly affected, and is a particularly common site to encounter NSAID-induced ulcers. Large ulcers are typically visible as dark, depressed areas of necrotic tissue, surrounded by an elevated rim of markedly reddened and thickened mucosa (Figure 49.12). Biopsy of the center of an ulcerated lesion is usually of little diagnostic value as the tissues are necrotic; this is also associated with risk for perforation of the ulcer. Biopsies for assessment should be taken from the rim at the periphery of the ulcer, as well as several biopsies from nearby apparently normal tissue to screen for infiltrative processes. Gastric ulceration due to NSAIDs cannot be differentiated from ulceration due to neoplasia, and as both NSAID and neoplastic processes are more common in older dogs, biopsy to rule out neoplasia is mandatory even in patients receiving NSAIDs.

Mural Masses

Mass lesions affecting the gastric wall may be visualized in any part of the stomach. Some potential causes of gastric mural lesions include chronic inflammatory change (polyps), lymphosarcoma, granulomatous lesions due to foreign body penetration, and tumors arising from smooth muscle (leiomyoma, leiomyosarcoma) or mesenchymal cells (gastrointestinal stromal tumor [GIST], fibrosarcomas). In areas with high regional prevalence of fungal or oomycete-induced disease, these infections may also result in intraluminal granuloma formation. Leiomyoma and leiomyosarcoma are rare in the gastrointestinal tract but when seen, are most commonly associated with the lower esophageal sphincter, and are most frequently identified in older, female dogs.

As mural mass lesions may primarily affect the deeper layers of the gastric wall, endoscopic biopsy samples are often nondiagnostic. Obtaining multiple biopsy "bites" from the same site, to allow sampling of the submucosa and muscularis layers, increases the utility of endoscopic biopsy samples for mural masses.

Gastric Parasites

Occasionally, gastric parasites, such as *Physaloptera* spp., are observed during gastroscopy, typically in patients being assessed for chronic vomiting. These are small parasites, being around 3–4 cm long and very slender. If the clinician does not suspect that they may be present, it is easy to overlook them. As these worms are susceptible to both pyrantel pamoate and most of the macrocylic lactone parasiticides (ivermectin, selamectin, etc.), this has become an uncommon diagnosis in client-owned animals.

Gastric Foreign Bodies

Gastric foreign body removal is a common indication for gastroscopy in companion animals. Foreign bodies may lodge in the antrum/pylorus or remain freely mobile within the gastric lumen. Freely mobile foreign bodies will usually be found in the left gastric body when the patient is in left lateral recumbence, due to the effect of gravity. Often, foreign bodies are associated with or surrounded by large aggregations of hair, grass, and other consumed materials, which can complicate assessment and accurate deployment of foreign body snares.

Foreign bodies lodged within the antrum/pylorus will be visualized during the approach along the greater curvature. Patients with foreign bodies in this location, particularly if they are thought to be fabric based (carpet, bedding material, wool, etc.), should be carefully assessed for evidence of linear foreign body entrapment in the small intestine before proceeding to gastroscopy, as patients with linear entrapment within the small intestine are best assessed at exploratory surgery.

Assuming successful removal of a foreign body from the stomach via endoscopy, it is strongly recommended to obtain biopsies of the gastric (and, if possible, small intestinal) mucosa before recovering the patient from anesthesia. Particularly in middle-aged to older animals, pica may be the only sign of significant inflammatory disease of the gastrointestinal tract.

Duodenoscopy

Indications

Duodenoscopy is commonly indicated for the assessment of small intestinal disease in companion animals. Mucosal assessment and biopsy are of value in cases with unexplained weight loss, poor appetite, vomiting, and diarrhea. Duodenoscopy may also yield useful information in patients with hematemesis or hematochezia, but this is less commonly the case and these clinical signs are not a primary indication for duodenoscopy. It is important to consider that the actual area of small intestine accessible via endoscopy is limited in most patients. It is unusual to be able to reach the jejunum in most veterinary patients, and thus large areas of the small intestine are inaccessible for routine endoscopy. Consequently, endoscopy is a poor choice for attempted assessment of small intestinal diseases that are discrete in nature, such as solitary ulcerative lesions or mural mass lesions.

Patient Positioning

Duodenoscopy procedures are almost invariably conducted with the patient in left lateral recumbence, as this places the pyloric sphincter and gastric wall in the optimum position for passage into the duodenum.

Equipment Choice

Standard 7–9 mm diameter, 125–150 cm flexible endoscopes with four-way tip deflection, air and water insufflation and an adequate working channel are useful in the vast majority of veterinary patients. Remanufactured/refurbished pediatric gastroscopes work well for cats and smaller dogs. In larger dogs (30 kg+), 9–11 mm 160 cm+ colonoscopes tend to have better reach into the duodenum.

General Technique and Landmarks

Navigation of the antrum and pylorus to enter the duodenum is one of the more challenging procedures in companion animal gastroduodenoscopy. Traversal of the stomach to the greater curvature, around to the entry to the antrum and the approach to the pylorus will often consume a large proportion of the working length of the endoscope, and multiple turns can result in the endoscope tip moving in directions that are counterintuitive relative to the control cluster and the operator's hands. Excessive insufflation of the stomach tends to increase the difficulty of this procedure, as it changes the anatomy of the antral opening, increases the distance of gastric wall that will be traversed, and tends to increase pyloric sphincter tone. If difficulty is experienced with this procedure, particularly if the endoscope is unable to pass the incisura angularis, gas should be removed from the stomach via suctioning.

The typical approach to the pylorus occurs by directing the endoscope towards the greater curvature, then deflecting the endoscope tip using a J-maneuver and torquing the endoscope to allow visualization of the incisura angularis. The endoscope is then advanced slightly (sliding along the greater curvature) and the upwards deflection is relaxed, allowing the end of the endoscope to relax onto the antral wall. Once the tip of the endoscope has entered the antrum, gentle forwards pressure on the body of the endoscope will usually result in forward motion of the working end of the endoscope into the antral lumen towards the pylorus. If the endoscope is repeatedly "flipping" out of the antrum, or shows paradoxical motion (the pylorus moving away as forwards pressure is applied), it is likely that there is excessive length of endoscope body within the gastric lumen due to excess insufflation. The endoscope is retracted into the gastric body, air is removed until the stomach is perceptibly deflating (rugae should be readily visible, at a minimum), and then the approach to the antrum can be repeated.

The pylorus is identified by careful examination of the center of the distal antral wall. In most animals, the circumferential muscle structure of the sphincter is easy to appreciate, in others there may be mucosal folds or more complex sphincter anatomy present, but most animals will show at least one fold or sulcus of the mucosa that is obviously deeper and more motile; this is the most likely point to find the pyloric sphincter. Entry to the sphincter typically involves incremental advancement of the endoscope body, while using progressive subtle tip deflections with the control wheels to maintain the pyloric sphincter within the center of view. As the endoscope tip impacts the mucosa, it is normal to have a complete loss of vision; gentle pressure is continually applied and the tip of the endoscope deviated slightly to the right and downwards. The endoscope operator should feel a forward motion and the mucosa "glides by" the end of the scope, the operator watches for a change in color of the mucosa from a light red (antral mucosa) to a darker red to yellow tinged color (duodenal mucosa and bile). When the mucosal color changes, the endoscope is advanced for several centimeters, then air is insufflated and the tip of the scope gently diverted in several directions to obtain a view of the lumen. Once the lumen is visible, the endoscope can be *slowly* retracted to allow examination of the very cranial aspect of the duodenum.

If the endoscope is carefully positioned in the very cranial duodenum, it is usually possible to identify the duodenal papillae. There are two papillae in dogs; the more cranial, larger papilla is the major duodenal papilla and drains both biliary and pancreatic secretions, while the smaller minor papilla drains only pancreatic secretions. In the cat, only one papilla is visualized, and drains both

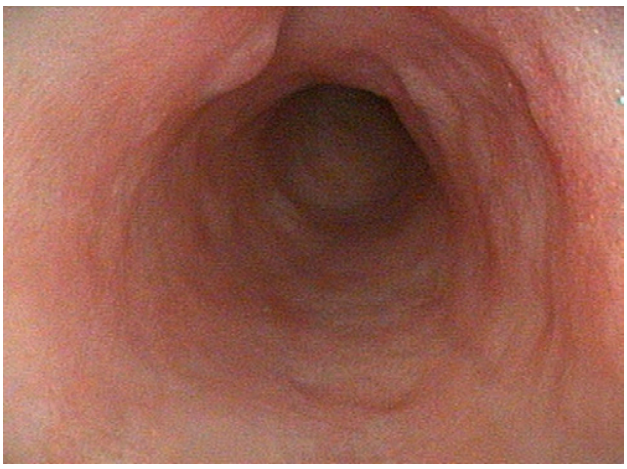


Figure 49.13 View of a normal descending duodenum from just distal to the pylorus, on initial entry to the duodenal lumen. The major duodenal papilla is visible to the upper left as a blunted protrusion into the lumen; this is a useful landmark for the upper duodenum.



Figure 49.14 Normal villi in the distal descending duodenum. This is the same patient as shown in Figure 49.13. Note that the villi are easily appreciated due to the clearly defined narrow lymph vessels circumscribing each villus. This is a normal finding (compare to Figures 49.9 and 49.15), but is usually only readily appreciated with high-resolution videoendoscopy equipment.

biliary and pancreatic secretions. The papilla(e) are a useful landmark indicating that the working tip of the endoscope is placed very close to the pyloric sphincter (Figure 49.13).

As the endoscope is advanced along the duodenum, a clear lumen is readily appreciated; this is the descending duodenum. As the end of this lumen is approached, the mucosa can be seen deviating to the left (assuming routine patient and endoscope orientation); this is the caudal duodenal flexure. If the endoscope can be coaxed around this corner (which depends heavily on the working length available and the size of the patient), it is possible to enter the transverse duodenum, and after a short distance another turn marks the beginning of the jejunum. It is relatively uncommon that this depth is reached in veterinary patients.

The leftward deviating mucosa at the caudal duodenal flexure is typically an easy site to biopsy. Biopsies are obtained from this wall, and then the endoscope is slowly withdrawn, 1–2 cm at a time, to allow biopsy of the descending duodenal mucosa. Biopsy samples are collected progressively as the endoscope retracts, until the working end falls back through the pylorus into the gastric antrum. At this point, the biopsy sample container should be changed and a new container used for gastric biopsy samples.

Normal Findings

As indicated above, observation of the duodenal papilla(e) is a normal finding, particularly in dogs. The duodenal mucosa should be pink to red, and show a fine granular to almost velvety appearance (representing the tips of the villi). Small amounts of bile and bile-stained mucus may also be observed and are normal. The duodenal mucosa is relatively delicate, and becomes more fragile in the presence of inflammatory disease, thus minor erosions and abrasions are commonly seen in areas where the endoscope has impacted the mucosa. These can be quite prominent, but are not a significant complication and require no further action. Occasionally, depending on the fasting state of the patient, the lacteals within the villi are apparent. Well-circumscribed, clean-edged lacteals visibly curving at the ends of the villus tips are not abnormal (Figure 49.14); visible lacteals in normal villi will often give the duodenal mucosa a "reptile skin," apparently scaly appearance.

Peyer's patches may be observed on the antimesenteric border of the duodenal mucosa. Peyer's patches are lighter than the surrounding mucosa, and are slightly depressed relative to the local mucosa. These represent aggregations of lymphoid tissue and are not abnormal.

Potential Abnormalities Observed in Duodenoscopy Procedures

Most of the abnormalities noted in endoscopic examinations of the duodenum relate to changes in the appearance or character of the mucosal surface. These changes are not specific to any particular disease process, but generally reflect changes in the cellularity and cellular makeup of the mucosa.

The characters most commonly assessed for evidence of abnormalities in the duodenum are granularity, friability, presence of erosions, and abnormalities in lymphatic drainage.

Increasing granularity results in a "heaped" appearance of the mucosa; with severe change, there may be apparent folds in the duodenal mucosa that do not dissipate with insufflation, while more subtle changes lead to a "cobble stone" appearance of the mucosa (see Figure 49.7).

Increasing friability is noted when impact with the endoscope leads to excessive mucosal stripping and bleeding from contact points. The mucosa is inherently somewhat friable, but contact of the endoscope with a normal mucosa should result in very minor to no loss of mucosal surface (see Figure 49.8).

Erosions are preexisting areas of loss or compromise of the mucosal surface. As some degree of mucosal contact is inevitable as the endoscope proceeds along the duodenal lumen, it is important to assess for the presence of erosions as the endoscope is advanced, not on withdrawal. Dramatic mucosal damage visible on withdrawal of the endoscope is more compatible with a change in friability than a diagnosis of erosions, as it represents greater iatrogenic damage rather than preexisting mucosal pathology.

Lymphatic drainage of the villi occurs via the lacteals, which normally contain milky white lymph due to the presence of fat micelles. This makes visualization of lacteals remarkably easy in many patients. Simply observing lacteals within the villi, even in animals that have had an overnight fast, is not evidence of a lymph drainage abnormality. Mucosal blebbing, representing rupture of the lacteals and infiltration of lymph into the interstitium, is an important finding. In patients with lymphangiectasia, the lymphatics become dramatically engorged and may occupy >80% of the volume of the villi. This degree of change is usually seen in patients with marked protein-losing enteropathies (Figure 49.15), either secondary to significant mucosal inflammatory disease or due to the presence of a primary lymphatic vessel abnormality.

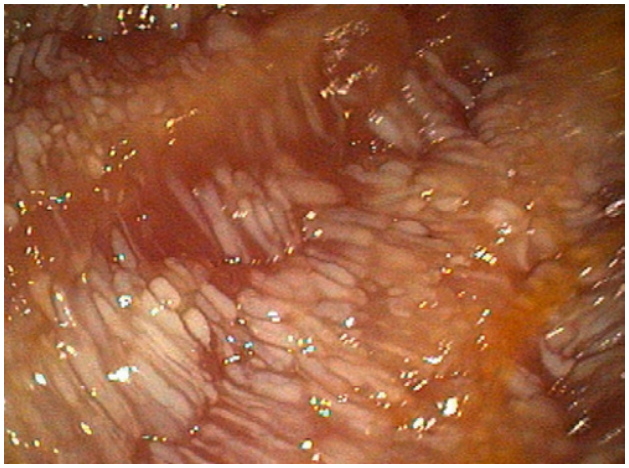


Figure 49.15 Severe lymphangiectasia in the very cranial aspect of the jejunum in a dog with severe protein-losing enteropathy. This is a more distal view of the small intestine of the same patient as in Figure 49.9. The great majority of the villi are dramatically engorged with milky white lymph. On histologic examination, >80% of the villus diameter was occupied by dilated lymph vessels.

None of the mucosal changes described above can be reliably detected in all cases of small intestinal disease, and the agreement between observation of these abnormalities and the presence of histologically important mucosal changes is poor at best. Small intestinal mucosal biopsy samples should always be obtained during duodenoscopy procedures.

Large Intestinal and Distal Small Intestinal Procedures

Patient Preparation

Adequate patient preparation is critical before colonoscopy and ileoscopy procedures. The esophagus, stomach, and upper small intestine will usually be emptied of ingesta with a 12–18-hour fast. The large intestine, however, normally contains a large amount of fecal material, mucus, and fluid that is not removed or resolved with fasting alone. Other procedures, including oral preparation solutions and enema treatments in concert with fasting, are necessary to allow adequate preparation for this procedure.

Failure to remove fecal material adequately is a major cause of incomplete or diagnostically misleading colonoscopy procedures. Visualization of the mucosa is often severely hampered (potentially resulting in failure to observe discrete lesions), and the time taken to complete the examination is markedly extended.

A number of different approaches to colonoscopy preparation have been described. Some practitioners use only warm water enemas (along with 24–48 hours of preprocedure fasting), or warm soapy water enemas. Care must be taken with enema solutions that they are not irritating (as can be the case with some solutions marketed mainly for relief of constipation in humans) and do not cause severe fluid or electrolyte shifts (phosphate-based enemas are notorious for this effect in cats).

The author's preferred approach is to use a combination of fasting with polyethylene glycol-based oral preparation solutions (GoLYTELY® or similar) combined with periprocedural enemas. The oral preparation solutions produce dramatic osmotic diarrhea, so it is often beneficial to hospitalize the patient for easier maintenance and cleaning. The solution is administered at a dose of approximately 20–25 mL/kg via orogastric intubation,

starting the evening before the procedure is planned. The solution is dosed three times (each at 20–25 mL/kg) at 2–3-hour intervals, starting approximately 18 hours before the procedure is planned (early afternoon the day before a planned morning procedure). The solution is administered via either intermittent orogastric intubation or by mixing it with plain vanilla ice-cream (one part ice-cream to two parts solution) and allowing the patient to drink it. Many dogs will readily consume the resulting solution. If oral intubation is used, the author considers nasogastric intubation and trickle infusion to be strongly contraindicated, as this is associated with increased risk of aspiration pneumonia, which can be severe and life threatening.

As the last of the evening doses of oral preparation solution is given, a warm water enema (also 20–30 mL/kg) is administered. The warm water enema is repeated early in the morning on the day of the planned procedure (around 7am for a 9am procedure), which should result in passage of clear fluid with little to no fecal material or mucus. If the morning enema continues to produce solid fecal material, ideally the procedure will be delayed by 1–2 hours to allow a second morning enema, followed by at least an hour of resting time to allow fluid absorption and resolution of transient irritation of the colonic mucosa.

An adequately prepared colon will allow easy and relatively unimpeded observation of the colonic mucosa over the length of the large intestine. Minor adherent material and mucus can usually be lavaged and flushed from the colon using endoscope suction. Specific colonoscope irrigation and washing pump systems are available and routinely used in human patients, and may be worth consideration in veterinary practices that carry out a large number of large intestinal procedures. While these pumps and washing systems can assist with final cleaning and visualization of the colonic mucosa, they are not a replacement for adequate preprocedural preparation.

Proctoscopy

Indications

Proctoscopy is a useful technique for the assessment of patients with predominantly or exclusively large intestinal symptoms, such as tenesmus, excess fecal mucus, fecal urge incontinence, hematochezia, dyschezia, and visible or palpable anorectal masses. As many of the mucosal diseases affecting the large intestine tend to be diffuse throughout the large intestinal lumen, and anorectal diseases are by definition limited to the distal large intestine and anal canal, proctoscopy may be all that is necessary to establish a useful working diagnosis in a large intestinal disease case.

Patient Positioning

Typically, the patient is placed in right lateral recumbence for isolated proctoscopy procedures without assessment of the transverse or descending colon and ileocolic junction. Right lateral recumbence causes any residual fluid from patient preparation to pool into the transverse colon (which is oriented vertically when the animal is in lateral recumbence), aiding in mucosal visualization.

Equipment Choice

Proctoscopy can be achieved with either flexible or rigid endoscopes. Refurbished human flexible colonoscopes, up to 11 mm diameter, can be effectively used in most dogs and cats, although some endoscope manipulations such a J-maneuvers (necessary for effective visualization of some very distal rectoanal lesions) can be challenging or impossible with this size endoscope in smaller dogs and most cats.

Rigid proctoscopes can be very valuable for these procedures, as they usually feature large endoscope lumens that allow passage of larger instruments, biopsy and cautery snares, and rigid forceps.

General Technique and Landmarks

The rigid proctoscope is lubricated well and introduced through the anal sphincter gently, while an obturator is in place. When resistance to passage of the proctoscope reduces, marking entry of the proctoscope into the rectum, the obturator device is removed and the lighting and visualization system (typically a rigid fiberoptic telescope and accessory camera) are attached. The proctoscope is then gently introduced into the colon lumen, while the operator closely observes the mucosa. Air insufflation is used as necessary to inflate and maintain the colonic lumen. Rigid proctoscopes should not be advanced if the lumen is not visible, as this increases the risk of colon wall perforation, which is a major and potentially life-threatening complication.

With the larger lumen of the proctoscope, there is the potential to use larger, rigid biopsy forceps and instruments to collect more substantial pieces of tissue than with typical biopsy instruments used in flexible endoscopes. Some rigid biopsy instruments feature angled biopsy cups, which make the process of sampling the mucosa through the rigid lumen somewhat easier. Rigid instruments with straight biopsy cups are still useful, but may require removal of a small amount of insufflated air to allow the mucosa to "drape" over the front of the endoscope lumen.

Normal Findings and Potential Abnormalities

Normal findings and potential abnormalities encountered during proctoscopy are identical to those seen

during flexible colonoscopy procedures, and are described in the flexible colonoscopy section below.

Colonoscopy

Indications

Colonoscopy is commonly indicated for the assessment of patients with predominantly or exclusively large intestinal symptoms, such as tenesmus, excess fecal mucus, fecal urge incontinence, hematochezia, dyschezia, and visible or palpable masses. Colonoscopy is also increasingly viewed as an important part of the overall approach to any chronic gastrointestinal disease case, a means of both assessing large intestinal involvement and collecting distal small intestinal biopsy samples via ileoscopy.

Patient Positioning

For most colonoscopy procedures, the patient should be placed in left lateral recumbence. As well as being convenient for combination upper and lower gastrointestinal tract procedures performed sequentially under the one anesthetic procedure, left lateral recumbence results in residual fluid pooling in the descending colon; this fluid is more readily suctioned from this position than if in the transverse or ascending arms of the colon. Colonoscopy procedures can also be carried out in sternal recumbence, which has the advantage that the anatomy of the colon is oriented in a "normal" position relative to the endoscope operator. However, scrupulous preparation is necessary to obtain optimum visualization if this position is used.

Equipment Choice

Navigation of the entire large intestine to the ileocolic junction requires the use of a flexible endoscope with four-way tip deflection, water and air insufflation, and a good sized working channel. Refurbished human colonoscopes with working lengths of 150–175 cm and 9–11 mm diameter are appropriate for many small animal patients and usually feature 2.8 mm working channels, allowing the use of larger biopsy instruments. In very small dogs and some cats, the use of these endoscopes may be more difficult, primarily due to the minimum turning radius of the endoscope tip rather than the endoscope diameter. In these smaller patients, a pediatric gastroscope may be a better choice.

General Technique and Landmarks

The lubricated endoscope tip is gently introduced via the anal sphincter. When a reduction in insertion pressure is noted, indicating that the tip of the endoscope has traversed the anal sphincter and is sitting within the distal rectum, the endoscopist should stop and insufflate while moving the tip controls gently in order to visualize a lumen. Unlike in the small intestine, where mucosal "fly by" procedures are common, in the large intestine it is generally best only to proceed forwards when there is a visible lumen. As air insufflation proceeds, the pressure of the accumulating gas may lead to leakage around the endoscope at the anal sphincter. This can be overcome by having an assistant apply gentle circumferential pressure around the anus; the same assistant can also advance the main endoscope body while the main operator utilizes the tip deflection controls and air/water insufflation to maintain visualization.

The distal rectum is assessed as soon as the lumen is insufflated, examining for preexisting erosions and the presence of mucosal masses. To obtain complete visualization of the distal rectum and the oral surface of the anal sphincter requires a maximally flexed J-maneuver, which may not be feasible in smaller patients.

As the endoscope is advanced, the descending colon wall is examined for changes in mucosal friability, granularity, and the presence of masses. If the patient is in left lateral recumbence, some fluid pooling is to be expected along the lumen of the descending colon; this fluid should be aspirated as much as possible to optimize mucosal visibility.

At the end of the descending colon, the lumen will make a marked deviation into the transverse colon. Ideally, this turn should be made with a target lumen visible, although this is not always feasible. Carefully assess what mucosa is visible from the descending colon before proceeding into the transverse colon; if severe ulceration or erosions are present, it may be more prudent to limit the examination to reduce the risk of perforation.

The transverse colon crosses the abdomen to reveal the short ascending colon and the ileocolic junction. This region is readily identified by the presence of a proud, intraluminal button of mucosa surrounding the ileocolic sphincter, while the nearby cecum is usually visible as a blind pouch close to the ileocolic sphincter. The cecal mucosa is usually arrayed in longitudinal folds similar to the rugae of the stomach. Lymphatic follicles can be quite prominent within the cecal mucosa.

Normal Findings

The normal colonic mucosa is smooth, a light pink in color and readily distensible with air insufflation. The ileocolic junction can be quite variable in appearance (Figure 49.16). Depending upon the trajectory of the endoscope approaching this region, the ileocolic sphincter may be visualized to the left or right, and the opening of the cecum is also quite variable, in some cases showing a prominent "ridge" of tissue around the opening, while in others the cecal opening is hard to distinguish from the colon lumen and is appreciated only as a blind sac near to the ileocolic sphincter.

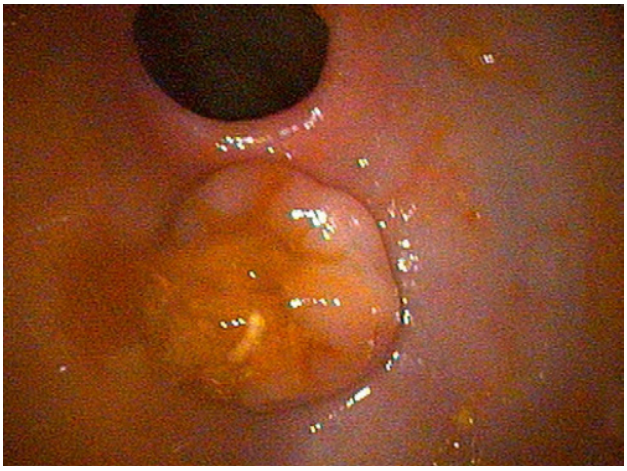


Figure 49.16 Colonic view of the normal ileocolic junction in a dog. The ileocolic sphincter, visible as a mushroom-like protrusion into the colonic lumen, occupies the lower half of the image. Above the ileocolic sphincter, the entry to the cecum is visible, surrounded by a "ridge" of normal colonic mucosa. The anatomy of this region, particularly the transition from colonic to cecal lumen, is highly variable in normal dogs.

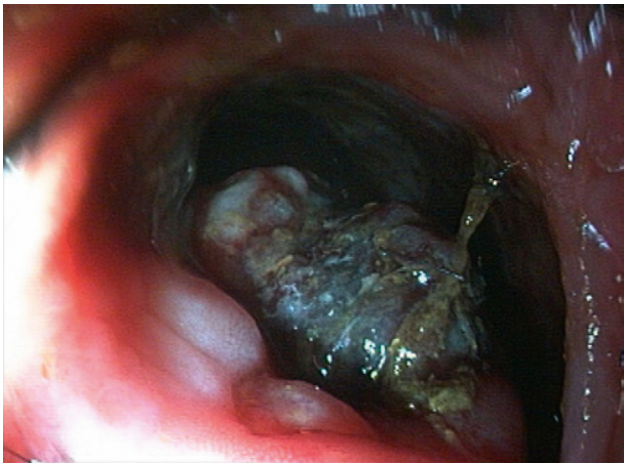


Figure 49.17 A large, severely ulcerated mass lesion in the descending colon of a canine patient. A marked increase in colonic mucosal granularity is also visible. Endoscopic biopsy of this lesion and the granular regions of colonic mucosa revealed lymphosarcoma.

Potential Abnormalities Observed during Colonoscopy Procedures

After careful assessment of the mucosa for consistency in appearance, texture, the presence of masses or erosions and ulcerations as the endoscope is advanced, biopsy samples should be obtained from areas of interest and several areas that are apparently normal as the endoscope is withdrawn. Mass lesions may also be biopsied but care must be taken to minimize the risk of colonic wall perforation. Mass lesions or ulcerative lesions with severe mucosal distortions (Figure 49.17) or deep mucosal defects are best assessed by collecting biopsies from the adjacent, more normal-appearing mucosa rather than the center of the mass, as biopsies from this region are usually of poor diagnostic quality due to tissue necrosis, and the risk of perforation is increased substantially.

Ileoscopy

Indications

Ileoscopy, while technically more challenging than many other gastrointestinal endoscopy procedures, is strongly recommended when endoscopic examination is being conducted as part of the approach to patients with gastrointestinal disease, regardless of whether the primary complaint is predominantly arising from upper or lower gastrointestinal tract signs. It is not unusual to document substantial histological disagreement between duodenal and ileal mucosal biopsy specimens, with the ileal mucosa often presenting with more severe changes. This holds true with both dogs and cats.

Patient Positioning and Preparation

As ileoscopy requires a transcolonic approach, ideally the patient will be placed in left lateral recumbence. This is consistent with the positioning for upper gastrointestinal procedures. Ideally, the patient will receive preprocedural preparation for colonoscopy. If there is no plan to fully assess the colonic mucosa and the sole reason for the procedure is to attempt to biopsy the ileal mucosa, a more abbreviated preparation protocol can be used, essentially several warm water enemas administered the evening before and once on the morning of the procedure (assuming a morning procedure time). This may provide sufficient space and visualization to allow traversal of the colon to the ileocolic junction, but there is a greater risk that the lower intensity preparation will result in inadequate visualization and failure of the procedure.

Equipment Choice

Ileoscopy requires a flexible colonoscope with four-way tip deflection, air/water insufflation and a large working channel, as used for colonoscopy procedures. Extra length will be necessary to allow navigation into and along the ileum, which may become limiting with larger canine patients.

General Technique and Landmarks

The ileocolic junction is approached at the end of the routine colonoscopy procedure, as described earlier. The endoscope tip is brought into contact with the center of the ileocolic sphincter, similarly to the antral approach to the pylorus. As with the pyloric approach, excessive air

insufflation can compromise attempts to traverse the sphincter. As there is little in the way of colonic wall close to the sphincter, due to the disparity in ileal versus colonic lumen diameters, full insufflation deprives the endoscopist of support from the colon walls.

If the endoscope can be successfully maneuvered into contact with the sphincter, gentle forwards pressure will usually result in entry to the ileum. If the ileum cannot be entered in this manner due to ileocolic anatomy, a flexible biopsy instrument can be threaded through the working channel and ileocolic sphincter to act as a guide wire. The instrument is advanced, cups closed, until it has penetrated the ileal lumen for 2–3 cm. The biopsy instrument is then held in place and the endoscope advanced over it. It is not recommended to simply follow the biopsy instrument with the endoscope, as this may result in significant trauma to the ileal mucosa (which has not been visualized).

Normal Findings

The normal ileal mucosa is grossly similar in appearance to the duodenal and jejunal mucosa. The normal villus structure results in a "velvet" appearance. The mucosa is more friable than the duodenum, even in normal individuals. Villus lymphatics are not readily appreciated.

Potential Abnormalities Observed during Ileoscopy Procedures

The ileal mucosa is assessed for changes in granularity, friability, the existence of preexisting erosions or ulcerative lesions and mass effects, and these changes documented if seen. Mucosal biopsy specimens should always be obtained from the ileum. If the endoscopist is unable to traverse the ileocolic sphincter, it is possible to obtain mucosal biopsy samples blindly by advancing a biopsy instrument through the sphincter, although this should be approached with caution as the risk of perforation is higher without the ability to visualize preexisting lesions.

Endoscopic Biopsy Technique

Endoscopic biopsies are an attractive option for more complete diagnostic assessment of the gastrointestinal tract, but are not without significant potential pitfalls. Correct biopsy technique, careful sample handling, and the collection of adequate sample numbers are all important to obtain the best diagnostic yield from these samples.

Flexible endoscopic biopsy instruments are available in several different types, including serrated or smooth jaws, and with or without central needles. Theoretically the central needle types are easier to lodge in the mucosa but in practice there seems to be little advantage to these types, and removal of the sample from the central needle can be difficult. The biopsies are inherently fragile and repeated "scraping" to remove the sample from the central needle can result in severe crush artifact distortion.

Endoscopic biopsy samples obtained using flexible instruments are unavoidably small. Even the largest of the flexible biopsy instruments that will fit in the endoscopes used most commonly in companion animal practice will typically only yield a 2.5–3 mm^3 tissue sample under most conditions. Most samples obtained endoscopically will have relatively little submucosal tissue present, and in many cases small intestinal biopsies may only yield villus tips. Correct technique is necessary to avoid excessive crush artifacts or villus degloving.

Because of the extreme wide-angle view and deep depth of focus of the endoscope lens, and lack of depth cues due to monocular vision, the distance between the end of the endoscope, the biopsy instrument, and the lesion to be biopsied can be difficult to judge. Once a site for biopsy is identified, the biopsy instrument is carefully deployed through the working channel until it is visible to the operator. Fine tip adjustments can then be made to align the instrument with the area to be biopsied, and then the instrument is advanced to make contact with the tissue. The flexible shaft of the biopsy instrument will start to bend slightly as the instrument is pushed up against the tissue. This bending is a good indicator that an appropriate amount of pressure is being applied to the tissue to provide the best chance of an adequate biopsy.

The biopsy instrument emerges from the distal face of the endoscope (Figure 49.18), which will usually result in the instrument running parallel to the gastrointestinal lumen. If the endoscope is maneuvered close to a naturally occurring fold or corner in the lumen, it is possible to directly sample tissue perpendicular to the distal scope face. For biopsies from the wall in an area that does not have a naturally occurring fold or local corner (such as in the descending duodenum), a number of strategies are available. Gently suctioning some of the insufflating gas may result in formation of rugal folds. After minor suction is applied, the endoscope tip is diverted towards the mural surface using the tip deflection controls, then the biopsy instrument is advanced out until just in view and close to, but not touching, the mucosa. The biopsy jaws should be open at this point. Full suction is then applied, which will cause the lumen to collapse and the mucosa to "drape" over the end of the scope. The biopsy instrument is advanced very slightly and then the jaws are closed. The biopsy is then collected.

The necessary action to collect an endoscopic biopsy is with a sharp "snapping" pull on the instrument at the control end of the scope. The aim is to avulse the mucosal sample by breaking the submucosal tissue. If the tissue is collected with a slower "drag" motion, it is not



Figure 49.18 A hemispherical jaw biopsy instrument exits the distal end of a videoendoscope perpendicular to the imaging components and parallel to the long axis of the gastrointestinal tract. Manipulation of the tip of the endoscope is typically necessary to bring the biopsy instrument into correct apposition against the mucosa to obtain adequate biopsies.

uncommon to yield only mucus, or to deglove the villi and retrieve only mucosal fragments. These samples are usually not of diagnostic quality, as the loss of architectural context limits the ability of the pathologist to accurately assess the mucosa.

After collection, the biopsy instrument is removed while leaving the endoscope in place. The instrument should be kept closed until the instrument has been fully removed from the endoscope and an assistant has restrained the end of the instrument. The instrument is then opened, and the tissue sample retrieved from within the biopsy cups. Often, the tissue will be adherent to the biopsy cups, and the tissue may need to be removed by *gentle* manipulation with a fine hypodermic needle (typically 25 ga). "Stickiness" of the biopsy to the instrument is more pronounced with smaller biopsy instruments and in samples from the small intestinal mucosa.

Given that each individual sample is very small, and may not be representative of the total of the pathologic changes present in the patient, it is important to obtain multiple biopsy samples from each organ sampled. Assuming adequate biopsy technique and handling, at least seven samples per site (i.e., seven each from upper and lower small intestine, stomach) in dogs and 10 in cats are necessary to achieve acceptable correlation with full-thickness biopsy results. If inadequate technique is used, particularly in cats, there is a very real chance that samples will have no diagnostic utility.

Biopsy of the gastric mucosa is somewhat more straightforward than in the small intestine as the stomach is more readily distensible and the greater space within the organ allows easier manipulation of the endoscope to a position perpendicular to the mucosa. The gastric mucosa is more robust than the small intestinal mucosa, and good-quality biopsies are easier to obtain from most areas of the stomach.

The esophageal mucosa is predominantly squamous epithelium, and difficult to adequately biopsy unless severe pathology is present.

Tissues from different sources (small intestine vs large intestine vs stomach) should be handled and submitted separately.

Postbiopsy handling of the tissues is also important for maximum diagnostic utility. Different pathology services may have differing requirements for sample submission but generally speaking, it is best to organize biopsy samples in a manner that will maintain consistent orientation as the samples are paraffin embedded and sectioned. If feasible, samples can be directly placed into sample handling cassettes, oriented with the mucosa perpendicular to the base of the cassette. It is important to use cassettes that are compatible with the sample handling systems of the pathology laboratory. The whole cassette can then be submerged in buffered formalin for histologic assessment. This will result in samples that are as close to parallel to the microtome blade as possible, yielding a greater proportion of longitudinal sections of the villi. This is important to allow the pathologist to assess characters such as villus blunting and the presence of inflammatory infiltrates within the crypts.

Endoscopic Interventions

PEG Tube Placement

Percutaneous endoscopic gastrostomy tubes are useful for providing long-term nutritional support to veterinary patients with severe esophageal or oral pathology, and also for those with poor appetite due other co-morbid

conditions. Placement of these devices is relatively simple, but care must be taken to minimize the risk of complications.

Indications and Patient Choice

Percutaneous endoscopic gastrostomy tube placement should be considered in patients with significant dysphagia, anorexia, esophageal or oral pathology with an anticipated need for nutritional support beyond 3–5 days. PEG tubes may be placed in both canine and feline patients, but are of particular use in dogs (particularly larger breeds) where the placement of esophagostomy tubes is more difficult due to the anatomy of the neck and cervical esophagus. PEG tubes have the advantage of larger lumens than are typically used in nasoesophageal or esophageal feeding, and are generally well tolerated such that they can be maintained for weeks to months. After formation of a stable adhesion of the gastric wall to the peritoneum and abdominal wall (generally after 10–14 days), it is feasible to convert PEG tubes to lower profile gastrostomy tubes that are somewhat easier for clients to maintain and do not feature extraabdominal tubing that must be restrained and maintained.

Placement of PEG tubes is straightforward in most patients. Difficulty can be encountered in patients with megaesophagus, due primarily to negotiating the lower esophageal sphincter in these patients. Large, deep-chested dogs can also be more difficult as the normal gastric position in these patients is high under the thoracic cage, these patients can require substantial insufflation of the stomach to allow access, and the resulting ostium and adhesions are under tension after the stomach is deflated. Larger breed, debilitated dogs have a greater risk of tube failure and peritonitis so in these patients it may be more prudent to place gastrostomy tubes surgically.

While the procedure is relatively easy to describe, and manufactured kits designed to make tube insertion simple are available, it is still prudent to have at least some guidance from an experienced endoscopist when first learning to place these tubes.

General Procedure

Percutaneous endoscopic gastrostomy tubes are placed exiting the flank on the left side, so the patient should be placed in right lateral recumbence. The left paracostal region is clipped and surgically prepared. The endoscope is passed into the stomach, and air insufflated to distend the stomach against the abdominal wall. While the endoscope operator is visualizing the gastric wall, an assistant wearing sterile gloves palpates and presses on the region of maximum distension, to allow the endoscopist to establish where the tube will eventually be placed. The endoscope is then manipulated to the point of compression and the gastric wall transilluminated to ensure that there are no major structures (particularly the spleen) present between the gastric and abdominal walls.

The description given below assumes that a manufactured PEG tube kit is being used, which are provided with the tube mechanically bonded to a loop of wire at the proximal end, and a guide wire that features a loop at the distal end. Techniques for the assembly of PEG tubes using sterile pipette tips and standard suture materials have been described, but with the ready availability of commercial PEG kits in the veterinary market, the manufacture of tubes from a miscellany of materials is no longer recommended.

Once the point of insertion is established, the sterile-gloved assistant passes a large hypodermic needle (typically 18–16 ga, 2+ inches) through the skin and gastric wall, typically placed just ventral and slightly caudal to rib 13. The endoscope operator monitors the hypodermic needle entry. Once the hypodermic needle is placed, a guide wire with a terminal loop is threaded through the lumen of the needle by the assistant, and captured by the endoscopist using either flexible alligator or cup biopsy forceps. Once the guide wire loop is captured, it is carefully pulled through the stomach, esophagus, and oral cavity by withdrawing the endoscope. The assistant should feed the guide wire via the needle, while monitoring closely to ensure that the full length of the guide wire is not pulled into the stomach lumen.

After the loop of guide wire is withdrawn via the mouth, it is attached to the proximal end of the tube by passing the tube mushroom tip through the guide wire loop, then through the tube's own bonded wire loop, resulting in the tube proximal end being attached to the guide wire via linked loops.

The guide wire and linked tube, bonded tip first, are withdrawn into the oral cavity, through the esophagus and into the stomach lumen by the sterile-gloved assistant. As the guide wire and linked proximal tube end encounter the gastric wall, the wall is pulled up against the flank. The bonded sharp tip of the tube is drawn through the abdominal wall by continuous gentle traction. A small stab incision will usually be necessary at the point of tube exit.

As the tube is withdrawn through the abdominal wall, the endoscopist replaces the endoscope into the gastric lumen and monitors the positioning of the distal mushroom tip against the gastric wall. The mushroom tip should be placed with sufficient tension to hold the gastric wall against the abdominal wall, but excessive tension should be avoided as this may lead to gastric wall necrosis below the mushroom tip and failure of the gastrostomy site. The mushroom tip should gently flatten the gastric mucosa, but blanching of the mucosa should not be visible on examination. If the mucosa is blanched,

the distracting tension on the tube must be loosened to reduce the risk of gastric wall compromise.

When the operator is satisfied that the tube is correctly positioned, the bonded sharp end is removed with heavy bandage scissors and the tube retained against the external flank using a retaining anchor system. The gastrostomy site is bandaged and the tube trimmed to length before assembly of a catheter tip closure to allow administration of food. The remaining tube should be loosely restrained against the body using stockinet tubing and/or an old t-shirt, and an Elizabethan collar applied for at least the first 4–5 days while a stable adhesion is being formed.

Assuming no complications in placement of the PEG tube, administration of fluids (water initially) and then liquid or blenderized diets can commence approximately eight hours after the patient recovers from anesthesia.

PEG-J Tube Placement

Percutaneous endoscopic gastrostomy-jejunostomy tubes are a refinement and addition to the PEG tube systems described above, with additional placement of a tube into the jejunum. A PEG tube is placed as described above, then a narrow feeding tube with a loop of suture material at the distal end is threaded into the gastric lumen via the gastrostomy tube. This second tube is captured at the loop of suture material, then the tube is carried through the pylorus and into the duodenum by the endoscope. The second tube is carried as far as possible distally by the endoscope, then gently threaded further to reach the jejunum. The PEG and J-tubes are then trimmed and retained as previously described. The addition of the J-tube allows the delivery of liquid diets into the jejunum, completely bypassing the duodenum. While nutrition is being delivered to the jejunum, gastric secretions and fluid can be suctioned via the PEG tube, which may help to control vomiting in patients with severe gastric or pancreatic inflammation. As the patient recovers and the stomach is more amenable to diet input, the J-tube can be removed and use of the PEG tube instituted.

While there are some theoretical benefits to the use of PEG-J tubes in animals with very severe pancreatic disease, the author rarely uses these tubes in these patients. Instead, a multimodal antiemetic protocol is used along with gastric tube or esophagostomy tube feeding. There is no evidence to support the contention that "pancreatic rest" is important for patients with pancreatitis, which is the main imperative behind J-tube feeding in most patients.

Foreign Body Removal

The use of endoscopy, either rigid (within the esophagus) or flexible (esophagus and stomach), is an attractive first-line option for management of this problem. The potential for removal without surgery allows more rapid recovery of the patient and reduces the risk of gastrointestinal perforation and/or wound dehiscence. This potential must be tempered by the reality that often the endoscopic removal of foreign bodies, particularly "slippery" gastric foreign bodies that can be quite fragile, can take long periods of time and may not be feasible. It is good practice to define an upper time limit for the endoscopic procedure before transitioning to surgical management.

A variety of retrieval devices is available, with varying strengths and indications (Figure 49.19). For esophageal foreign bodies, it is often possible to use long, rigid forceps to grasp the foreign body. This is particularly helpful if using a rigid endoscope for the esophagoscopy, but can also be carried out with flexible endoscopy equipment by carefully introducing the retrieval instrument beside or above the endoscope that is viewing the foreign body. Other retrieval instrument options include flexible alligator forceps, deployable wire cages, three-pronged graspers, Foley catheters, wire loops and snares, and old endoscopy biopsy forceps. The use of biopsy forceps for foreign body retrieval will usually result in dulling of the edges and loss of effective biopsy function so older forceps should be used.

There is no one technique or device that reliably succeeds in grasping and removal of all foreign bodies of any specific type. While some general observations can be made, such as alligator forceps have no utility with rounded, smooth-surfaced objects, most foreign body retrievals will require the use of several different types of instrument. For instance, flexible alligator or old biopsy forceps may be used to reposition an object within the gastric lumen, allowing application of a wire basket for the actual retrieval process. Some foreign bodies will require reorientation several times to allow a graspable surface to be visualized. As wide a selection of retrieval instruments as possible should be available to the endoscopist. Foley catheters can be used to manipulate and reposition some objects by threading them past the obstruction, then inflating the balloon before applying gentle distracting pressure.

It is particularly attractive to attempt esophageal foreign body removal endoscopically wherever possible, as removal of foreign bodies from the thoracic esophagus via thoracotomy and esophagotomy is technically difficult and has a high risk of wound dehiscence and subsequent development of pneumomediastinum, pneumothorax, and pyothorax. As a general observation, endoscopic removal of esophageal foreign bodies becomes increasingly difficult as the time since obstruction increases. Esophageal mucosal swelling and erosion/ulceration can occur rapidly, and these changes result in the foreign body becoming more and more

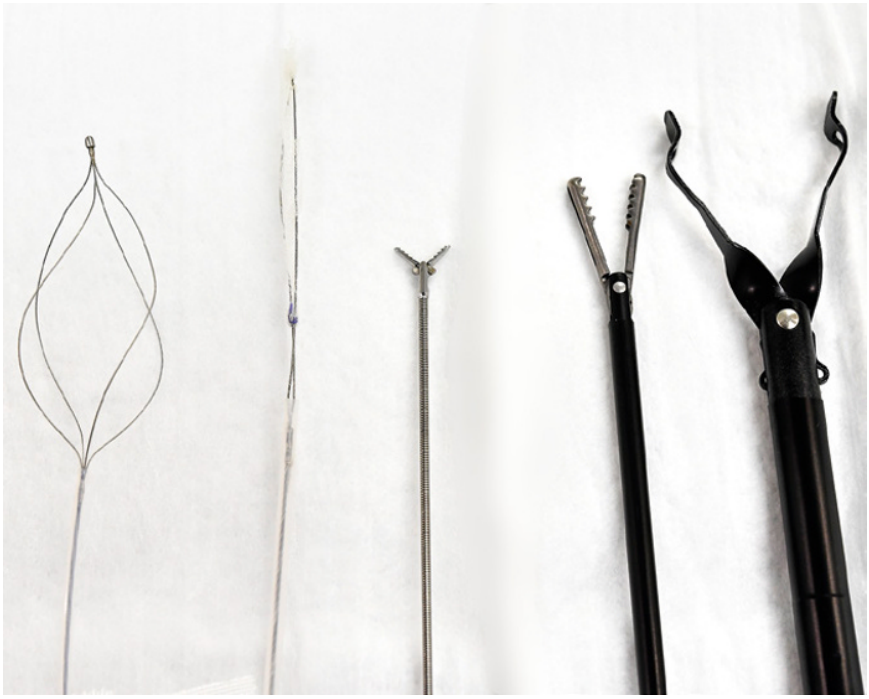


Figure 49.19 A selection of manipulating and retrieval instruments, which may be useful in retrieval of foreign bodies within the esophagus and/or gastric lumen. The rightmost two instruments are repurposed laparoscopic surgery graspers. From left to right, a four-wire basket forceps, a netting loop snare, and flexible alligator forceps. The flexible instruments are appropriate for use through the working channel of a larger endoscope, and can be utilized in the esophagus and stomach, but lack significant grasping power. The repurposed laparoscopic instruments have much larger working graspers and better grasping power. These rigid instruments are introduced to the esophagus either through a large rigid endoscope or along the side of a flexible endoscope. They are not appropriate for use in the gastric lumen.

firmly wedged. If the foreign body can be solidly grasped, a number of attempts to remove it via the oral cavity can be made, but if the object is not mobilized by moderate traction and the esophageal mucosa is showing increasing evidence of trauma/hemorrhage, a new strategy should be followed. If the foreign body can be pushed aborally into the stomach, this is often a preferable option. Many bone foreign bodies or impacted dog chews will dissipate once within the gastric lumen, while indigestible foreign bodies can be removed via celiotomy and gastrotomy with much lower risk of complications than arise from a transthoracic route.

When attempting to retrieve foreign bodies, great care should be taken that the gastrointestinal tract wall is not compromised, either by excessive force application or inadvertent perforation by sharp objects (bone fragments, needles, etc.) as they are withdrawn. It is also critical to assess the site of impaction after withdrawal for evidence of mucosal ulceration and abrasion. Within the gastric lumen, it is usually possible to visualize the site of impaction after initial grasping of the object, but with esophageal foreign bodies it will be necessary to reintroduce the endoscope to assess the mucosa. Severe circumferential mucosal damage, particularly if there is exposure of the submucosa, leaves the patient with a high risk for esophageal stricture formation. It is also recommended to obtain thoracic radiographs following removal of esophageal foreign bodies to assess for early signs of esophageal perforation such as pneumomediastinum or pneumothorax. If the patient has evidence of severe esophagitis and mucosal ulceration/abrasion, placement of a PEG tube for postoperative nutritional support is strongly recommended.

Esophageal Stricture Management

Esophageal stricture recognition and management via either bougienage or balloon dilation are discussed in detail in Chapter 52.

Future Directions of Gastrointestinal Endoscopy

After the unavoidably small size of biopsies achievable using flexible endoscopy, probably the greatest limitation of endoscopy in the gastrointestinal tract of veterinary patients is the lack of ability to assess the entire gastrointestinal tract. While many diseases that affect the gastrointestinal tract are diffuse, and thus duodenoscopy and distal ileoscopy will commonly result in meaningful diagnostic findings, solitary lesions in the deeper jejunum and proximal ileum are not unknown.

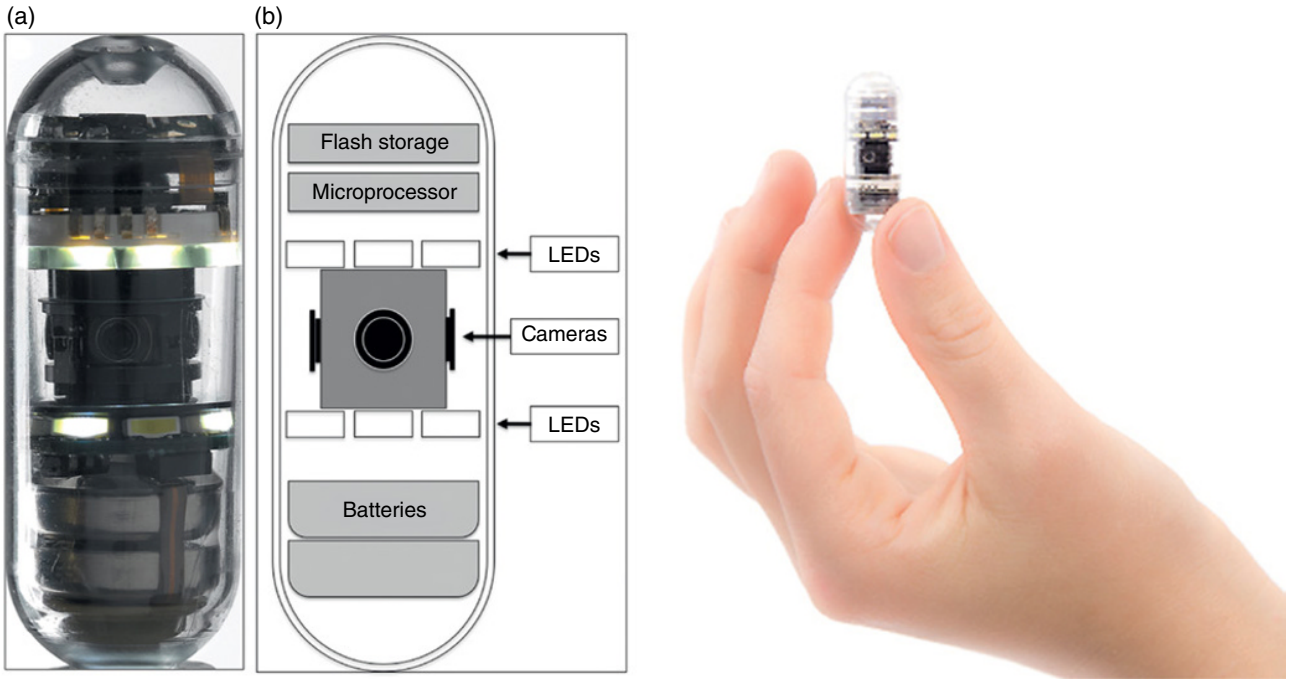


Figure 49.20 Composite image showing relative size and internal structure of a capsule endoscope system suitable for use in dogs. *Source:* Image courtesy of Infiniti Medical, LLC. www.Infinitimedical.com

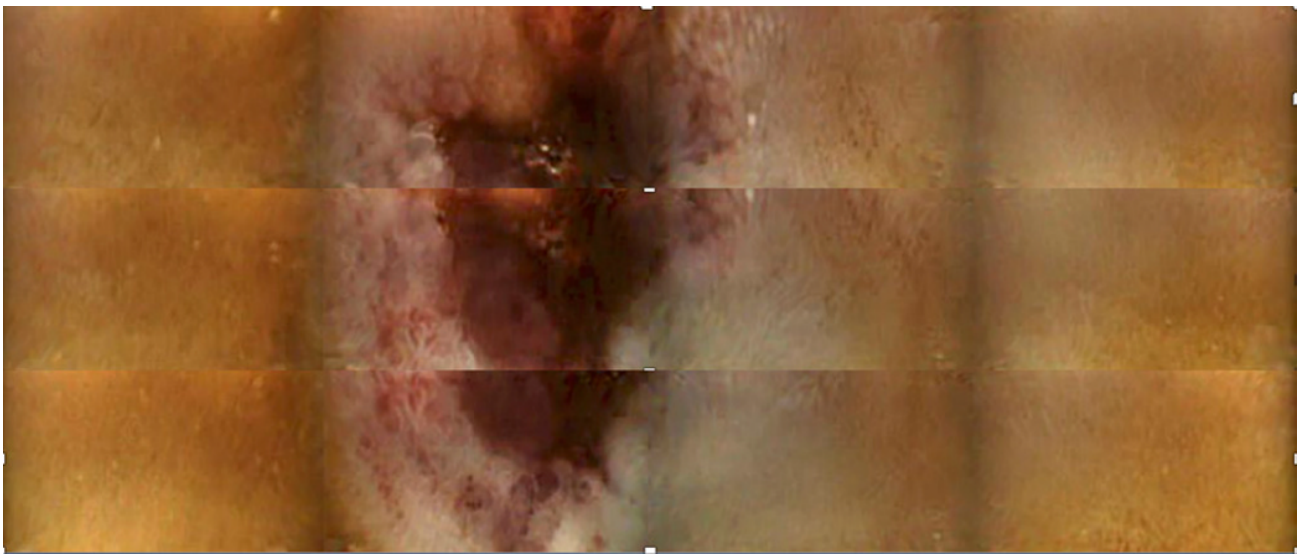


Figure 49.21 Composite image showing several captures from a capsule endoscopy system as it transits the small intestine of a canine patient. Marked mucosal erosion and ulceration are apparent. *Source:* Image courtesy of Infiniti Medical, LLC. www.Infinitimedical.com

A number of newer systems and strategies have been described that have the potential to allow direct visualization of much larger proportions of the gastrointestinal tract. The two most promising are double balloon push and pull enteroscopy and the use of capsule endoscopy systems.

Double Balloon Enteroscopy

Double balloon push and pull enteroscopy is carried out using an endoscope with an inflatable balloon, similar to a Foley catheter balloon, incorporated into the distal endoscope tip, and an additional balloon on a mobile

cuff that surrounds the distal endoscope. These balloons are sequentially inflated and deflated, and the endoscope advanced, as the small intestinal loops fold up behind the outer cuff. This technique has been described in a limited number of canine patients at the time of writing, and has some limitations due to the overall diameter of the specific endoscope/cuff combination (13.2 mm) and the increased stiffness and turning radius of the endoscope. The full exploration of the gastrointestinal tract using this endoscope is also a longer procedure than is typical for upper gastrointestinal endoscopy. An advantage of this approach is that biopsy samples can be obtained from a greater proportion of the gastrointestinal tract, and discrete lesions within the jejunum may be able to be sampled.

Capsule Endoscopy

Complete assessment of the entire gastrointestinal tract of dogs can be obtained in a minimally invasive manner through use of self-contained capsule endoscopes. These devices include cameras with 360° field of view, light sources, and digital storage space within a plastic enclosure that is similar in size and shape to a large capsule (Figure 49.20). The capsule is administered to the patient orally, and after transit through the entire gastrointestinal tract is recovered to allow downloading of digital image files. These systems have advantages in avoiding the need for anesthesia and postprocedural recovery, and arguably allow assessment of the gastrointestinal tract in a more natural state as the vascular changes induced by patient preparation and anesthesia are avoided.

An obvious limitation of the capsule endoscopy systems is that they are unable to retrieve biopsies, and the actual location where a lesion is observed cannot be determined with great accuracy as the images are typically not accessible until after complete transit through the gastrointestinal tract. This approach is very useful, however, for a complete assessment of the gastrointestinal tract for focal lesions, bleeding ulcers, discrete mucosal pathology changes, etc. (Figure 49.21). Anatomic landmarks, such as the pylorus, major duodenal flexure, and ileocolic junction, are usually easily identified, allowing some degree of certainty of the specific section of the gastrointestinal tract that can be observed.

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50

Diseases of the Oral Cavity and Salivary Glands

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A history of ptyalism or drooling saliva, perioral +/– oculonasal discharge, anorexia, weight loss, unkempt hair coat, vocalizing when eating, pawing at the mouth, rubbing the face on the furniture or carpeting, bruxism, chattering, and/or hesitation to have the head or face touched should prompt the clinician to perform a thorough intraoral and extraoral examination. Oral and salivary gland diseases can have various presentations, and often the duration of clinical signs along with the distribution of the lesions can aid in determining the etiology of the condition (Table 50.1). Histologically, oral lesions can range in appearance from areas of ulceration to vesicles to even proliferation of tissues, whether it is through hyperplasia, neoplasia or granulation tissue formation, to areas of necrosis. Salivary gland enlargement follows a spectrum, with the noninflamed form, known as sialadenosis, followed by sialadenitis and finally necrotizing sialometaplasia. Neoplasia can also occur in the salivary glands. It is important to keep in mind that some systemic diseases can manifest with oral lesions. Additionally, some systemic diseases that lead to immunosuppression can predispose patients to oral disease.

Healthy Oral Tissues and Salivary Glands

The masticatory and lining mucosa are the primary tissues affected by oral inflammation. The epithelium of the masticatory mucosa is moderately thick and frequently ortho-keratinized. It is inextensible and well adapted to withstanding abrasion. The epithelium of the lining mucosa is thicker than that of masticatory mucosa and is nonkeratinized. The surface is flexible and the submucosa is elastic, allowing it to stretch. Taste buds, gingival crevicular fluid, and normal bacterial flora play a role in protecting the oral cavity from insults. Taste buds reject potentially toxic materials. The gingival crevicular fluid is believed to cleanse the gingival sulcus, improve adhesion of the epithelium to the tooth via plasma proteins, possess antimicrobial properties, and exert antibody activity to protect the gingiva. The normal bacterial flora of the oral cavity plays a role in the innate resistance by preventing colonization and growth of foreign microbes.

There are four major pairs of salivary glands: mandibular, sublingual, parotid, and zygomatic. Minor salivary glands can be found on the palate, alveolar, labial and buccal mucosa, tongue, and along some of the ducts of the major salivary glands. Cats have an additional pair of mixed salivary glands found on the lingual aspect of the mandibular first molar tooth, known as the linguomolar gland. Secretory cells can be predominantly serous, predominantly mucous, or mixed. The secretory cells of the salivary glands form acini, surrounding a central draining space that empties into the intercalated, striated, and excretory ducts, successively. These ducts play a major role in determining the composition of saliva. Saliva cleanses the mouth, maintains tooth integrity, dilutes noxious materials, contains antibodies and antimicrobials, maintains the pH in the oral cavity, and plays a role in the formation of the bolus of food and initial digestion, depending on the species. The ducts and acini are surrounded by connective tissue carrying blood vessels and nerves.

Gingivitis and Periodontitis

Periodontal disease is commonly seen in dogs and cats characterized by inflammation of the supporting structures of the tooth. Ninety-six percent of 109 adult cats, with a mean age of 6.2 +/– 5.2 years, showed evidence of gingival inflammation in one study. A recent study

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Table 50.1 Nomenclature of oral and oropharyngeal inflammation according to the American Veterinary Dental College (AVDC)

Location	Term	Definition
Gingiva	Gingivitis	Inflammation of gingiva
Periodontal ligament, alveolar bone and cementum	Periodontitis	Inflammation of nongingival periodontal tissues
Bone and bone marrow	Osteomyelitis	Inflammation of the bone and bone marrow
Alveolar mucosa	Alveolar mucositis	Inflammation of alveolar mucosa (i.e., mucosa overlying the alveolar process and extending from the mucogingival junction without obvious demarcation to the vestibular sulcus and to the floor of the mouth)
Sublingual mucosa	Sublingual mucositis	Inflammation of mucosa on the floor of the mouth
Labial/buccal mucosa	Labial/buccal mucositis	Inflammation of the lip/cheek mucosa
Mucosa of the caudal oral cavity	Caudal mucositis	Inflammation of mucosa of the caudal oral cavity, bordered medially by the palatoglossal folds and fauces, dorsally by the hard and soft palate, and rostrally by alveolar and buccal mucosa
Palatal mucosa	Palatitis	Inflammation of mucosa covering the hard and/or soft palate
Lingual mucosa	Glossitis	Inflammation of mucosa of the dorsal, lateral and/or ventral tongue surface
Lip	Cheilitis	Inflammation of the lip (including the mucocutaneous junction area and skin of the lip)
Mouth	Stomatitis	Inflammation of the mucous lining of any of the structures in the mouth; in clinical use the term should be reserved to describe widespread oral inflammation (beyond gingivitis and periodontitis) that may also extend into submucosal tissues (e.g., marked caudal mucositis extending into submucosal tissues may be termed caudal stomatitis)
Palatine tonsil	Tonsillitis	Inflammation of the palatine tonsil
Pharynx	Pharyngitis	Inflammation of the pharynx

looking at the prevalence of disorders recorded in dogs in attending primary care veterinary practices in England revealed periodontal disease to be the second most frequently identified disorder. Gingivitis is inflammation of the gingiva, which may remain stable throughout the life of the animal. However, with the aid of additional factors and in a cyclical fashion, it may progress to periodontitis. Periodontitis is inflammation of the periodontal ligament, cementum and alveolar bone, resulting in pocket formation, gingival recession, and alveolar bone loss (Figure 50.1).

Histologically, the pulp tissue of teeth with advanced periodontitis may undergo changes including acute and chronic pulpitis, vascular congestion, and pulp necrosis. These changes may be the result of occlusion of the vascular channel by secondary or tertiary dentinal deposition, increased mobility of teeth with severe attachment loss, or, less likely, the centripetal spread of infection or inflammation into the pulp.

Up to 13% of cats suffering from periodontal disease may have evidence of aggressive periodontitis. There is also a strong association between periodontal disease and type I tooth resorption. In one study, up to 72% of teeth with type I resorption showed periodontitis, as opposed to approximately 16% of teeth with type II resorption. Tooth resorption has also been reported in dogs but not necessarily in association to periodontitis. It can occur in association to endodontic disease or with oral neoplasia at tumor sites and at sites distant from tumors.

A strong suspicion for a genetic predisposition towards dental disease exists in cats and dogs. Pure-bred cats are said to develop dental calculus more commonly than domestic shorthair cats. Additionally, rapidly progressive and refractory periodontitis has been reported to occur more commonly in young Somali and Abyssinian cats exhibiting stomatitis or feline immunodeficiency virus (FIV) involvement. A condition known as juvenile hyperplastic gingivitis has been described in cats younger than 2 years of age (Figure 50.2).

In dogs, a familial predisposition to gingival hyperplasia has been found in the boxer. Smaller breeds and brachycephalic pets can have crowding of their teeth and malocclusion that can predispose them to periodontal

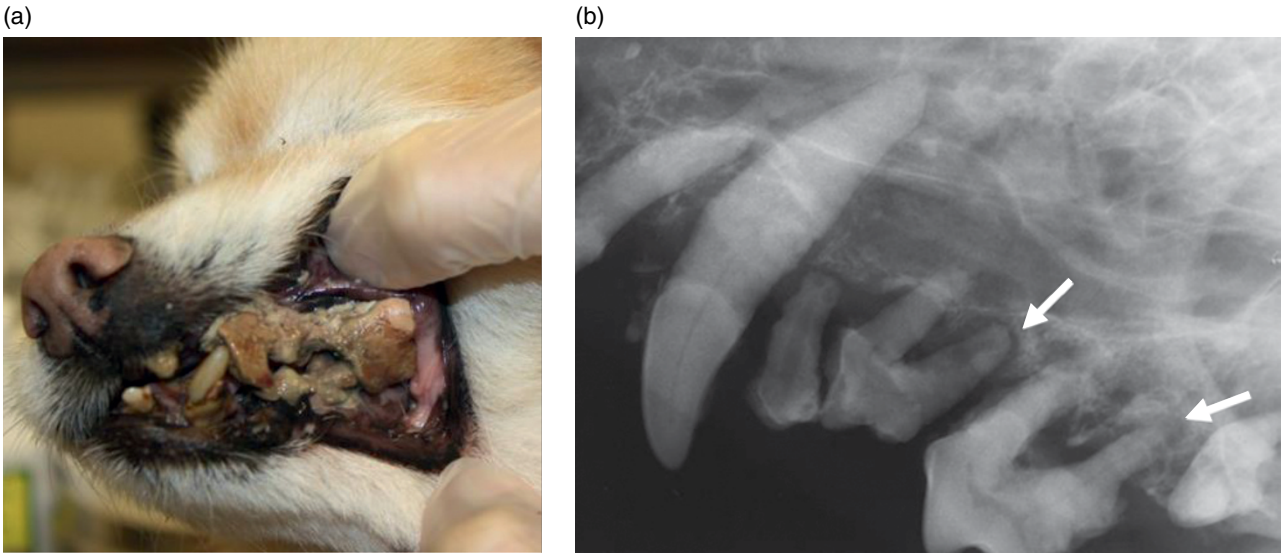


Figure 50.1 (a) Photograph of a 15-year-old Pomeranian, showing severe calculus and plaque accumulation along with multiple missing teeth. (b) Intraoral radiographs of the same patient showing severe alveolar bone loss with extension into the endodontic system as evidenced by the formation of periapical lucencies (*arrows*). Copyright 2015 Alexander M. Reiter.

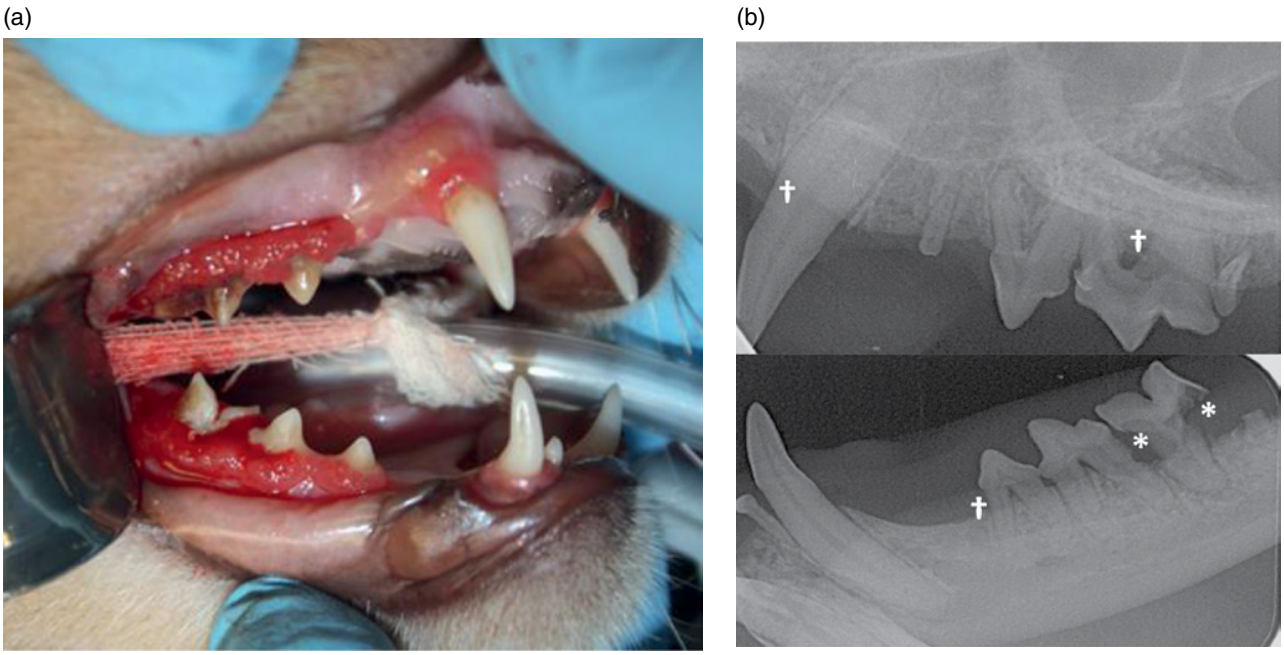


Figure 50.2 (a) Photograph of a 2-year-old Abyssinian, showing severe gingivitis and gingival enlargement along with multiple missing incisors. (b) Intraoral radiographs of the same patient showing moderate alveolar bone loss (†) and type I tooth resorption (*). Copyright 2015 Alexander M. Reiter.

disease. Miniature schnauzers and greyhounds have a propensity to localized juvenile periodontitis and refractory rapidly progressing periodontitis.

In humans, periodontitis has been associated with abnormal phagocytic activity as well as immunosuppressive states. Hypoplasia of root cementum has also been implicated as a cause specifically in human cases of juvenile periodontitis. Single amino acid variations because of mutation in interleukin (IL)-6, IL-10, and lactoferrin genes may result in a change in their functionality which could play a role in the development of disease. However, this has yet to be confirmed in pets.

Periodontal disease treatment has the goal of cleaning and eliminating deep pockets with closed or open

techniques, restoring a normal gingival contour via careful gingivectomy and gingivoplasty, extracting teeth with severe attachment loss, and instituting rigorous home oral hygiene until elimination of potential causes of the disease.

Medical management with antibiotic treatment may occasionally be considered as an adjunct to definitive treatment, in preparation for the procedure or in patients where anesthesia is not an option. Amoxicillin-clavulanic acid (Clavamox®, Pfizer) has the highest *in vitro* susceptibility against all isolates and all anaerobes isolated from the subgingival spaces of cats. Additionally, enrofloxacin (Baytril®, Bayer) shows high *in vitro* susceptibility for the anaerobes isolated in cats. In dogs, amoxicillin-clavulanic acid has the highest *in vitro* susceptibility against all isolates, all aerobes, and all anaerobes. For dogs, enrofloxacin showed the highest *in vitro* susceptibility for gram-negative aerobes. Anaerobic bacteria oral bacteria in dogs appear to be susceptible to amoxicillin-clavulanic acid, doxycycline, and erythromycin, while aerobic bacteria are often also susceptible to sulfa-trimethoprim.

Despite the slight differences in susceptibility, no major differences are found between the subgingival floras of dogs and cats with gingivitis. Evaluation of the effects of systemic doxycycline use in dogs has shown a significant improvement in gingival attachment and bleeding with oral subantimicrobial doses of 2 mg/kg per day. A short-term (42 days) study evaluating the efficacy of control of gingivitis with use of cefovecin sodium (Convenia®, Pfizer) after a professional dental cleaning showed no significant difference when compared to oral administration of clindamycin.

In feline cases where professional dental cleaning and extraction of severely affected teeth do not resolve periodontal inflammation, patients should be tested for feline immunodeficiency virus (FIV)/feline leukemia virus (FeLV) seropositivity. A greater prevalence and increased severity of oral inflammation were noted in cats infected with FIV. The disease was worse in those with co-infection of FIV with feline calicivirus (FCV), or with FCV and FeLV.

When evaluating the systemic effects of periodontal disease in dogs, a strong association has been found between increasing severity of attachment loss with changes in systemic inflammatory variables and renal indices. Additionally, in dogs with advanced periodontal disease, increases in systemic nitric oxide levels two weeks after periodontal treatment have been reported, but the response is idiosyncratic. In cats, the severity of periodontitis has been associated with increases in globulins, alanine aminotransferase, and IgG blood levels, suggesting that periodontal disease is not simply a localized disease but may also affect patients systemically.

Stomatitis

Stomatitis is a complex, chronic, and destructive inflammatory process affecting the epithelium and lamina propria, with frequent extension into the submucosal tissues. This more widespread inflammation of the oral mucosa is estimated to affect 0.7% of cats presented to veterinary practices.

The etiology of stomatitis is not fully understood, but it is suspected to be multifactorial and a response to chronic stimulation by a still unidentified antigen. This contrasts with the contact stomatitis or contact mucosal ulceration that results from mucosal contact with an irritant, allergen or antigen most often in areas of heavy plaque burden. This condition is known as canine chronic ulcerative stomatitis and chronic ulcerative paradental stomatitis. However, the lesions are commonly referred to as "kissing ulcers" or "contact ulcers." Two cases of concurrent osteomyelitis and paradental stomatitis have been reported. Epitheliotropic T cell lymphoma and erythema multiforme have also been reported as causes of an ulcerative stomatitis with minor to no significant abnormalities in complete blood counts and blood biochemical profiles of affected dogs. Whereas cats are likely affected by the idiopathic form of this disease, in dogs the oral inflammation is often associated with a systemic disease. Vesiculobullous autoimmune disease, although sometimes confined to dermal tissues, can present as oral lesions in up to 90% of patients with pemphigus vulgaris and 50% of those with bullous pemphigoid.

A similar type of lesion, called pyogenic granuloma, that is proliferative rather than ulcerative in nature develops in the alveolar or buccal mucosa distobuccal to the mandibular first molar tooth in cats (Figure 50.3). The lesions may result from continued trauma secondary to a tight caudal occlusion between the maxillary fourth premolar and the mandibular first molar, or due to continued trauma from the maxillary fourth premolar on an area of inflammation on the distobuccal aspect of the mandibular first molar. Surgical excision of the mass and blunting or extraction of the involved tooth or teeth have been reported to be 100% effective.

Some of the common bacterial isolates in cats with stomatitis include *Pasteurella pneumotropica*, *Pasteurella multocida*, and *Capnocytophaga canimorsus*. Prior exposure to viral diseases such as FCV, feline herpesvirus (FHV), FeLV, and FIV is thought to be a risk factor for developing stomatitis. This is likely due to the progressive decline in immune functions caused by infection with FIV and FeLV. On the other hand, FCV does seem to play a more direct role as shown by persistent shedding of this virus in all cats with chronic ulceroproliferative stomatitis compared to only about 20% in normal cats.



Figure 50.3 Photograph of a pyogenic granuloma in a 5-year-old domestic shorthair. Copyright 2015 Alexander M. Reiter.

Ulcers on the tongue, philtrum, and palate can be seen in cases of FHV, but they are infrequent compared to FCV infection. Infection with FIV, FeLV, and FCV may also influence disease severity. The role of infection with *Bartonella* remains controversial. Infection with feline panleukopenia virus, feline syncytium-forming virus, feline infectious peritonitis, and *Candida albicans* have also been implicated as causes of stomatitis.

In cats with stomatitis, immunohistochemistry (IHC) has shown that the number of CD79a+ cells, L1+ cells and CD3+ T cells and the level of MHC class II expression tend to correlate with disease severity. Additionally, CD8+ T cells are more numerous than CD4+ T cells, and most of the plasma cells are of the IgG isotype. The number of cells labeled for CD3, CD4, CD8, CD79a, IgG, IgA or L1 and the number of mast cells within the lamina propria and submucosa are significantly increased in affected patients. The epithelial compartment also has more CD3+ T cells compared to healthy cats. Mast cell density is also significantly increased in gingival tissues adjacent to areas affected by stomatitis. IHC has proven value in reaching a definitive diagnosis in dogs with stomatitis due to erythema multiforme and epitheliotrophic T cell lymphoma. Immunohistochemistry, clonality testing, repeated biopsies, and close follow-up are recommended in such difficult cases.

Animals affected by stomatitis will often show signs of oral discomfort when eating, grooming, or when manipulating their mouths. In addition to the often symmetric, bright, ulcerated or proliferative lesions of the area lateral to the palatoglossal folds, multiple areas can be affected by inflammation including the gingiva, alveolar mucosa, labial and buccal mucosa, the lateral margins of the tongue and the areas of the hard palate that are in contact with the teeth (Figure 50.4).

Physical examination findings may include a poor hair coat and decreased body condition. Of cats with stomatitis, 49–61% show radiographic evidence of resorption of multiple teeth. Periodontal disease is seen in all cases, and retained tooth roots can be found in 56% of cases. Differentiation into squamous cell carcinoma has been reported in some cats.

Acutely, treatment for cats consists of controlling the inflammation via immunosuppression or immune modulation along with symptomatic control. In dogs, treatment of the underlying cause is extremely important. Glucocorticoids such as prednisone or prednisolone are typically used at a dose of 0.5–1 mg/kg by mouth once daily and can be effective in 73–86% of cases. Antibiotics may also be used. However, only 30% of cases respond, and the response is only transient. Amoxicillin-clavulanic acid (13.75 mg/kg q12h, PO) or clindamycin (5–11 mg/kg q12h, PO) are most commonly used. Nutritional support is sometimes necessary, especially in chronic cases with severe weight loss and evidence of dehydration. Otherwise, the patient should only be offered soft food. If symptoms resolve or the patient improves significantly, plaque control measures, namely daily tooth brushing, should be instituted. However, many pets are too painful to allow this. Pain control with sublingual buprenorphine (0.01 mg/kg q8–12h, PO) or a transdermal fentanyl patch should also be considered.

Chronically, treatment with glucocorticoids is not recommended due to the undesirable long-term side-effects that may develop, including diabetes mellitus, polyuria, and polydipsia. Full-mouth extraction is recommended in cats which has achieved a nearly 80% success rate with either a complete cure in 60% of cases or a clinical cure in 20% of cases. In severe cases, transient treatment with glucocorticoids (0.5–1 mg/kg q24h, PO) immediately after full-mouth extraction may be necessary. A recent study comparing full-mouth versus partial-mouth extraction in cats showed the extent of extractions not to be associated with the overall response of treatment. Additionally, the 68.8% of symptomatically or clinically cured cats required extended medical management for a finite period to achieve a positive outcome. In dogs, a staged approach by removing severely diseased teeth is recommended, and extraction of teeth directly in contact with the areas of inflammation can be considered. A professional dental cleaning should also be performed until the underlying disease process is controlled.

When cases are refractory, treatment with interferon omega may be considered. Daily use of this medication (0.1 mU q24h, PO) in cats has resulted in significant improvement of pain scores at 60 and 90 days post

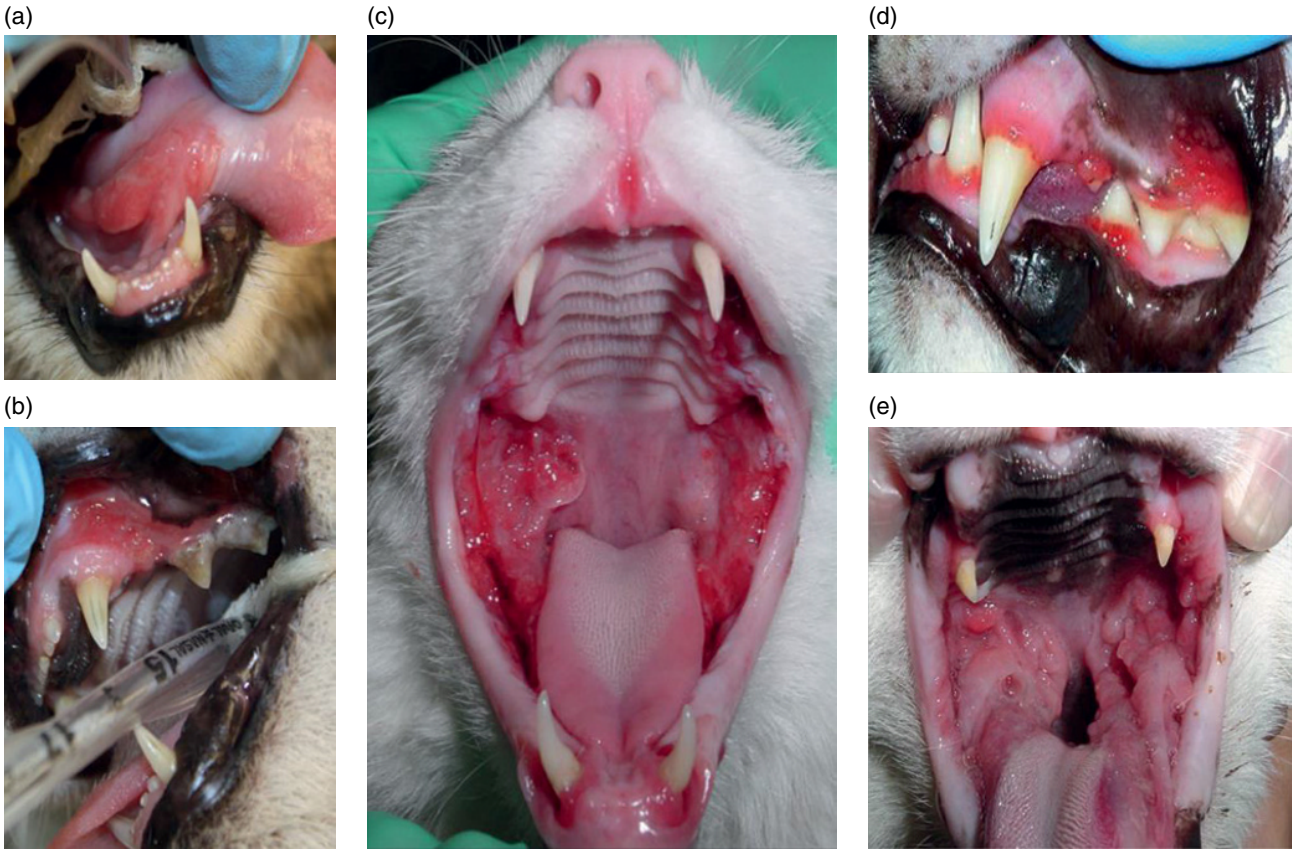


Figure 50.4 Photographs of multiple patients showing varying presentations of feline stomatitis. (a) Sublingual. (b) Diffuse alveolar. (c) Ulcerative, caudal and lateral to the palatoglossal folds. (d) Focal alveolar. (e) Proliferative, caudal and involving the palatoglossal folds. Note that the hard and soft palate are usually not involved in this classic type of stomatitis. Copyright 2015 Alexander M. Reiter.

treatment. Intralesional injections with interferon omega can be considered prior to oral administration. Finally, ablation of inflamed tissues in cats using CO_2 laser has been reported to promote fibrosis after repeated treatments in a refractory case. When treating with interferon omega or CO_2 laser, the owners need to understand that repeated treatments are often necessary before even slight improvements are seen.

Autologous mesenchymal stem cell therapy has also been used for treatment of refractory stomatitis, with success being seen in five out of seven cats that completed the study. Cats that responded to treatment also exhibited systemic immunomodulation demonstrated by decreased numbers of circulating CD8+ T cells, a normalization of the CD4:CD8 ratio, decreased neutrophil counts, and interferon gamma and IL-1-beta concentration, and a temporary increase in serum IL-6 and tumor necrosis factor-alpha concentration.

Stomatitis can be a frustrating condition for the pet, the owner, and the veterinarian. Retroviral status should be assessed prior to therapy, as this may affect prognosis. In dogs, prognosis is largely dependent on the underlying systemic disease process.

Odontogenic Tumors and Cysts

Odontogenic tumors are more common in dogs than cats. Acanthomatous ameloblastomas are more commonly seen, followed closely by peripheral odontogenic fibromas and focal fibrous hyperplasia. Acanthomatous ameloblastoma commonly arises in the rostral lower jaw whereas peripheral odontogenic fibromas and focal fibrous hyperplasia tend to be more commonly seen in the rostral upper jaw. A breed predisposition for development of acanthomatous ameloblastoma has been suggested, with golden retrievers, Akitas, Shetland sheepdogs, and cocker spaniels being more commonly reported. Peripheral odontogenic fibromas may also have a predilection for castrated male dogs.

Azithromycin in systemic and toothpaste forms has been used in the management of gingival hyperplasia secondary to ciclosporin treatment in dogs. In this report, there was a significant decrease in gingival sulcus depth for the capsule group at week 8 and for the toothpaste group at weeks 2, 4, and 8. Gastrointestinal adverse events occurred in all groups, but more frequently in the patients treated systemically. Gingival recontouring to

reduce the pseudopockets created by hyperplastic gingiva along with periodontal treatment can also be recommended.

Extent of resection required to prevent tumor recurrence depends on the tumor type. A study describing the clinical behavior of acanthomatous ameloblastoma revealed 0% of patients had incomplete histopathologic margins when 2 cm intended surgical margins were utilized compared to 33% when 1 cm intended surgical margins were utilized. However, it was found that regardless of postsurgical neoplasia-free margin, no gross local recurrence was noted in the oral cavity for a minimum follow-up of 12 months after surgery.

Odontogenic cysts are also commonly seen, with more than half arising from unerupted teeth, mainly the mandibular first premolar teeth. This type of cyst is known as a dentigerous (or tooth-containing) cyst, and brachycephalic dogs appear to have a predisposition to development of these lesions. Dentigerous cysts are thought to arise from the proliferation of basal cells in the lining epithelium or the epithelium of the tooth crown but may also arise from cell rests of Malassez. If the tooth fails to erupt, the follicle remains and produces the sac lined by stratified mucus or cutaneous epithelium. Cysts can be very expansile, causing weakening of the bone involved and root resorption of neighboring teeth. A potential for pathologic fractures and tooth loss arises if these cysts are not treated. Even though radiographic findings are virtually pathognomonic, biopsy is always recommended to confirm the clinical diagnosis and rule out any malignancies that have been reported to arise in long-standing cases. In a survey of epithelial odontogenic tumors and cysts in dogs and cats, six cystic lesions gave rise to basisquamous cell carcinoma. This is thought to be associated with the deregulation of cell death in the lining epithelium derived from odontogenic origin as shown by immunoreaction for amelogenin and ssDNA.

Four other types of cysts have been described including the lateral periodontal, radicular, gingival inclusion, and odontogenic keratocyst. Thorough removal of the cyst lining, extraction of the unerupted tooth, and extraction of teeth affected by cyst expansion should be performed. In cases of extensive lesions and those in which complete removal of the cyst lining is challenging, sclerotherapy with tetracyclines can be considered.

Malignant Melanoma

Melanoma is the most common malignant neoplasia in the canine oral cavity. In a retrospective study of 338 canine oral melanomas, chow chows, golden retrievers, and Pekingese/poodle mixes were overrepresented, and the gingiva and labial mucosa were the most commonly affected sites. Melanomas can be amelanotic in some cases, posing a diagnostic challenge. However, Melan A is a specific and sensitive marker for canine melanoma. Dogs with melanomas of the labial mucosa may have an increased survival time (310 days) compared to those with oral melanomas at other sites (123 days). This difference was, however, not statistically significant. In this same study, postsurgical survival time was 173 days. Survival was significantly associated with the presence of KIT anywhere in the section of a melanoma. This also becomes important when considering the use of c-kit inhibitors such as toceranib phosphate (Palladia®, Pfizer Animal Health) in the treatment of oral melanomas. When evaluating the effects of multimodal therapy with adjuvant treatment with carboplatin, the median overall survival for all dogs was 440 days. In a study evaluating the use of radiation therapy with an alternate-day schedule of 4 Gy/fraction for a total of 48 Gy over four weeks, 8% of dogs had acute reactions, and 7.6% of dogs showed chronic effects including osteonecrosis and the development of fistulae. Local efficacy was determined by tumor size, and systemic metastasis influenced long-term survival in patients with tumor recurrence.

Antiangiogenic therapies have also been evaluated after the discovery of higher vascular endothelial growth factor (VEGF) levels in the plasma and serum of dogs with malignant melanomas than in a control population. In a study describing the effect of radiation on the expression of VEGF and VEGF receptor in the canine melanoma cell line TLM 1, radiation induced significantly higher VEGF production in the 8 and 10 Gy group, which may have contributed to tumor resistance. The enhanced secretion of VEGF may increase survival by decreasing apoptosis, stimulating proliferation, and increasing angiogenic potential.

When evaluating the efficacy of a xenogenic vaccine targeting tyrosinase as an adjuvant treatment, results have been contradictory. One study found no difference between progression-free survival, disease-free interval or median survival time in dogs that received this treatment. A study evaluating the safety of administration of this vaccine in cats revealed side-effects of grade 1–2 in 11.4% of cats, suggesting a minimal risk of adverse effects.

Oral melanoma is highly metastatic and recurrent, with age, size, site, and stage being reliable prognostic indicators. A subset of well-differentiated melanocytic neoplasms in dogs has been described, and these tumors have shown a mean survival of 23.4 months and a median survival of 34 months after local excision without adjuvant therapy.

Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is the most common oral tumor in domestic cats and the second most

common oral tumor in dogs. This tumor can vary in appearance and may present as an ulcerated area or a mass. In cats, sometimes the ulcerated area appreciated on oral examination may represent the "tip of the iceberg" (Figure 50.5).

Although historically, the sublingual/lingual region has been reported to be the most commonly affected site, recent reports show the gingiva on the mandible and maxilla to be most often involved. Metastasis to mandibular lymph nodes in these cases, as evaluated by fine needle aspiration cytology, has been documented to be as high as 31–36%. A significant association between mandibular lymph node metastasis and survival time has not been found. Evidence of pulmonary metastasis, which had been evaluated by three-view thoracic radiography or necropsy, was present in 10% of cases but was not a significant negative prognostic factor. Interestingly, tumor volume appeared not to be a predictor for regional and distant metastasis, as no significant association was seen between tumor size and metastasis.

Feline oral SCC is generally considered to carry a poor prognosis, and outcome has been largely dependent on the degree of primary tumor invasion at diagnosis. Most cats with oral SCC succumb to the effects of progressive local disease and treatment failure. The prognostic impact of completeness of surgical margins is unclear, and studies evaluating multimodal treatment have shown improved survival times compared to monotherapy. A study evaluating multimodal therapy for nonresectable tumors found survival times with complete remission of up to 759 days. Twenty-one cats treated with 10, once-daily fractions of 4.8-Gy showed a median overall survival of 174 days.

Squamous cell carcinoma in dogs commonly arises in dentate areas, although well-differentiated tumors have been reported to arise more commonly in edentulous areas and the tongue. A retrospective study evaluating 84 dogs with a diagnosis of oral and oropharyngeal SCC reported different subtypes, including conventional (well differentiated, moderately differentiated, and poorly differentiated), papillary, basaloid, adenosquamous, and spindle cell carcinoma. Neutered female dogs, dogs aged 10–15 years, English springer spaniels and Shetland sheepdogs were overrepresented in this retrospective study.

Papillary SCC is the term used for a well-differentiated variant of this tumor that grossly as well as microscopically shows papillae or fronds on the surface. Papillary SCC appears to carry the best prognosis. Thought to be a tumor of young dogs, papillary SCC has recently been shown to be a tumor of adult dogs as well, with a retrospective study revealing that more than 75% of the affected canine population was older than 6 years of age. In this study, two distinct histologic presentations were described that correlated with the appearance on imaging studies: the cavitating and noncavitating patterns.

Predominance of large breeds and the rostral maxilla as the most common location in dogs with papillary SCC have also been reported. In this study, surgical excision with 1–2 cm margins allowed for a mean tumor-free interval of 12.1 months. Neither study found regional or distant metastasis. A hemangiosarcoma-like mass composed of numerous vascular clefts and variable numbers of keratinizing epithelial cells was described in a case report of an 8-year-old female mixed breed with a caudal maxillary mass. The mass was characterized as a pseudoangiomatous SCC, a well-recognized human variant of acanthomatous SCC that shares histopathologic similarities with canine gingival hemangiosarcoma. A study evaluating risk factors for nontonsillar SCC in dogs showed that surgical treatment can decrease the risk of death for these patients by 91.4%. Perineural, lymphatic and vascular invasion, as well as peritumoral inflammation, may play a role as a prognostic indicator when looked at together as a combined score. In a study evaluating the effects of combining cisplatin with piroxicam in dogs with oral melanoma and SCC, about 50% of dogs

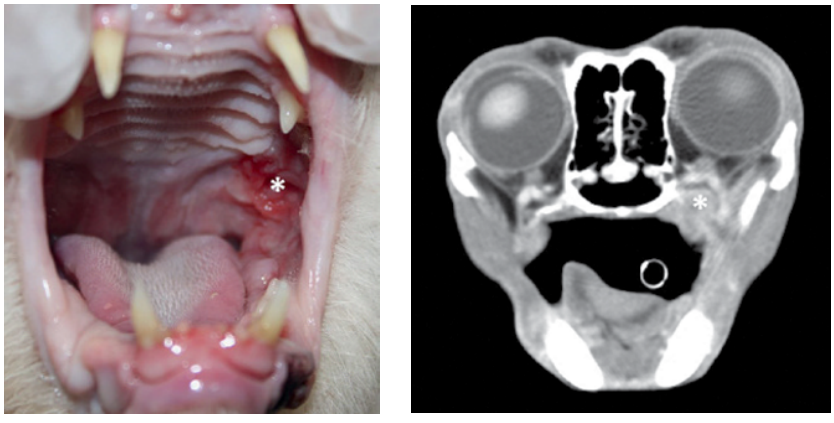


Figure 50.5 Photograph (a) and transverse computed tomographic image in soft tissue algorithm obtained after IV administration of contrast medium (b) of a 12-year-old Persian with squamous cell carcinoma (*white asterisks*) of the left caudal upper jaw. Note orbital invasion of the tumor. Copyright 2015 Alexander M. Reiter.

with SCC responded to treatment versus 18% of patients with oral melanoma. The most commonly reported side-effect for this combination of treatment was renal toxicosis, so close monitoring of renal values is recommended.

A protocol of accelerated chemoradiotherapy using 14 fractions of 3.5 Gy over nine days, combined with carboplatin as a radiosensitizer (total dose 180 mg/m^2 in feline and 300 mg/m^2 in canine cases) resulted in a complete tumor response in most cases (4/5 feline and 3/3 canine) with acceptable acute and long-term side-effects. Overall response rate in both dogs and cats treated with bleomycin enhanced with electroporation (ECT) was 89%, with 21 showing a complete response (CR) and two a partial response (PR) whereas controls had a response rate of 33% (4 CR and 3 PR). Median time to progression in the ECT group was 30.5 months, whereas in controls (bleomycin alone) it was 3.9 months (P <0.0001). Median time to progression for ECT cohorts was 24.2 months for the periocular cohort and 20.6 in the advanced head SCC cohort, respectively.

Eosinophilic Granuloma

Eosinophilic granuloma is a disease that results from underlying antigenic stimulation. The eosinophil is one of the players in type I inflammatory reactions. The most commonly identified underlying causes in cats include ectoparasites and other insects, environmental allergens (i.e., atopic dermatitis), and food hypersensitivity. Eosinophilic granulomas are exfoliative, and thus diagnosis can be reached through fine needle aspiration or impression smears. However, histopathologic examination is useful to rule out other differential diagnoses such as neoplasia or infection. Distinctive histopathologic features of eosinophilic granuloma are small foci of collagen degeneration in which degenerated collagen fibers are surrounded by degranulated eosinophils, resulting in flame figures. Clinically, these lesions are characterized by a proliferative or ulcerative component with yellow pinpoint areas consistent with sulfur granules. Granulomatous nodules can be seen in the tongue, palate and/or glossopharyngeal arches (Figure 50.6).

Indolent ulcers, also known as rodent ulcers, another presentation for this type of inflammatory process, are commonly seen near the midline of the (usually) upper lip but can also be seen on the lower lip. A puffy lip or a diffuse, firm sublingual swelling are rare manifestations of this disease. Some cats are asymptomatic, and in some the disease may be self-limiting.

Ulcerative eosinophilic palatitis has been described in Cavalier King Charles spaniels. Some can have full or near resolution of lesions with glucocorticoid therapy whereas others may resolve spontaneously. Eosinophilic granuloma has also been reported in the Siberian husky in which a hereditary cause has been proposed. Treatment involves removing the underlying cause by recommending flea prevention, a hypoallergenic diet, and switching to stainless steel bowls. Additionally, immunosuppressive therapy with prednisone or prednisolone at 0.5–1 mg/kg q24h PO may be necessary. Recently, a study evaluating the efficacy of treatment with amoxicillin-clavulanic acid in cats for 21 days showed a 42.6% reduction in mean lesion size for lip ulcers and a 96.2% reduction in skin plaques. If the area shows evidence of chewing trauma or exposure to foreign objects, debulking may be considered as well as intralesional glucocorticoid injections (e.g., triamcinolone). Treatment with palmitoylethanolamide (PLR120), a downregulator of mast cell degranulation, showed clinical improvement in 67% of affected cats. For cats with severe ulcerative cutaneous or oral lesions that are unresponsive to glucocorticoid treatment, FHV-1

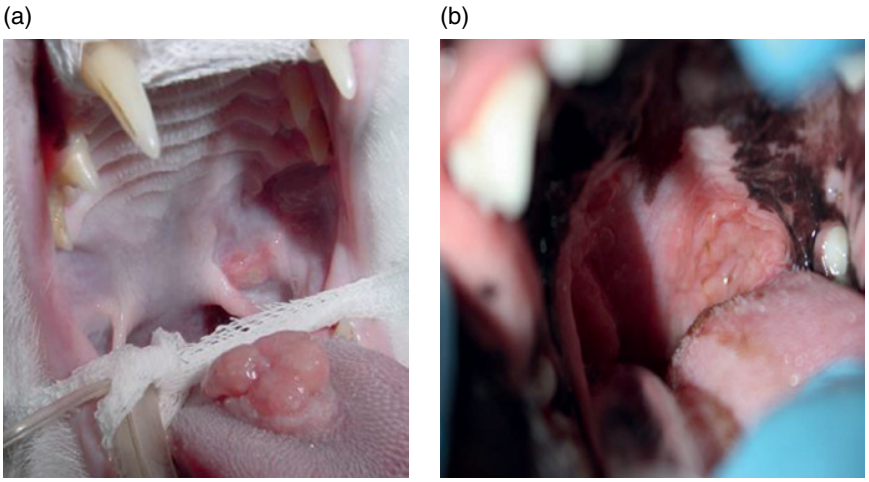


Figure 50.6 Photographs of eosinophilic granuloma involving the dorsal tongue surface and left caudal oral cavity in a 9-year-old domestic shorthair (a) and eosinophilic palatitis in a 3-year-old Cavalier King Charles Spaniel (b). Copyright 2015 Alexander M. Reiter.

infection should be considered, and the diagnosis can be achieved via immunohistochemistry or polymerase chain reaction. Eosinophilic vasculitis, which is a rare disease seen in dogs and cats in association with arthropod and insect-induced lesions and occasionally in mast cell tumors, can also be present along with cutaneous eosinophilic granulomas and plaques in the absence of cutaneous vasculitis.

Foreign Body

A retrospective study evaluating gastrointestinal foreign bodies in dogs and cats showed that 63% of linear foreign bodies originated from the base of the tongue in cats as opposed to 3% in dogs. English bull terriers and springer spaniels were overrepresented in this study. The most common types of foreign object recovered from cats were string, rope, or fishing lines. Burdock and fox tails can also become entrapped in the oral mucosa, and in dogs they have been reported to elicit a type of granular stomatitis. These oral lesions most often occur on the tip and lateral edges of the tongue and the rostral portions of the gingiva, usually at the mucogingival junction and the labial mucosa of the upper lip. Occasionally, the philtrum is involved. Initially, they appear as small papules that can then coalesce, and eventually a necrotic center may develop. Removal of the foreign body along with thorough debridement and flushing of the wound is the treatment of choice. Oral antibiotics and soft food may also be considered.

Oropharyngeal and esophageal stick penetration injuries in dogs can pose a challenge, as studies have shown that foreign bodies can be found in only about half or less of the affected patients. Surgical exploration, local debridement, and thorough lavage, however, have shown a favorable outcome in both studies. Esophageal penetration injuries carry the worst prognosis, and thus a ventral medial surgical approach has been recommended in cases where cervical emphysema is seen radiographically. Advanced diagnostic imaging with magnetic resonance imaging and/or computed tomography may improve the rate of recovery of patients with such foreign bodies.

Immune-Mediated and Autoimmune Diseases

Failure of desmosomal adhesion can result from genetic, autoimmune, or infectious causes. Pemphigus represents the most common autoimmune blistering dermatosis in domestic animals. Pemphigus vulgaris (PV) is a deep, acantholytic dermatosis. It is rare in cats, with an estimated incidence of one per 10 000 veterinary dermatology cases per year. It is more commonly seen in mature cats. This condition is also rare in dogs, with no age predisposition but a predilection for certain breeds such as German shepherds and collies, and a predisposition for males. PV can have mucosal and mucocutaneous manifestations. In most dogs, lesions first develop in the oral cavity or mucocutaneous junctions. Lesions on haired skin predominate over pressure points. Presentation can be acute or chronic, and the direct Nikolsky sign is usually positive. Lesions can present as erythemas, erosions, ulcerations, scales, and crusts. Light microscopy shows suprabasal acantholysis and cleft formation. Erosive lesions are preferentially located in the oral cavity and mucocutaneous junctions. Oral involvement may also include gingivitis, stomatitis, or glossitis. Most patients with PV show signs of systemic disease such as anorexia, lethargy, weight loss, and fever. Spontaneous resolution of cases has been reported. However, 40% of dogs were reported to have a fatal outcome due to either their local disease or systemic manifestations.

Of the autoimmune subepidermal blistering dermatoses, 80% of patients with bullous pemphigoid develop oral lesions at the initial onset of disease or later during its course. Bullous pemphigoid represents 50% of subepidermal autoimmune blistering dermatoses in cats and 26% in dogs. As opposed to PV, this disease can afflict animals of any age, even before puberty. Lesions consist primarily of turgid vesicles, erosions, ulcers, and crusts. Oral lesions can be seen in 60% of dogs, but in cats few lesions are present. In cats as well as in horses, subepithelial vesicles exhibit fewer inflammatory cells, and special stains are needed to visualize degranulating eosinophils. Long-term remission of bullous pemphigoid has been seen in one cat treated with corticosteroids.

Mucous membrane pemphigoid, although uncommon, has been reported in at least two cats, and the authors have witnessed one additional case. Laminin 5 and 6, collagen XVII, and integrin alpha-6/beta-4 have been implicated as autoantigens in both humans and dogs. However, only laminin-5 has been recognized in the feline homologue of this disease.

Canine systemic lupus erythematosus (SLE) occurs mainly in pure-breds including spaniels, pointers, retrievers, German shepherd dogs, and Doberman pinschers ranging from 2 to 6 years of age. SLE has been reported in at least two cats with palatine and glossal ulceration. Behavioral changes, nonerosive polyarthritis, fever, lymphadenomegaly, weight loss, and leukopenia are primarily seen with this condition, and dogs tend to have one or two systemic signs. The oral ulceration is likely a complication of the systemic vasculitis that occurs.

Erythema multiforme (Figure 50.7) accounts for 0.11% of dermatology cases seen in the feline population at an academic institution. In this report, only 38% of dogs showed oral lesions, and no oral lesions were reported in the only cat described. In a case report of erythema multiforme in a cat, lesions first developed on the face and head, but there were no visible lesions in the oral cavity. This patient did not respond to withdrawal of current medications, but a significant improvement was noted approximately one week after treatment with human immunoglobulin. Toxic epidermal necrolysis and idiopathic vasculitis have also been reported to occur in a small number of cats and dogs.

The diagnosis of these disorders is based on both morphologic and immunologic criteria. Proper site selection, biopsy technique, and sample handling are extremely important to reach a definitive diagnosis. Biopsy of the leading edge of a lesion when an intact blister is not found may be sufficient. Preserving the samples in Michel's solution is also preferred by some pathologists. This is a transport medium that preserves tissue antigenicity at ambient temperatures.

Treatment for these conditions should be considered life-long, and owner commitment for periodic monitoring is imperative. Animals must be routinely monitored with complete blood counts and serum chemistry panels. Although glucocorticoids have been reported to be successful in treating most of these conditions, some cases require other forms of immunosuppressive or immune-modulating therapy. Some immune-mediated skin diseases have also been treated with tetracycline, niacinamide and pentoxifylline which together can have

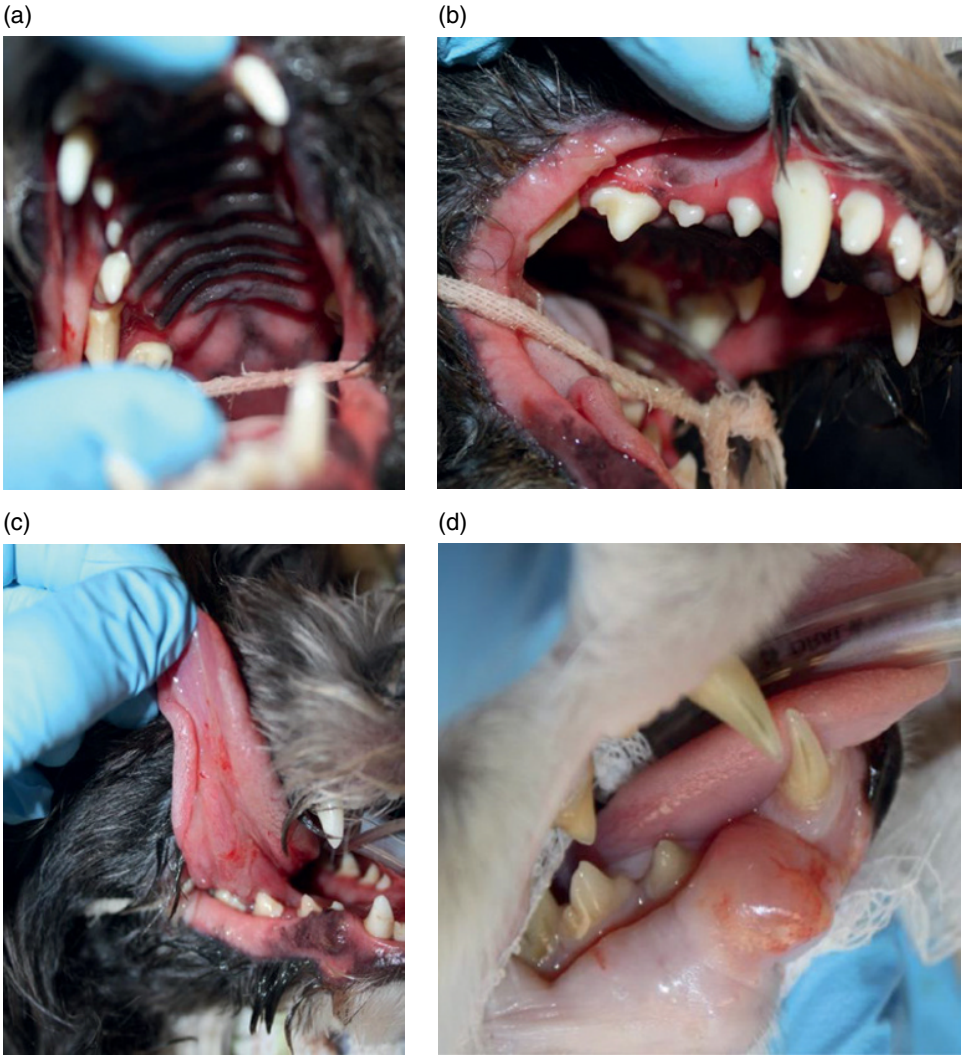


Figure 50.7 Photographs of a 6-month-old mixed breed with erythema multiforme manifesting on the hard palate (a), gingiva and lips (b), as well as the sublingual area (c). Photograph of a 9-year-old domestic shorthair with mucous membrane pemphigoid on the right lateral lip frenulum (d). Copyright 2015 Alexander M. Reiter.

immune-modulating and antiinflammatory effects. Antibiotics should be prescribed in cases with a secondary infection. Symptomatic treatment is required acutely, including nutritional support and pain control until long-term therapy takes effect. Idiopathic vasculitis can also cause oral ulcerations.

Metabolic Disease

Nutritional deficiencies, although uncommon, can have oral manifestations. In the acute setting, tacky mucus membranes can indicate dehydration or hypovolemia, and pale mucus membranes can indicate shock or anemia. Oral manifestations of metabolic disease may resurface with the recent increase of owners opting to feed their pets home-cooked diets. Protein deficits can cause ulceration of the dorsal surface of the tongue. Severe niacin deficiency can cause hyperemia and ulceration of mucosal surfaces, especially the tongue. Severe biotin deficiency causes salivation and scaling of the lips. Hypervitaminosis A can lead to gingival enlargement and delayed development and early exfoliation of incisor teeth. Primary or secondary hyperparathyroidism can lead to a condition known as "rubber jaw" which is characterized by a diffuse decreased radiographic density in the bones, primarily of the lower jaw.

Acute uremia is defined as a rapid decline in renal function leading to retention of uremic wastes. The incidence of acute uremia in animals is unknown, but in humans it accounts for 1% of hospital admissions. Uremic halitosis and oral ulcerations are common findings on physical examination of severely affected patients. This occurs especially at the labial and buccal mucosa, lateral margins of the tongue, sublingual mucosa, lateral lip frenula, and lip commissures. Uremic vasculitis and thrombosis lead to necrosis and sloughing of the mucosa. Hypothyroidism can also lead to vasculitis and petechiation on the gingiva and tongue. Halitosis is often a feature of this syndrome, as the lesions become secondarily infected. In severe cases, there may be extensive necrosis that leads to sloughing of the tip of the tongue. The lesions are often very painful and contribute to the anorexia often observed in animals with kidney disease. Any condition that can produce a hypercoagulable state may lead to thrombi formation and subsequent sloughing of the affected areas.

Treatment for these conditions is symptomatic until the inciting cause can be removed or resolved. Symptomatic treatment includes pain management (buprenorphine 0.01 mg/kg q8–12h, IV), bypassing the mouth with supplemental enteral or parenteral nutrition, and use of gastric protectants (sucralfate 0.5–1 g q4–6h, PO). Topical mouthwashes such as a mixture of diphenhydramine, sucralfate or aluminum and magnesium hydroxide (Maalox®, Novartis), and lidocaine may provide some local pain control. Dilute (0.12%) chlorhexidine rinses also play a role in preventing secondary infection of the necrotic areas. Other metabolic disease such as diabetes mellitus, liver failure, and respiratory disease as well as immunosuppressive medications have also been reported to lead to oral ulceration and necrosis.

Burns

Burns can be caused by electricity, chemicals, heat, friction or radiation (Figure 50.8).

Chewing on household power cords is the most common cause of electric burns in dogs and cats, and these are likely low-voltage injuries. The electrical current can cause damage through its direct effect as well as via transformation of electric energy into heat. The pet should be evaluated for cardiac arrhythmias and neurogenic pulmonary edema prior to evaluating the oral cavity under sedation or anesthesia. Edema and necrosis are typically seen in the tongue, palate, and lip commissures. Discoloration of adjacent teeth secondary to pulpitis can also be seen. Some of the long-term effects of electric burns include development of an oronasal fistula and sloughing of necrotic portions of the tongue. Patients should be treated symptomatically for at least 7–10 days or until the tissues fully claim themselves. Until definitive surgery can be performed, antibiotics and pain medication should be instituted. Nutritional supplementation should be considered when patients refuse to eat soft food. Definitive therapy consists of debridement of the lesions unless these are superficial enough to heal by contraction and reepithelialization.

Chemical burns can result from exposure to household cleaning products, phenolic compounds, essential oils, heavy metal (thallium) or plant toxins (i.e., *Diffenbachia*). The rostral and dorsal aspects of the tongue and the palate are usually affected. The poison control center should be contacted in these cases for treatment of any ingested substances. Similar to electric cord injuries, treatment should be symptomatic, but debridement is less often necessary. Patients should be evaluated for esophagitis and gastritis and treated accordingly. The hair of affected patients should be clipped or washed with dish detergent if grooming caused the chemical to contact oral mucosa. Thermal injuries can be encountered in animals that are fed home-prepared diets or heated milk. Injuries are like those seen with chemical burns, with the lips and nasal plane also being affected. With both chemical and electric burn injuries, symptomatic treatment and client education are necessary.

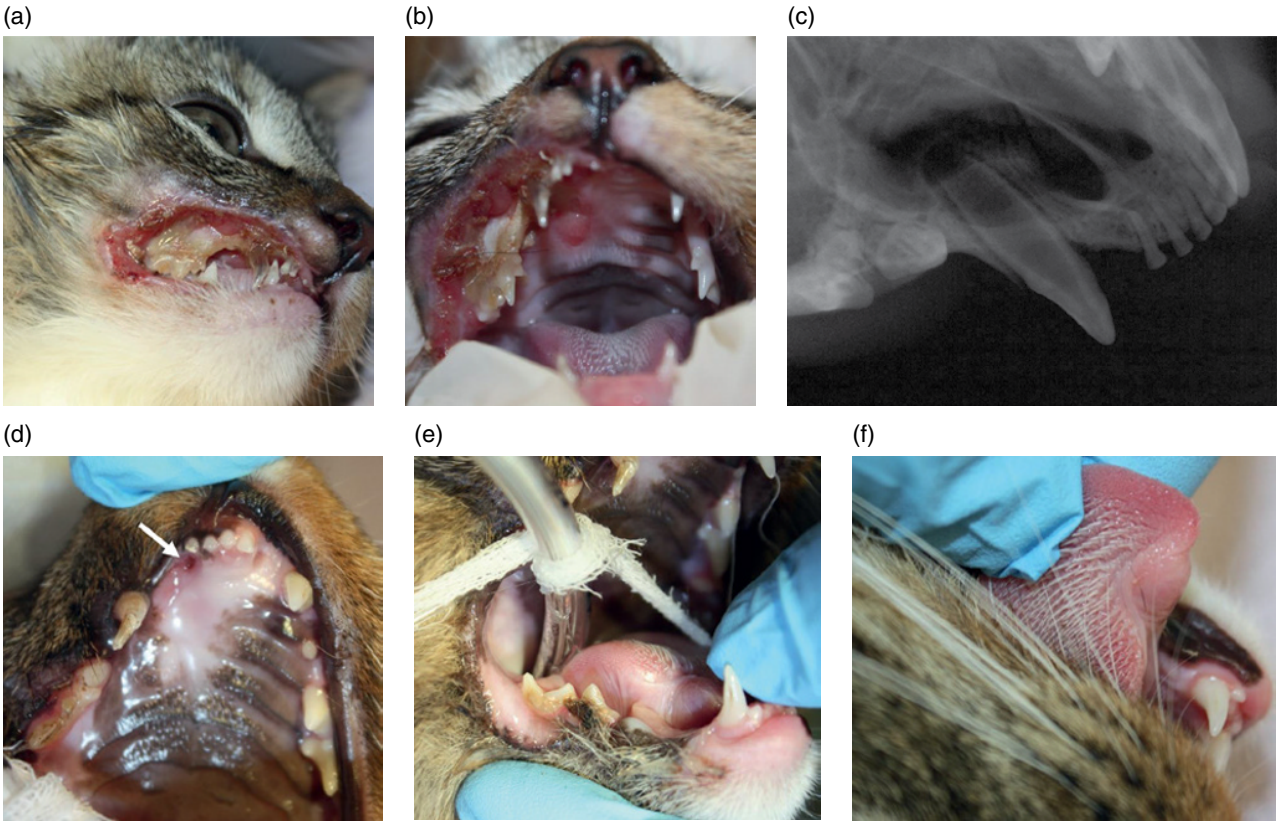


Figure 50.8 Photographs of a 1-month-old domestic shorthair with electric burns and extensive tissue necrosis at the lips, cheeks, and hard palate (a,b). Intraoral dental radiograph of the same patient one year post injury showing the resultant oronasal fistula (c). Photographs of the same patient one year post injury showing scarring of the palate with a small, right-sided, persistent oronasal fistula (*arrow*) (d); scarring of the cheeks along with developmental enamel and dentin defects of multiple teeth (e); and scarring of the tongue (f). Copyright 2015 Alexander M. Reiter.

Salivary Gland Disease

The prevalence of salivary gland disease in dogs and cats in a retrospective study was 0.3% , with dogs accounting for two-thirds of the population studied. Salivary gland neoplasia accounted for 30% of the cases seen, followed by, in order of decreasing frequency, sialadenitis (26%), degenerative or fibrotic lesions (11%), sialoceles (9%), and infarction (8%).

Salivary gland neoplasia appears to have different behaviors in the dog and cat. Cats tend to have more advanced disease at the time of diagnosis. A possible familial predisposition in Siamese cats has also been reported. Despite this, survival times in dogs and cats appear to be similar, at 500–550 days. Masses are usually detected by owners, although halitosis, dysphagia, and exophthalmia have been reported. Adenocarcinoma is the most common histologic type of tumor seen. A sialolipoma of a minor salivary gland and lymphosarcoma of major salivary glands have also been reported.

Sialadenosis typically is a bilateral and painless enlargement of the salivary glands. Although the exact cause of this disease is unknown, concurrent gastrointestinal disease, certain medications, hormonal disorders or primary disorders affecting the sympathetic innervation to the glands have been implicated. Retching and gulping are the most common clinical signs seen with this condition. Differential diagnoses for this disease include inflammatory variants including necrotizing sialometaplasia, granulomatous giant cell sialadenosis, and spirocercosis. Both sialadenosis and necrotizing sialometaplasia have shown response to treatment with phenobarbital at an anticonvulsant dose (starting at 2 mg/kg, PO BID). Cases of spirocercosis also respond to phenobarbital treatment, but this is in addition to macrocyclic lactones used to eliminate the microorganism. Granulomatous disease has responded to treatment with glucocorticoids at an anti-inflammatory dose. Necrotizing sialometaplasia has been reported in a few cats. In contrast to dogs, excision of the affected salivary glands in cats provided resolution of signs with no recurrence reported.

Salivary mucoceles, also known as sialoceles, are swellings created by the extravasation of saliva from the ducts or salivary glands themselves. Extravasation of saliva can not only cause a localized swelling, but also the inflammation that results can lead to signs of discomfort. Although trauma, foreign bodies, sialoliths, aberrant parasite migration, and neoplasia have been reported to lead to sialocele formation, sometimes the exact cause for these swellings cannot be determined. With these differentials in mind, advanced diagnostic imaging such as CT or ultrasound should be considered for evaluation. A difference in the imaging characteristics of these lesions can be found when comparing acute with chronic cases, and dystrophic mineralization can occur in very long-standing cases. In dogs, sialoceles arise more commonly in the cervical and sublingual regions. However, the sublingual area seems to be more commonly affected in cats. Sialoceles in the cervical, sublingual, and pharyngeal regions can all lead to difficulty swallowing and breathing. Surgical removal of the glands involved is the treatment of choice, and different approaches have been described for the resection of mandibular/sublingual and zygomatic glands to increase exposure and also decrease the morbidity that can be associated with these surgeries.

Conclusion

Examination of the oral tissues and dental structures is an essential component of physical examination. Dental and oral disease is very commonly seen in our pets. The systemic health of the patient should be thoroughly assessed before attributing a presenting complaint of anorexia to dental and oral disease alone. The anamnesis will also prove to be helpful in guiding your treatment approach when dealing with patients with concurrent conditions. Staging treatment and triaging are at times favorable for these patients to prevent very prolonged anesthetic episodes that may endanger the health of our compromised patients.

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51

Gastritis and Gastric Ulceration in Dogs and Cats

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Normal Gastric Mucosal Barrier Function

The gastric mucosal barrier is provided by the luminal production and secretion of protective factors, an intact epithelial lining, and a rich mucosal blood supply. Mucosal secretions including bicarbonate, mucus, immunoglobulins, and anti-bacterial substances promote the integrity of the mucosa and protect the underlying epithelium from noxious insults. Potential insults to the gastric mucosa include diffusion of luminal acid and pepsin, fluctuations in temperature and osmolality, and translocation of ingested bacteria. The gastric mucosal barrier is bolstered by a single layer of epithelial cells which is capable of rapid repair following injury. The local production of prostaglandins acts to stimulate bicarbonate and mucus secretion, decrease gastric acid secretion, and promote a healthy gastrointestinal mucosa. The total flow of blood through the gastric mucosa can be increased to clear noxious substances produced during the inflammatory response and deliver oxygen and bicarbonate to injured epithelium. Breakdown of the gastric mucosal barrier is a primary source or consequence of nearly all causes of gastritis and gastric ulceration.

Etiology and Pathophysiology of Gastritis

Canine and feline gastritis is defined as inflammation of the stomach and occurs in response to many stimuli. Gastritis can be classified by duration of clinical signs (acute or chronic) and by histopathologic changes (e.g., lymphoplasmacytic, eosinophilic, fibrosis, atrophy). The release of a variety of inflammatory mediators, including pro-inflammatory cytokines and chemokines, eicosanoids (prostaglandins, leukotrienes, and thromboxanes), neuropeptides, nitric oxide, peroxidases, and proteinases, perpetuate gastritis through increasing exposure of the denuded epithelium and underlying mucosa to toxic insults (e.g., gastric acid, bile acids, pepsin). As well as exerting direct effects on the gastric mucosal cells, many of these mediators act to alter mucosal permeability and blood flow.

Gastric ulceration, which can be a sequel of severe or prolonged gastric inflammation and ischemia, is defined as a defect in the gastric mucosa extending to the muscularis mucosa or through the muscularis propria. Ulcers can be full thickness (perforating) or partial thickness. Perforating ulcers can be associated with hemorrhage and septic peritonitis and therefore are considered life threatening when left untreated. Gastric ulceration is more frequently reported in the dog than the cat, but as observed with gastritis, toxic agents, drug-induced reactions, neoplasia, severe systemic illness, and infectious organisms can be injurious to the gastric mucosa in both species.

A variety of etiologies have been implicated in the development of canine and feline gastritis and gastric ulceration (Tables 51.1 and 51.2). These include mechanical irritants, drugs, systemic illness, infections, breed-associated diseases, motility disorders, and occupational and exercise-related stressors.

Gastric foreign bodies and dietary indiscretion are common causes of acute gastritis in dogs and cats. Although the stomach is not the primary site of protein absorption, dietary protein intolerance and food responsive disease can also be linked with gastritis in both dogs and cats, albeit less frequently. The presentation of food antigens to the gut-associated lymphoid tissue in the small intestine can initiate immediate or delayed hypersensitivity reactions capable of inducing vomiting with

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Table 51.1 Causes of gastritis in dogs and cats

Category	Dogs	Cats
Primary gastric	Dietary indiscretion, foreign body, IBD, food allergic, gastric neoplasia (carcinoma, leiomyoma, leiomyosarcoma, mast cell tumor)	IBD, alimentary small cell lymphoma, foreign body, gastric neoplasia (lymphoma, carcinoma, leiomyoma, leiomyosarcoma, mast cell tumor)
Systemic	Acute or end-stage organ (hepatic, renal) dysfunction, anaphylactoid reaction, hypoadrenocorticism, pancreatitis, sepsis, hypercoagulable states (Cushing disease, PLE, PLN), portosystemic shunts	Acute or end-stage organ (renal) dysfunction, pancreatitis, sepsis, hypereosinophilic syndrome, eosinophilic fibrosing gastritis
Infectious	Viral (distemper, parvo, corona), bacterial (*Helicobacter*, *Clostridium*, *Salmonella*, *Campylobacter*, *E. coli*), fungal (*Histoplasma*), helminth (*Gnathostoma binucleatum*, *Physaloptera* spp., *Toxocara canis*), oomycete (*Pythium*)	Bacterial (*Helicobacter*), helminth (*Aonchotheca putorii*, *Ollulanus tricuspis*, *Gnathostoma binucleatum*, *Toxocara cati*), feline dirofilariasis
Medication related	NSAIDs, antibiotics (penicillins, tetracyclines, chloramphenicol, lincosamides), chemotherapeutics	Same as dogs
Hyperacidity	Pancreatic gastrinomas, mastocytosis	Same as dogs
Stress, exercise induced	Surgery, Alaskan sled dogs (exercise induced)	Surgery, prolonged hospitalization
Breed related	Basenjis (immunoproliferative enteropathy), Norwegian lundehund (atrophic gastritis, lymphangiectasia), Rottweilers (eosinophilic enteropathy)	None known
Miscellaneous	Benign gastric hypertrophy, bilious vomiting syndrome	

IBD, inflammatory bowel disease; NSAID, nonsteroidal antiinflammatory drug; PLE, protein-losing enteropathy; PLN, protein-losing nephropathy.

Table 51.2 Causes of gastric ulceration in dogs and cats

Category	Specific causes
Ulcerogenic drugs	NSAIDs (selective and nonselective), steroids (in combination with NSAID or additional risk factor)
Primary gastric	Neoplasia (carcinoma, lymphoma, mast cell tumor, leiomyosarcoma), IBD, gastric foreign body
Systemic disease	Hepatic dysfunction, hypoadrenocorticism, GDV, pancreatitis, sepsis, hypercoagulability (DIC, PLE, PLN), hyperacidity (gastrinoma, mastocytosis)
Stress	Surgery, severe critical illness
Infectious	Helminths (*Aonchotheca putorii*, *Ollulanus tricuspis*, *Gnathostoma binucleatum*, *Toxocara cati*), fungal (histoplasmosis), oomycete (pythiosis)
Miscellaneous	Toxic/caustic substances, ingestion of sharp/perforating objects, thermal injury secondary to foodstuffs, occupation related (Alaskan sled dogs), iatrogenic (perforation during gastroscopy)

DIC, disseminated intravascular coagulation; GDV, gastric dilation-volvulus; IBD, inflammatory bowel disease; NSAID, nonsteroidal antiinflammatory drug; PLE, protein-losing enteropathy; PLN, protein-losing nephropathy.

secondary gastritis. Inflammatory bowel disease (IBD) is considered to be a predisposing factor for gastric ulceration, but this is a relatively uncommon complication of IBD.

Invasive gastric and nongastric tumors resulting in gastric hyperacidity cause physical damage to the gastric mucosal barrier that can incite the development of secondary gastritis and gastric ulceration. Primary gastric neoplasms represent 1% of all cancers diagnosed in companion animals. Gastric carcinoma (most common in the dog), lymphoma (most common in the cat), leiomyomas, leiomyosarcomas, and mast cell tumors are the most frequently reported in association with gastritis. Mast cell tumors, systemic mastocytosis, and pancreatic gastrinomas increase the risk of ulceration due to the overproduction of histamine and gastrin, respectively. Mast cell tumors and gastrinomas were overrepresented in one large literature review of cats with gastroduodenal ulceration.

Nonneoplastic, proliferative masses associated with gastritis include gastric polyps and benign gastric hypertrophy or hyperplasia with accompanying gastritis.

Chronic hypertrophic pyloric gastropathy has been documented in many breeds and usually manifests with clinical signs of pyloric outflow obstruction.

Drugs, household chemicals, and plants are also a frequent cause of gastritis in dogs and cats. A list of common plants and household chemicals associated with gastritis may be found in an excellent review by Webb and Twedt (see Further Reading list).

Nonsteroidal antiinflammatory drugs (NSAIDs), a leading cause of gastritis and gastric ulceration in companion animals, are both directly and indirectly injurious to the gastric epithelium as a result of being weak acids and via their inhibitory effect on prostaglandin production, respectively. Aspirin, flunixin meglumine, indomethacin, ibuprofen, acetaminophen, ketorolac, deracoxib, and carprofen have all been associated with the development of gastric lesions. Nonselective COX NSAIDs (e.g., aspirin) are the most ulcerogenic and should be used with caution. NSAID-induced ulcers are often localized to the pyloric antrum and pylorus. COX-2 selective NSAIDs (e.g., meloxicam) are considered less ulcerogenic than nonselective inhibitors, but careful monitoring is still advised as all NSAIDs can be ulcerogenic as well as delay healing of epithelial injury. NSAIDs should be considered contraindicated and used sparingly in companion animals that have concurrent diseases with ulcer-inducing potential.

Corticosteroids at high doses can cause gastritis, but they are unlikely to be the sole cause of gastric ulceration except when given concurrently with an NSAID or in the presence of other risk factors. Other drugs commonly associated with gastritis in either species include some antibiotics (e.g., penicillins, chloramphenicol, lincosamides, tetracyclines) and chemotherapeutic agents. Ingestion of noxious chemicals (e.g., phenols/alcohols), toxic substances (e.g., lead, *Dieffenbachia*), foodstuffs capable of producing thermal damage and foreign bodies has also been reported to cause gastritis and ulceration. Systemic illness (e.g., hepatic, renal, neurologic or endocrine disease) and/or conditions causing poor gastrointestinal (GI) perfusion (e.g., hypoadrenocorticism, gastric dilation-volvulus, thromboembolic disease) can trigger gastric inflammation and/or gastric ulceration. Ulcer development in animals with hepatic dysfunction most commonly results from compromised hemodynamics. Although severe renal dysfunction results in decreased elimination of uremic toxins and gastrin, gastric ulcers are uncommonly documented in dogs and cats with end-stage renal failure.

Infectious causes of gastritis include a variety of bacterial species, helminths, oomycetes, fungi, and viruses. Most infectious agents rarely cause gastric signs alone, however, and therefore are not discussed in detail in this chapter. Although uncommon, infectious and parasitic etiologies (e.g., pythiosis, gnathostomiasis, *Aonchotheca putorii*, *Toxocara cati*) have also been associated with gastric ulceration. In cats, heartworm infection may cause vomiting and gastritis, while this is uncommon in dogs.

Bilious vomiting syndrome, a frequently encountered yet poorly understood gastric motility disorder in dogs, can induce gastritis through reflux of injurious bile salts into the stomach. Affected dogs generally vomit early in the morning following an overnight fast.

Other less commonly encountered causes of gastritis and gastric ulceration include occupational stress (e.g., racing Alaskan sled dogs) and breed-related gastropathies, including atrophic gastritis in the Norwegian lundehund and immunoproliferative enteropathy in basenjis. Hypereosinophilic syndrome, particularly in Rottweilers, and both hypereosinophilic syndrome and feline gastrointestinal eosinophilic sclerosing fibroplasia (FGESF) in cats can cause severe gastritis and gastric ulceration. Hospitalization and postoperative stress may be a more common cause of ulceration in cats than in dogs.

Helicobacter pylori and Related Organisms

The relationship between colonization with *Helicobacter* spp. in canine and feline patients and the occurrence of gastritis and gastric ulceration is unclear. *Helicobacter pylori* is an important cause of gastritis and ulceration in humans but not in companion animals, and the role of other *Helicobacter* species as gastric pathogens in dogs and cats is less well defined. Multiple *Helicobacter* spp. (*H. heilmannii*, *H. pylori*, *H. felis*, *H. bizzozeronii*) have been isolated in both dogs and cats with varying degrees of gastritis. Thus, *Helicobacter* infection should only be considered as a cause of clinical signs in dogs and cats when associated with histopathologic evidence of gastric inflammation, and after other causes have been excluded.

Epidemiology of Gastric Disease

Consideration of the animal's signalment aids in the prioritization of differentials for gastritis and gastric ulceration. For example, foreign body ingestion, dietary indiscretion, and infectious causes of gastritis are more commonly identified in younger animals. Dachshunds and other chondrodystrophic breeds predisposed to intervertebral disc disease might be at higher risk for subclinical gastric ulceration with concurrent steroid and/or NSAID therapy. German shepherd dogs have been reported to be at greater risk for gastric ulceration following ibuprofen administration.

Gastritis resulting from inflammatory bowel disease, systemic disorders, and neoplasia is more common in middle-aged to older companion animals. Breed-related gastritis, however (seen in Norwegian lundehunds, Rottweilers, and basenjis) can occur at any age.

Adenocarcinomas develop in middle-aged dogs (<10 years) more frequently than other gastric neoplasms, and are usually located in the pyloric antrum or gastric body (greater curvature). Collies, German shepherd dogs, Staffordshire terriers, Bouviers des Flandres, Norwegian elkhounds, and Belgian shepherds have been identified as breeds at higher risk for developing gastric carcinoma. Male dogs are overrepresented among dogs with gastric neoplasms in some reports, although a sex predisposition is not yet widely recognized. The Norwegian lundehund is at higher risk for development of neuroendocrine carcinoma secondary to chronic, severe atrophic gastritis. Lymphoma is more prevalent in older cats, while middle-aged cats are more likely to be diagnosed with inflammatory bowel disease. No breed predispositions are recognized for primary gastric cancer in cats, but one report exists of two related Persians with confirmed gastritis and adenocarcinoma.

Large-breed, deep-chested and working dogs (Great Danes, standard poodles, Irish wolfhound, Newfoundland, Weimaraner, mastiff and hound breeds, German shepherd dogs) are at higher risk for gastric dilation-volvulus (GDV) and secondary ulceration.

Young to middle-aged, spayed female dogs are more likely to develop hypoadrenocorticism and gastritis secondary to vomiting. Breeds such as the standard poodle, Novia Scotia duck tolling retriever, Rottweiler, Great Dane and Portuguese water dog are overrepresented.

Geographic location influences the risk of development of fungal gastritis. *Histoplasma capsulatum* is one of the most common canine mycotic pathogens in the United States and manifests primarily with signs of gastrointestinal disease in young to middle-aged dogs. *Histoplasma* spp. infection should be ruled out in dogs displaying signs of gastrointestinal disease that are living in endemic regions such as the mid-western, southern, and Gulf Coast regions of the US, as well as Central America. There is a higher prevalence of histoplasmosis in males compared to females, with pointers, Weimeraners, and Brittany spaniels identified as predisposed breeds. *Pythium insidiosum* has been documented in dogs with a travel history to or residing in tropical regions, the Gulf Coast and mid-western states, and northern California. Male Labrador retrievers and German shepherd dogs are overrepresented. Dogs infected with parvovirus, distemper virus, and coronavirus are often younger (less than 3 years of age), unvaccinated and from multidog environments (kennels, shelters).

Environmental history may also give clues towards identification of uncommon causes of feline gastritis. The nematode *Ollulanus tricuspis* is found in cats throughout the US, whereas *Aonchotheca putorii* is more common in tropical, temperate areas worldwide. Feline dirofilariasis occurs more commonly in the mid-west and south-east, with a higher prevalence also reported in northern California and Florida.

History and Clinical Signs of Gastritis

The duration (acute versus chronic) and severity of signs in dogs and cats with gastritis and gastric ulceration vary depending on the underlying etiology. Clinical signs can range from overt gastrointestinal signs to only weight loss. For animals with "garbage gut" or those that have ingested caustic substances, toxins, ulcerogenic medications or foreign bodies, the onset of clinical signs is often rapid (usually within a few hours). Clinical signs in patients with gastric foreign body obstruction often include lethargy, inappetence, vomiting, and antisocial or "hiding" behavior. Owners should be questioned regarding the possibility of exposure to yarn, string, tinsel, needles or hair ties accessible in the house. Intoxications secondary to chocolate (theobromine), macadamia nuts, mycotoxins (e.g., mushrooms, sago palms, blue-green algae, molds), and marijuana should be considered in dogs exhibiting vomiting in association with an acute onset of neurologic abnormalities.

Viral etiologies should be suspected when there is an outbreak of gastrointestinal signs in multiple dogs from the same shelter or household. Viral gastroenteritis can cause inappetence, fever, lethargy, vomiting, and small bowel diarrhea. Distemper is known to cause severe neurologic signs, but manifests as gastrointestinal (inappetence, vomiting, diarrhea) and respiratory signs early in the course of infection.

As the vast majority of episodes of drug-induced gastritis and GI ulceration in the dog are caused by NSAID use (with or without steroids), a full drug history should be obtained for any dog (or cat) presenting with signs of gastric disease. Dogs receiving chronic NSAID therapy with gastrointestinal signs should be regularly evaluated for gastritis. A change as subtle as hyporexia should raise concern. A recent history of antibiotic administration preceding development of clinical signs should raise suspicion for an adverse reaction to medication.

Infectious gastritis should be suspected if there is travel history to an endemic area or there has been ingestion of uncooked or raw foods. Vomiting in animals with pythiosis or histoplasmosis is often accompanied by other clinical signs including diarrhea, cutaneous lesions, lymphadenopathy, and ocular abnormalities

(uveitis, retinal lesions). Dogs suffering from fungal mycosis may also exhibit anorexia and rapid weight loss, and succumb quickly to their disease. Puppies or younger dogs, especially those that have not received a broad-spectrum anthelminthic, are at higher risk for parasitic disease.

Animals with neoplasia-induced gastric disease may have a more chronic history, with progressive signs of gastrointestinal disease (e.g., weight loss, lethargy, anorexia, ptyalism, vomiting, diarrhea). Clinical signs of lymphoma in cats are often protracted and mimic those of inflammatory bowel disease, although cats with lymphoblastic lymphoma often exhibit a more rapid deterioration. Some gastric neoplasms can lead to gastroesophageal reflux, thus these animals can present with signs of esophagitis including regurgitation or ptyalism following meals (see Chapter 52). Animals with mastocytosis or gastrinomas can have evidence of hematemesis, depending on the severity of gastric lesions. Cutaneous lesions can also accompany systemic mastocytosis and fungal disease.

Inflammatory bowel disease and food responsive gastroenteritis are two of the most common causes of gastritis in young and middle-aged dogs. Common clinical signs in animals with IBD can include weight loss (with or without good appetite), lethargy, hyporexia or anorexia, intermittent vomiting and either large or small bowel diarrhea with large bowel diarrhea being more common. Beef, wheat, lamb, egg, chicken, soy, and wheat are common dietary allergens, but any protein or carbohydrate source is capable of eliciting an immune reaction. Younger dogs that are presented with mild clinical signs and predominantly diarrhea of large bowel origin are more likely to have food-responsive disease. Cats with inflammatory bowel disease often exhibit weight loss, hyporexia, anorexia, ptyalism, vomiting, and diarrhea.

Cutaneous lesions, lower airway abnormalities (coughing, tachypnea) and palpably thickened intestinal loops on exam should increase the clinical suspicion for eosinophilic gastroenteritis or hypereosinophilic syndrome in cats.

Dogs and cats that develop gastritis secondary to systemic disease often have other clinical signs related to the primary system involved. Hepatic dysfunction can result in polyuria and polydipsia (PU/PD), petechiae or ecchymosis secondary to coagulopathy, and neurologic signs indicative of encephalopathy in severely affected cases. Portosystemic vascular anomalies should be ruled out in younger dogs with chronic or intermittent gastrointestinal and neurologic signs and inability to gain weight. Suspicion of a shunt is particularly high if the animal's owners report a history of worsening neurologic signs following ingestion of a meal. Vomiting secondary to advanced kidney disease should be suspected in dogs with PU/PD, weight loss, and a poor hair coat. Dogs with hypoadrenocorticism commonly present for waxing and waning lethargy, hyporexia, vomiting and soft stools or small bowel diarrhea.

Cats with secondary causes of gastritis (e.g., hyperthyroidism, chronic kidney disease [CKD] or liver disease) also typically display extragastrointestinal clinical signs. Owners might note hyperactivity, weight loss, dull hair coat, alopecia, and occasionally aggression in hyperthyroid cats. Clinical signs of renal and liver disease mimic those seen in dogs, although uremic ulceration of the tongue and palate might be noted more frequently in cats. Uremic gastropathy, characterized by erosive or ulcerative gastritis, has been a previously reported sequel of renal dysfunction. Recent studies, however, suggest this is not a common finding in cats with CKD.

Physical exam findings in companion animals with gastritis or gastric ulceration are variable and depend on the underlying etiology. Slightly thickened or "ropey" small intestinal loops are often appreciated in both dogs and cats with inflammatory bowel disease. Many of these patients are moderately to severely underweight. Abdominal lymphadenomegaly might be noted on abdominal palpation in cats with IBD or GI lymphoma. Pruritus and/or signs compatible with allergic dermatitis might be noted in patients with food-responsive gastritis. Cranial abdominal pain might be appreciated on physical examination in cases of foreign body ingestion, pancreatitis, gastric neoplasia, and/or severe GI ulceration. These animals might also be febrile. Linear foreign bodies may become anchored to the base of a cat's tongue, so careful inspection of this area on physical examination is critical. Depending on the severity and chronicity of disease, patients can exhibit signs of dehydration, hyperthermia, and/or hypovolemic or septic shock. Cardiac arrhythmias can also be noted secondary to hypovolemia and ischemia. Frank blood or tarry stools may be identified on rectal examination, but the absence of these signs does not rule out gastric bleeding. Severe or prolonged blood loss is often associated with pale mucous membranes.

Neurologic abnormalities (e.g., myoclonus, nystagmus, tremors, seizures or inappropriate mentation, head pressing, star gazing) are often observed in animals with distemper virus, intoxications or hepatic dysfunction. Pyrexia, cutaneous lesions, lymphadenopathy, and ocular lesions (uveitis, tapetal hyper- or hyporeflectivity, fundic lesions) can occur with fungal infections. Tapetal hemorrhage or a detached retina might be visible (secondary to systemic hypertension) during the fundic exam of patients with renal dysfunction.

Cutaneous lesions such as edema, ulceration, and abscessation are often found in dogs with systemic mastocytosis and fungal disease.

Diagnostic Approach to Suspected Gastritis

Clinicopathologic Examination of the Gastritis Patient

A minimum database of clinicopathologic testing, including a complete blood count, serum chemistry, urinalysis, and total thyroxine (in middle-aged to older cats), is typically recommended for dogs and cats being presented with moderate to severe signs and/or a chronic history of disease, prior to more invasive testing. Clinicopathologic abnormalities vary depending on the underlying etiology, duration, and severity of disease. Patients with peracute causes of gastric inflammation or ulceration (e.g., foreign body ingestion, intoxication or GDV) can lack bloodwork abnormalities in the early stages of the disease. However, baseline bloodwork and imaging are recommended as they can demonstrate evidence of GI bleeding or other co-morbidities or reveal an underlying predisposing cause. Anemia is the most common laboratory finding in dogs and cats with gastroduodenal ulceration. Depending on the severity and chronicity of gastric bleeding, the anemia can vary from regenerative to nonregenerative with clinicopathologic features of iron deficiency (e.g., microcytosis, hypochromasia). Peripheral eosinophilia may be observed in dogs or cats with infectious causes of gastritis or gastric ulceration, hypoadrenocorticism or the eosinophilic enteropathies such as hypereosinophilic syndrome or eosinophilic IBD. Neutrophilic leukocytosis can be observed in patients with hyperadrenocorticism, IBD or infectious diseases.

An elevated blood urea nitrogen:creatinine ratio in the presence of anemia strongly argues for further assessment of possible GI bleeding. Electrolyte derangements may be present as a result of gastrointestinal losses (vomiting, diarrhea). The absence of a stress leukogram, with or without altered serum sodium and potassium ratios (<27:1) and/or hypoglycemia, hypocholesterolemia, and hypoalbuminemia would support pursuit of additional testing for hypoadrenocorticism.

Coagulation testing should be included as part of the minimum database in patients with unidentified causes of GI bleeding. Common causes of prolonged clotting times in dogs with clinical signs of gastric disease include septicemia, hepatic failure, and rodenticide intoxication.

Fecal flotation, examination of vomitus, and empirical anthelminthic treatment are recommended in animals where parasitic disease is likely or before pursuing more invasive diagnostic testing such as gastroscopy or exploratory laparotomy.

Diagnostic Imaging in Gastric Disease

Survey radiographs and abdominal ultrasonography (AUS) can have variable results in patients with gastritis and gastric ulceration. Neither condition should be excluded on the basis of normal abdominal imaging. Abdominal radiographs performed in patients with signs of gastric disease can reveal radiopaque foreign bodies, gastric and extragastric neoplasms (if large enough to distort normal anatomy) and/or other causes of inflammation and ulceration (e.g., pancreatitis, GDV). Gastric neoplasms in both cats and dogs are rarely identified with radiographs alone, except in cases of calcified (radiopaque) carcinomas. Abdominal effusion and pneumoperitoneum are not specific for gastric perforation, but signal the need for urgent exploration with additional imaging modalities or exploratory surgery in a patient with compatible clinical signs. Mediastinal and esophageal masses can be observed in dogs with pythiosis, so thoracic radiographs are recommended for dogs with compatible clinical signs. Ultrasonographic abnormalities observed in some patients with gastric disease, particularly gastric ulceration, include disruption of normal wall layering and/or focal gastric wall thickening. Hepatomegaly, splenomegaly, and abdominal lymphadenopathy can be present in dogs with neoplastic and/or infectious causes of gastric disease. Gastric masses are often visible on AUS, but the absence of a mass does not rule out infiltrative neoplasia. Most commonly, changes on abdominal ultrasound are nonspecific with abnormalities suggestive of, but not diagnostic for, gastritis or gastrointestinal disease.

Gastric Histopathology

Histopathologic evaluation of biopsies (endoscopic or full thickness) is required for the definitive diagnosis of gastritis while diagnosis of ulceration is generally made by visualization of the ulcerated mucosa and acquisition of biopsies with endoscopy or exploratory surgery. However, the underlying cause is often not identified on evaluation of gastric tissue, thus correct diagnosis often requires consideration of the patient's signalment, history, clinical signs, bloodwork, and imaging.

Gastroscopy or abdominal exploratory surgery are the only antemortem methods for obtaining a definitive diagnosis of gastric ulceration and gastric mucosal biopsy specimens for histopathologic examination. Animals with very diseased, friable tissue or preexisting ulceration are at greater risk for endoscopic-induced perforation, so caution is warranted with gastroscopy in patients where there is a suspicion of gastric ulceration. Ulceration secondary to NSAID administration is found more often in the pyloric antrum than other sites of the stomach. Mastocytosis typically causes multiple diffuse

ulcerative lesions in dogs. Gastrointestinal disease secondary to infectious etiologies often requires histopathologic or immunohistochemical identification of the organism. *Helicobacter*-associated gastritis in cats and dogs is definitively diagnosed by identification of the organism in gastric biopsies using fluorescence *in situ* hybridization (FISH) or polymerase chain reaction (PCR). Increased tissue urease activity and positive urea breath tests have been correlated with the presence of *Helicobacter*, but are also identified in the presence of other urease-producing bacteria and thus lack specificity. Special staining methods (Steiner staining) and immunohistochemistry methods can aid in species differentiation.

Gastritis and/or gastric ulceration secondary to gastric neoplasms (carcinomas, lymphoma, mast cell tumors) or gastrinomas can be identified via histopathologic examination of tissue (e.g., stomach, pancreas) biopsies. Serum gastrin measurement provides a noninvasive test when gastrinoma is suspected. Marked hypergastrinemia in the presence of gastroduodenal ulceration is suggestive of a pancreatic gastrinoma. Thus, a serum gastrin measurement should be performed in any patient presenting for chronic gastritis and gastroduodenal ulceration where other systemic diseases are eliminated as causes. Serum gastrin concentration should be interpreted cautiously in the face of acid suppressant treatment, which can result in increased serum gastrin concentrations.

Ancillary Diagnostic Testing in Gastric Disease Patients

Testing for the presence of bacterial enteropathogens such as *E. coli*, *Clostridium*, *Campylobacter* and *Salmonella* spp. might be considered as an ancillary diagnostic test for dogs presenting with fever, acute hemorrhagic diarrhea, and vomiting. However, results should be interpreted with caution, as these organisms have been isolated from the feces of healthy dogs and cats.

In cases where there is a high suspicion of gastrointestinal mycosis or oomycete disease, multiple diagnostics are available for antemortem diagnosis. Pythium testing includes serology, enzyme-linked immunosorbent assay (ELISA), PCR or immunohistochemistry (IHC) of infected tissues or blood. A quantitative urine antigen enzyme immunoassay is available for *Histoplasma* detection. Pyogranulomatous lesions and visualization of fungal organisms can be noted in biopsies obtained from dogs with fungal gastritis within the liver, spleen, lymph nodes, or gastrointestinal tract. If present, biopsies of cutaneous lesions should be submitted for histopathology and fungal culture. Gastritis in the Norwegian lundehund is often secondary to lymphangiectasia (diagnosed by endoscopic visualization and histopathology). Evidence of protein-losing enteropathy is variably present on bloodwork. It has been hypothesized that this syndrome can also lead to development of gastric carcinoma as a result of chronic, severe gastritis.

Treatment of Gastritis and Gastric Ulceration

The best course of therapy for animals with gastritis or gastric ulceration is removal of the offending agent, if possible, and amelioration of mucosal injury. Specific therapies will depend on the identified cause (e.g., azole treatment for *Histoplasma* infection, chemotherapy/surgery for neoplasia).

Nonspecific, supportive treatment for animals with gastritis and vomiting should begin with restoration of fluid deficits and normalization of electrolyte imbalances, if present. A list of commonly used medications for gastritis and gastric ulceration is provided in Table 51.3.

Acid suppressants (e.g., histamine-2 receptor antagonists [H_2RAs] and proton pump inhibitors [PPIs]) are recommended in vomiting animals with clinical signs of vomiting-induced esophagitis but should not be used prophylactically. H_2RAs are competitive inhibitors for the interaction of histamine with its receptor on the gastric parietal cell but differ in potency (famotidine > ranitidine > cimetidine). In contrast, PPIs (e.g., omeprazole, pantoprazole, esomeprazole) are inactivators of the proton pump and are more effective than H_2RAs in raising both feline and canine intragastric pH. Thus, PPIs, administered twice-daily, are considered the treatment of choice when concern for acid-induced tissue injury exists. Preliminary evidence suggests that PPIs are more effective when given alone than in combination with H_2RAs in dogs for the treatment of upper GI ulceration. Antiemetics (e.g., 5-HT_3 and neurokinin receptor antagonists) may be administered to vomiting animals once mechanical obstruction has been ruled out as a cause of the clinical signs.

Cytoprotective agents (e.g., sucralfate) can be given, once vomiting is controlled, if there is evidence or suspicion of gastrointestinal bleeding. Sucralfate is most effective at an acidic pH and can interfere with appropriate absorption of pH-dependent drugs. Thus, sucralfate should be administered as a slurry at least 1–2 hours before or after administration of meals and other medications. The PGE_1 analog misoprostol is indicated for use in NSAID-induced toxicoses but does not promote healing in non-NSAID-induced causes of GI ulceration.

Table 51.3 Commonly used medications for canine and feline gastritis

Drug	Mechanism of action	Formulations	Doses
Omeprazole; Esomeprazole	Proton pump inhibitor (PPI): inactivator of parietal cell H+ - K+ - ATPase pumps; inhibits acid production	Tablet, capsule (Prilosec Over the Counter®) Omeprazole reformulated paste (Gastrogard®; Nexium®)	1 mg/kg PO BID (canine, feline) 1 mg/kg IV BID (canine)
Pantoprazole	Same as above (PPI)	Injectable (Protonix®)	1 mg/kg slow IV BID (canine)
Famotidine	Histamine-2 receptor antagonist: competitive inhibitor of histamine receptors on gastric parietal cell, decreases acid production; tolerance with repeated dosing	Tablet (Pepcid AC®) Injectable	1 mg/kg PO BID (canine, feline) 1 mg/kg IV BID (canine, feline)
Ranitidine	Same as above although less efficacious; prokinetic activity	Tablet	1.5–2.0 mg/kg PO BID (canine, feline)
Sucralfate	Cytoprotective agent: sucrose-sulfate-aluminum complex that cross-links with acid to form protective barrier	Tablet (administered as liquid slurry) Oral liquid suspension (Carafate)	250 mg PO TID (small dogs, cats) 500 mg PO TID (small to medium dogs) 1 g PO TID (large dogs)
Misoprostol	Prostaglandin $(PGE)_1$ agonist: used for prevention of NSAID-induced gastrointestinal injury	Tablet (Cytotec)	3 µg/kg PO BID (canine)
Metoclopramide	Antiemetic (dogs only): dopamine receptor antagonist which acts to decrease nausea and vomiting; prokinetic activity	Tablet (Reglan) Injectable (Reglan)	0.2–1 mg/kg PO, SC QID (canine) CRI: 1 mg/kg/day (canine)
Chlorpromazine	Antiemetic (dogs only): same mechanism of action as metoclopramide	Tablet (Thorazine) Injectable	4–8 mg/per dog (do not exceed 0.5 mg/kg) PO BID (canine) 0.2–0.4 mg/kg SC, IM TID (canine)
Maropitant	Antiemetic: neurokinin (NK1) receptor antagonist that works at the chemoreceptor trigger zone (CRTZ) to decrease nausea and vomiting	Tablet (Cerenia®) Injectable	1 mg/kg SC q24h (canine, feline) 2 mg/kg PO q24h (canine, feline)
Ondansetron	Antiemetic (canine, feline): serotonin 5-HT3 receptor antagonist, no effect on dopamine receptors	Tablet (Zofran®) Injectable (Zofran®)	0.1–0.2 mg/kg IV BID (canine) 0.1–1 mg/kg PO q24h BID (canine) 0.5 mg/kg IV, PO BID (feline)
Cisapride	Prokinetic: increases lower esophageal peristalsis and increases gastric emptying. Also effective colonic prokinetic	Compounded tablet or suspension	0.1–0.5 mg/kg PO BID-TID (canine) 2.5 mg PO TID (felines <10 lb), 5 mg PO TID (felines >10 lb)

ATP, adenosine triphosphate; BID, twice a day (*bis in die*); CRI, constant rate infusion; IM, intramuscular; IV, intravenous; NSAID, nonsteroidal antiinflammatory drug; PO, by mouth (*per os*); QID, four times a day (*quater in die*); SC, subcutaneous; TID, three times a day (*ter in die*).

Prokinetic drugs (e.g., cisapride, ranitidine, erythromycin, metoclopramide) canbe used for the treatment of gastric motility disorders (e.g., bilious vomiting syndrome) when mechanical obstruction has been ruled out.

Dietary restriction (<24 hours with access to water at all times) can be considered for dogs with nonobstructive acute gastritis but should be used with caution in cats as they are predisposed to hepatic lipidosis with even short periods of dietary rest. Dietary modification (hydrolyzed, limited ingredient, and/or low fat) is necessary for animals with chronic gastritis where diet is suspected to be the cause of gastric signs.

Broad-spectrum anthelminthic drugs are recommended in animals when an underlying cause of gastritis cannot be identified and/or prior to pursuit of invasive diagnostics (e.g., endoscopy, surgery). Triple antimicrobial therapy with amoxicillin, metronidazole, and bismuth subsalicylate has been used in dogs to treat *Helicobacter*-associated gastritis, but this course of therapy might not eradicate infection.

Prognosis

The prognosis for patients with gastritis and/or gastric ulceration ranges from excellent to guarded depending on the underlying etiology, severity of disease at presentation, and individual response to therapy. Uncomplicated, acute disease in younger, otherwise healthy animals without significant co-morbidities is usually associated with a good prognosis. In contrast, onset of significant gastric disease and ulceration in older animals with chronic histories of gastrointestinal disease or other co-morbidities is often associated with progression of an underlying disease process and can carry a more guarded prognosis.

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52

Disorders of the Esophagus

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Normal Esophageal Anatomy and Physiology

The esophagus is a readily distensible, muscular tube that transports ingested material from the oropharynx to the stomach. It is divided into three sections –the cervical, thoracic and abdominal segments – and enclosed at each end by a muscular sphincter (the upper and lower esophageal sphincters).

The esophageal wall has four distinct layers: adventitia, muscularis, submucosa, and mucosa. The entire muscularis layer in the canine esophagus is composed of skeletal muscle, whereas the distal one-third of the feline esophagus consists of smooth muscle. This difference in muscular structure may partly explain the differing prevalence of esophageal disease in dogs and cats, with cats relatively rarely presenting with esophageal diseases other than foreign bodies or squamous cell carcinoma. The upper esophageal sphincter is composed of fibers from the cricopharyngeus muscle and thyropharyngeus muscle. In dogs, the lower esophageal sphincter is composed of an outer layer of striated muscle and an inner layer of smooth muscle, while in cats the lower esophageal sphincter consists of smooth muscle only.

Swallowing is a complex motor reflex requiring coordinated action of the tongue, oropharynx, upper esophageal sphincter, and esophagus to ensure that food enters the gastrointestinal tract and not the upper airways. When swallowing is not occurring, the upper and lower esophageal sphincters are tightly closed and the esophagus is relaxed. During swallowing, the upper esophageal sphincter relaxes and the food bolus is pushed into the cervical section of the esophagus. A primary peristaltic wave is generated, transferring the bolus to the stomach. This primary peristaltic wave will be followed by secondary waves if the esophagus is not cleared of material. Relaxation of the lower esophageal sphincter accompanies the primary peristaltic wave, allowing entry of the food bolus into the stomach.

The most common esophageal disorders encountered in private practice include esophagitis, megaesophagus, esophageal strictures, and esophageal foreign bodies. Less commonly encountered disorders include great vessel anomalies, lower esophageal hiatal disorders, esophageal neoplasia, spirocercosis, cricopharyngeal dysphagia, esophageal diverticulae, and esophageal fistulae.

Recognition of Esophageal Disorders

Common clinical signs of esophageal disease include regurgitation, dysphagia (difficult swallowing), ptyalism (excessive salivation), extension of the head and neck, repeated swallowing attempts, and pain. Regurgitation is a hallmark sign of esophageal disease and needs to be differentiated from vomiting. Regurgitation is defined as the passive retrograde expulsion of material from the esophagus while vomiting is an active process mediated by a central reflex. Vomiting is usually associated with abdominal contractions and might show prodromal signs of nausea (lip smacking, increased salivation, discomfort or anxiety) or the presence of bile in the ejected material.

Oropharyngeal dysphagia, a less common clinical syndrome, should be differentiated from regurgitation. Clinical signs of oropharyngeal dysphagia include multiple swallowing attempts with a single bolus, dropping food or water from the mouth or nostrils, and difficulty drinking. When possible, having the owner video record the episodes may be helpful in distinguishing oropharyngeal swallowing disorders from esophageal motility disorders.

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One of the most frequent complications of esophageal disorders is aspiration pneumonia; this is the most common cause of death in animals with esophageal motility disorders. Dogs with aspiration pneumonia secondary to esophageal disease can present with fever, inappetence, coughing, mucopurulent nasal discharge, and pulmonary crackles. Dogs with chronic and severe esophageal dysfunction may present with weight loss and poor body condition scores secondary to inadequate food intake. Dogs with foreign bodies or esophagitis are usually painful during swallowing. Foreign bodies are often associated with an acute onset of regurgitation. The presence of esophageal disease at the time of weaning is more commonly seen with congenital idiopathic megaesophagus, vascular ring anomalies or congenital stenosis. The history may indicate a recent anesthetic procedure that could cause reflux esophagitis and potential stricture, exposure to caustic medications (e.g., doxycycline) or foreign bodies. Signs of concurrent neuromuscular disease can be seen in dogs with megaesophagus secondary to myasthenia gravis.

Diagnostic Approach to Esophageal Disease

Plain thoracic and cervical radiographs are the initial step in all animals with clinical signs and histories consistent with esophageal disease. Radiographs are useful in the identification of megaesophagus, radiopaque foreign bodies, and hiatal defects. In addition, the lungs and mediastinum can be evaluated for any evidence of aspiration pneumonia or pneumomediastinum associated with esophageal perforation.

A contrast esophagram should be considered when plain radiographs do not identify a lesion. The contrast study can be performed under fluoroscopy or using plain radiography (see Chapter 53). The use of fluoroscopy helps in the evaluation of esophageal motility. Contrast studies can be useful in the identification of radiolucent foreign material, strictures or neoplasia. Contrast esophagram studies are usually contraindicated in animals with megaesophagus because of the high risk of aspiration pneumonia. A water-soluble iodinated contrast agent is preferred if esophageal perforation is suspected.

Esophagoscopy can be useful for the diagnosis of esophageal neoplasia, esophagitis, strictures, and perforation. This minimally invasive procedure allows the direct visualization of the esophageal mucosa and lumen and can be used to obtain biopsies, retrieve foreign bodies, balloon esophageal strictures or deploy esophageal stents.

Specific Esophageal Disorders

Megaesophagus

Congenital Megaesophagus

Megaesophagus is a condition characterized by diffuse esophageal dilation and decreased or absent esophageal motility. Megaesophagus may be a congenital or acquired (adult-onset) disease. A familial predisposition has been identified in several breeds including the Great Dane, German shepherd, Irish setter, Chinese shar-pei, Newfoundland, miniature Schnauzer, Labrador retriever and fox terrier breeds, as well as Siamese cats. In the wirehaired fox terrier, congenital megaesophagus is inherited as a simple autosomal-recessive trait, while in miniature Schnauzers it is transmitted as either a simple autosomal-recessive or dominant trait. Affected dogs usually start having clinical signs of regurgitation at or shortly after weaning.

The main differential diagnosis that should be considered in young dogs with regurgitation at the time of weaning is a congenital vascular ring anomaly. Plain radiographs are usually sufficient to differentiate between these disorders, although contrast studies are necessary in some cases.

The etiopathogenesis of congenital megaesophagus is unclear. Esophageal motility and nerve stimulation studies in dogs with megaesophagus indicate a defect in the afferent neural pathway, while the efferent neural pathway appears to be intact.

The prognosis for congenital megaesophagus is guarded to poor. Some dogs can be managed for months to years while others rapidly succumb due to uncontrolled regurgitation and aspiration pneumonia. Breeding of affected patients is not recommended. Treatment details for megaesophagus are discussed below.

Acquired Megaesophagus

Acquired megaesophagus can occur in any breed or age. Acquired megaesophagus may be primary (idiopathic) or secondary to multiple disorders, particularly diseases causing neuromuscular dysfunction.

The most common cause of secondary acquired megaesophagus in dogs is myasthenia gravis(MG). MG may be congenital (rare) or acquired. Acquired MG is an autoimmune disorder characterized by autoantibodies directed against the acetylcholine (Ach) receptors of skeletal neuromuscular junctions. These antibodies bind to the Ach receptors, reducing the number of receptors available for normal neuromuscular transmission. When acetylcholine is released from presynaptic vesicles at the nerve terminal, it is unable to bind to the receptors on the postsynaptic muscle fiber membrane. Depending on

the clinical presentation, MG can be classified as generalized, focal or acute fulminant. Generalized MG usually presents with generalized muscular weakness that worsens after exercise; megaesophagus has been well documented in these cases. Acute fulminant MG usually presents as a flaccid tetraparesis and acute respiratory distress.

The gold standard for the diagnosis of acquired MG is the detection of serum autoantibodies directed against Ach receptors. An Ach receptor antibody concentration of ≥0.6 nmol/L is considered positive. Approximately 2% of dogs with generalized MG, however, are negative for Ach receptor antibodies. A presumptive diagnosis can be made by a positive response to an ultra short-acting anticholinesterase agent (Tensilon test: edrophonium chloride IV at 0.1–0.2 mg/kg). This test can lead to a cholinergic crisis in nonmyasthenic patients or if accidentally overdosed, producing bronchoconstriction, bradycardia, salivation, lacrimation, retching, diarrhea, and vomiting. In this situation, atropine sulfate should be administered IV (0.02–0.04 mg/kg IV). Dogs with focal or generalized MG are treated with anticholinesterase agents such as pyridostigmine bromide (1–3 mg/kg PO q8–12 h or 0.01–0.03 mg/kg/h as a constant rate IV infusion) or neostigmine bromide (2 mg/kg/day PO in divided doses to effect or 0.04 mg/kg IM q6h).

Focal MG usually affects the motor fibers of cranial nerves innervating the larynx and pharynx. Megaesophagus associated with focal MG can be misdiagnosed as idiopathic acquired megaesophagus, and assessment of anticholinesterase antibody titers is strongly recommended in the work-up of the great majority of dogs with esophageal motility disorders.

Endocrine diseases such as hypoadrenocorticism and hypothyroidism have historically been associated with megaesophagus. Megaesophagus has been reported in dogs with primary, secondary and atypical hypoadrenocorticism. Proposed causes include altered muscle carbohydrate metabolism due to a lack of physiologic cortisol production, and the effects of abnormal sodium and potassium concentrations on membrane polarization. An adrenocorticotropic hormone (ACTH) stimulation test is necessary for the diagnosis. Although a definitive association between hypothyroidism and megaesophagus has not been proven, there are reports of dogs with hypothyroidism and megaesophagus. There is also an association between MG and hypothyroidism and thyroid function should be evaluated concurrently with diagnostic testing for MG.

Megaesophagus has also been described as a paraneoplastic syndrome. According to one study, megaesophagus was present in 40% of dogs with thymoma. Thymoma also has been associated with MG in dogs and cats. Complete thymus resection can result in resolution of megaesophagus. However, nonresectable thymoma in dogs with megaesophagus has a poor prognosis.

Idiopathic megaesophagus is the most common cause of megaesophagus in dogs. It usually affects large-breed dogs between 5 to 12 years old. The etiopathogenesis is unknown. There is no sex or breed predilection. Many dogs affected with idiopathic megaesophagus have a very dilated and aperistaltic esophagus.

Treatment of Megaesophagus

The treatment of dogs with idiopathic megaesophagus is entirely supportive and symptomatic, while animals with acquired megaesophagus should be treated specifically for the underlying disease. Thoracic radiographs are recommended to monitor and document esophageal dilation and evaluate for aspiration pneumonia.

Frequent feeding of small, high-calorie meals with the patient in a cranially elevated position will help meet nutritional requirements and reduce regurgitation. Upright feeding, holding the dog in vertical position, or using "Bailey" chairs are often effective strategies for controlling regurgitation in many dogs. Very weak patients or those in whom the regurgitation is uncontrollable might benefit from placement of a gastrostomy tube. The optimal food consistency depends on the patient and should be tailored to each individual dog.

The most common complications of megaesophagus are aspiration pneumonia and esophagitis. Aspiration pneumonia should be treated using broad-spectrum antibiotics. Culture and sensitivity testing of a transtracheal wash or bronchoalveolar lavage sample is useful to guide antibiotic choice. Esophagitis can also worsen megaesophagus and lead to strictures.

The use of prokinetic medications in dogs with megaesophagus has not been shown to have any benefit. Metoclopramide and cisapride exert their actions on smooth muscle and do not have any action on skeletal muscle, thus they are not useful in dogs with esophageal hypomotility. These medications may also increase the tone of the lower esophageal sphincter, decreasing esophageal emptying. In cases of esophageal reflux, however, these medications might be useful because they decrease the episodes of reflux and esophagitis. Bethanecol binds and stimulates cholinergic (muscarinic) receptors and may be helpful in stimulating esophageal propagating contractions.

Prognosis for Animals with Megaesophagus

The prognosis for patients with megaesophagus depends on the underlying disease and the presence of secondary complications such as aspiration pneumonia. In dogs with MG, resolution of megaesophagus can occur within

the first six months. Dogs with congenital megaesophagus have a more guarded prognosis. Some dogs can recover and acquire normal esophageal function if dietary management is begun early. The prognosis for idiopathic megaesophagus in adult dogs is poor and spontaneous recovery rarely occurs. Most dogs eventually die due to aspiration pneumonia.

Esophagitis

Esophagitis can be defined as chronic or acute inflammation of the esophageal mucosa. Esophagitis can be caused by a chemical or caustic injury (acid, drug-induced), esophageal foreign body, gastroesophageal reflux, radiation, or food retention secondary to megaesophagus. The degree of inflammation can be mild, with lesions localized in the mucosa, or severe, affecting the muscularis layer.

The administration of oxytetracycline and doxycycline has been associated with esophagitis in cats. Other orally administered medications including clindamycin, nonsteroidal antiinflammatory drugs, and bisphosphonates can also produce esophagitis.

Esophageal foreign bodies can cause severe esophageal inflammation in dogs and cats. They are usually located in the thoracic inlet, at the base of the heart or the lower esophageal sphincter.

Gastroesophageal reflux is a consequence of movement of gastric content into the esophagus. Exposure of the mucosa to the refluxed gastric acid, digestive enzymes, and bile acids can rapidly induce inflammation. Gastroesophageal reflux has been associated with anesthesia, hiatal hernias, neoplasia affecting the distal esophagus or lower esophageal sphincter, and delayed gastric emptying. Anesthesia is a known risk factor for gastroesophageal reflux. The duration of the anesthesia and preanesthetic agents used appear to influence the risk of gastroesophageal reflux. Medications that decrease the lower esophageal tone, such as thiopentone, propofol, morphine, xylazine, and atropine, can increase the risk of reflux. Prolonged fasting (24 hours) before anesthesia is associated with a higher risk of gastroesophageal reflux.

Clinical signs of esophagitis include decreased appetite, odynophagia (painful swallowing) or dysphagia, ptyalism, coughing, and regurgitation. Some animals only show subtle signs with decreased appetite and increased salivation. Clinical signs consistent with esophagitis 1–4 days after an anesthetic procedure are suggestive of esophageal reflux, and should be managed aggressively to decrease the risk of esophageal stricture formation. Dogs with chronic vomiting should be monitored closely. The final diagnosis of esophagitis is done by direct visualization of the esophageal mucosa via endoscopy. Focal or diffuse mucosal erythema with increased friability is often seen.

Treatment

Treatment of esophagitis is focused on the elimination of the underlying cause and allowing inflammation to resolve. Esophageal foreign objects need to be treated as an emergency and retrieved as soon as possible. Administration of drugs associated with esophagitis (doxycycline, oxytetracycline, clindamycin) should be discontinued. The main cornerstones of the treatment of esophagitis are acid suppression, mucosal protection via sucralfate administration, and supportive care. In some cases, supportive care may require interventions to provide nutritional support, such as percutaneous endoscopic gastrostomy (PEG) tube placement. The use of prokinetic medications is controversial, but is recommended when reflux esophagitis is suspected.

The most common acid suppressants used in dogs and cats are proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H_2-blockers). Proton pump inhibitors covalently bind to and irreversibly inhibit the H^+-K^+-ATPase proton pumps. PPI medications are available in both oral (omeprazole) and parenteral (pantoprazole, esomeprazole, lansoprazole) formulations. H_2-blockers act by blocking the action of histamine on parietal cells in the gastric mucosa, decreasing the production of acid by these cells. PPIs have proven to be more effective at raising intragastric pH than histamine-2 receptor antagonists. Administration of PPIs twice daily (0.7–1 mg/kg q12h) rather than once daily is recommended to effectively increase the intragastric pH in both dogs and cats. The combination of PPIs and H_2-blockers is not superior to the administration of a PPI alone.

Sucralfate is an aluminum salt of a sulfated disaccharide that, when activated in an acidic environment, forms a paste-like material that binds to and protects exposed submucosa and the mucosa from acid exposure. Sucralfate is generally administered as a slurry 3–4 times per day, separate from food and other medications.

Prokinetic medications such as metoclopramide and cisapride are useful to increase the tone of the lower esophageal sphincter and enhance gastric motility. In cases of gastroesophageal reflux, the use of metoclopramide (2 mg/kg q24h as a constant rate infusion [CRI]) or cisapride (0.5 mg/kg q8h PO) is recommended.

Anesthesia is the main cause of gastroesophageal reflux and esophagitis in dogs and cats. The position during anesthesia has not been identified as a risk factor. The frequency of reflux is greatest in abdominal procedures. When acid reflux is confirmed, esophageal lavage

with water, followed by 20 mL of 4.2% bicarbonate, is recommended.

In severe cases of esophagitis, placement of a gastrostomy tube may be indicated to ensure adequate caloric intake, while also reducing esophageal pain and further irritation of the esophageal mucosa.

Esophageal Strictures

Esophageal strictures arise as the result of severe esophageal inflammation affecting the muscularis layer. During the healing process of these lesions, intramural fibrous contraction may occur, leading to a band of scar tissue that produces a circumferential narrowing of the esophageal lumen.

The main clinical signs associated with esophageal strictures are regurgitation, weight loss, coughing, salivation, anorexia, odynophagia, and vomiting. Benign esophageal strictures are usually a consequence of severe esophagitis due to esophageal reflux secondary to anesthesia or foreign bodies. Malignant esophageal strictures are associated with neoplasia. Strictures secondary to gastroesophageal reflux are often located between the thoracic inlet and the diaphragm, whereas strictures cranial to the thoracic inlet are usually associated with foreign body injuries.

Clinical signs and the history of the patient will typically suggest the presence of an esophageal stricture. Barium contrast studies, using conventional radiography or fluoroscopy, are useful diagnostic tools. Endoscopic visualization of esophageal stricture is the most reliable method of diagnosis, and has the advantage that treatment can be immediately initiated. Circumferential narrowing of the esophagus, with intraluminal fibrous tissue bands, is usually visualized.

Treatment

There are two preferred techniques typically used for the treatment of benign esophageal strictures: bougienage and ballooning.

Bougienage involves the use of rounded, rigid or semi-rigid instruments that are pushed through the esophagus to progressively stretch the stricture. Different sizes are used serially to gradually open the stricture. The bougienage technique applies both radial and shearing forces to the fibrous tissue at the site of the stricture. Wire-guided bougienage appears to be safe and is commonly associated with a good outcome.

Esophageal ballooning is performed by passing an inflatable balloon into the stricture. The balloon dilates and becomes rigid when inflated, applying a radial force to the stricture. The balloons are positioned into the lumen using endoscopy or fluoroscopy guidance. Balloon dilation does not apply shearing forces to the stricture tissue.

Esophageal ballooning and bougienage are reportedly equally safe and effective. The number of repetitions of the dilation necessary varies between patient (with most requiring 1–4 sessions); both methods have success rates of 70–88%. The interval between dilation attempts is usually 7–10 days. Both methods have been associated with complications, including mucosal tearing, hemorrhage, and esophageal perforation. When dilating an esophageal stricture, the aim is to return the patient to normal or at least manageable swallowing function that will allow sufficient nutritional intake. Dilation of the esophagus to the prestricture diameter is usually unnecessary, as many animals will show marked improvement in swallowing function with less than complete dilation of the esophagus.

During the series of dilation treatments, it is critical to aggressively manage esophagitis and prevent further damage from gastroesophageal reflux. Sucralfate suspensions, antacids (PPIs), and prokinetics (cisapride, metoclopramide) are generally indicated to protect the mucosa, reduce acid secretion and increase the tone of the lower esophageal sphincter. The use of systemic corticosteroids is controversial in these patients and further studies are necessary to evaluate their efficacy. Intralesional corticosteroid injection using triamcinolone can be used instead of systemic corticosteroids. Mitomycin-C can also be used topically at the stricture site, after dilation, to reduce collagen formation and the risk of recurrence of the stricture.

Esophageal Foreign Bodies

Esophageal foreign bodies are more common in dogs than in cats. The most common foreign bodies in dogs are bone fragments and rawhide type chews. In cats, string or linear foreign bodies attached to the base of the tongue are the most frequently encountered. Esophageal foreign bodies are most commonly found between the base of the heart and the diaphragm.

Clinical signs associated with foreign bodies include regurgitation, gagging, anorexia, and retching. The severity of esophageal damage depends on both the type and duration of the obstruction. Animals with esophageal perforation or aspiration pneumonia commonly present obtunded, febrile, anorectic, and with coughing.

Radiopaque foreign bodies can be diagnosed using thoracic radiographs. Thoracic radiographs are also useful to rule out the presence of aspiration pneumonia or esophageal perforation. Contrast radiography is useful to reveal radiolucent foreign material. Direct visualization

of the foreign body using esophagoscopy confirms the diagnosis, and is typically a prequel to treatment.

Treatment

Esophageal foreign bodies are considered medical emergencies. Esophagoscopy can be used to confirm and retrieve the foreign material using a variety of grasping instruments. Foreign bodies located close to the lower esophageal sphincter may be able to be pushed into the stomach. The long-term prognosis is usually excellent although short-term complications are common. The most common complications include esophagitis, aspiration pneumonia, and esophageal perforation (pneumothorax). Dogs with moderate and severe esophagitis are more prone to develop strictures.

When extensive esophageal perforation or necrosis is present, surgical removal is recommended. Esophageal surgery has been associated with a higher risk of esophageal dehiscence due to the segmental blood supply, the absence of a serosal layer and the movement and tension of the surgical site. The most common complications include dehiscence, pyothorax, and pleuritis. Transthoracic esophagostomy retrieval of foreign bodies has been associated with a survival rate of 77–93%.

Medical treatment for esophagitis is necessary after retrieving the foreign material. Recheck thoracic radiographs are useful to identify pneumothorax and/or pneumomediastinum secondary to esophageal perforation. Small esophageal perforations may be able to be medically managed with antibiotics and supportive care. In cases of severe esophageal injury, after retrieval of the foreign body, the placement of a gastrostomy tube should be considered.

Vascular Ring Anomalies

Vascular ring anomalies (VRAs) are congenital malformations of the embryonic aortic arches that affect both dogs and cats, producing esophageal constriction. Persistent right aortic arch (PRAA) is the most common anomaly in dogs and cats; this anomaly is associated with entrapment of the thoracic esophagus. PRAA occurs when the aorta develops from the embryonic right fourth aortic arch rather than the left fourth aortic arch. As a consequence, the esophagus is constricted between the ligamentum arteriosum (LA) dorsally, pulmonary artery on the left, aorta on the right, and the heart ventrally. Although VRAs have been reported in many breeds of dogs and cats, German shepherds, Irish setters and the Labrador retriever may be predisposed.

Regurgitation and failure to thrive are the most common clinical signs and are often present at the time of weaning. Thoracic radiographs often reveal dilation of the esophagus cranial to the base of the heart; plain radiography is also useful to screen for concurrent aspiration pneumonia. When plain radiographs are nondiagnostic, a barium contrast study may aid in visualization of esophageal obstruction at the base of the heart. Direct visualization of the esophageal mucosa via esophagoscopy may be useful to differentiate between extraluminal and intraluminal compression.

Treatment

Definitive treatment of PRAA involves surgical ligation and transection of the ligamentum arteriosum via thoracoscopy or thoracotomy. Esophageal hypomotility and regurgitation may persist after surgical ligation and the risk of this outcome increases with the duration of clinical signs. In a recent study evaluating the short- and long-term outcome following surgical repair of PRAA, the long-term outcome for dogs was excellent in 30%, good in 57%, and poor in 13%. Patients with persistent regurgitation after surgery are treated supportively as described for idiopathic megaesophagus, with upright feeding, small, frequent meals, and restraint of the animal in a "Bailey" type chair.

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53

Motility Disorders of the Alimentary Tract

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Gastrointestinal (GI) motility disorders are a diagnostic and therapeutic challenge. They can consist of delayed or accelerated transit times as well as impaired or inappropriate relaxation anywhere in the GI tract. Delayed transit is the most common form. This may be a primary localized neuromuscular disorder, part of a more generalized GI motility disturbance (e.g., dysautonomia) or secondary to systemic health problems (metabolic, toxic, inflammatory, neoplastic, obstructive, etc.).

Motility Disorders of the Esophagus

Physiology of Esophageal Motility

The esophagus acts as a simple tube for the transport of food from the oral cavity to the stomach. Between swallows, it is collapsed but can distend markedly to accommodate a food bolus. Structurally, it is of similar composition to the remainder of the GI tract, but it lacks a serosa. In dogs, the muscular layer (responsible for the motor function) is composed of two layers of striated muscles spiraling in oblique bundles and crossing each other at right angles. In cats, there is a transition zone from striated to smooth muscle at the level of the heart.

There are two sphincters: the upper esophageal sphincter (UES), consisting of the cricopharyngeus muscle, and the gastroesophageal sphincter (GES), which is a thickening of the esophageal muscle at the junction to the stomach.

Esophageal transport of a food bolus – as part of the complicated swallowing act – is under complete autonomic neuronal control. Efferent neurons from the nucleus ambiguous in the medulla oblongata innervate the striated muscle (dogs and cats) and the smooth muscle (cats) via the vagus nerve. Once the food bolus is voluntarily pushed caudally into the oropharynx, a complex reflex is instituted, that starts with cricopharyngeal relaxation. The food bolus is then passed through the UES into the cervical esophagus. Immediately thereafter, the UES closes, preventing material from entering the trachea or being pushed back into the pharynx. Continuous peristaltic contractions move the food aborally, where it passes through the relaxed GES (primary esophageal peristalsis). In a case where the first peristaltic wave is inadequate for complete transport, secondary esophageal peristalsis occurs, where local esophageal distension generates another peristaltic wave.

Clinical Signs of Esophageal Motility Disorders

The classic clinical sign of esophageal disease is regurgitation. Additional common complaints are dysphagia, hypersalivation, retching and gagging, odynophagia, and repeated swallowing attempts. Less common signs are anorexia and lethargy. Both dogs and cats can show signs of aspiration pneumonia (fever, tachypnea, coughing, dyspnea).

On physical examination, low body condition score/weight loss or poor growth might be apparent. Rarely, a dilated esophagus can be palpated in the cervical region. Bradycardia, loss of pupillary light reflexes, decreased tear production (demonstrated by a Schirmer tear test), dry mucous membranes, and constipation/diarrhea in combination with megaesophagus are indicative of a dysautonomia.

Causes of Esophageal Motility Disorders

In small animals, primary esophageal motor dysfunction is poorly defined and infrequently recognized, except for idiopathic megaesophagus and esophageal diverticula in dogs. A high prevalence of subclinical primary esophageal dysmotility has been reported in certain dog breeds

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(Chinese shar-pei, bouvier des Flandres) and in young dogs (up to 2 years of age). The reported prevalence of abnormal esophageal motility in cats is 0.05%.

Secondary esophageal dysmotility is seen in most animals with obstructive or inflammatory esophageal disease; these will not be covered in detail in this chapter (see Chapter 52). Obstructive disorders can be grouped into intraluminal (foreign body), intramural (neoplasia, granuloma, stricture) or extraluminal (vascular ring anomaly, mediastinal mass), whereas inflammation (esophagitis) is frequently due to gastroesophageal reflux disease (GERD).

Megaesophagus

Megaesophagus is defined as generalized esophageal dilation with hypo- or amotility and can be primary (idiopathic) or secondary (acquired). It has to be differentiated from localized esophageal dilation, which can be frequently observed proximal to obstructive disorders. However, early cases of megaesophagus might have only segmental dilation, which may become generalized with time. In addition, not all dogs with abnormal esophageal motility progress to megaesophagus.

Idiopathic megaesophagus may be congenital or acquired. In some dog breeds (Great Dane, German shepherd, Irish setter, golden retriever, Labrador retriever, greyhound, Newfoundland, shar-pei), a familial predisposition is reported, while in others (miniature schnauzers and fox terriers) an autosomal dominant inheritance trait has been discovered. In cats, megaesophagus is uncommon. The acquired adult-onset form is most commonly idiopathic (>70%) or secondary to other systemic disorders, especially those causing neuromuscular dysfunction.

The pathogenesis of megaesophagus in dogs is still poorly understood, but defects in afferent neural pathways have been suggested, while efferent neuromuscular pathways seem to be intact. Decreased motor responses of the UES and GES to intraluminal stimuli have been reported.

Ancillary diagnostic tests are performed in dogs with megaesophagus with the intent to detect an underlying cause (e.g., myasthenia gravis), as treatment of the underlying disorder might lead to complete resolution of esophageal dilation, and to identify co-morbidities such as aspiration pneumonia. Initial tests can include a complete blood count (CBC) and determination of C-reactive protein (or other acute phase proteins) as a measure of the severity of secondary inflammation/infection. Measurement of acetylcholine receptor antibody (AchRA) titer by an accredited laboratory can aid the diagnosis of myasthenia gravis and should be done in all dogs with megaesophagus. Focal myasthenia gravis occurs in the absence of muscle weakness and is the second most common cause (≈25% of cases) of acquired megaesophagus. Endocrinopathies such as hypoadrenocorticism and hypothyroidism have frequently been implicated as a cause of megaesophagus in the dog. However, the association of megaesophagus with hypoadrenocorticism is rare. In almost all dogs that simultaneously suffered from hypoadrenocorticism and megaesophagus, Na:K ratios were abnormally low. Consequently, an adrenocorticotropic hormone (ACTH) stimulation test is only indicated in these dogs if electrolyte abnormalities (hyponatremia and hyperkalemia with a Na:K ratio <27) are observed.

Other potential tests that could be considered in dogs with megaesophagus, on an individual basis, include blood lead concentrations (lead poisoning), edrophonium chloride challenge test (generalized myasthenia gravis) or electromyography in a dog with generalized muscle weakness (polyradiculoneuritis, polymyositis, etc.).

Diagnostic Tests to Assess Esophageal Motility

Survey radiographs do not assess esophageal motility, but can be informative regarding luminal obstructions, dilation/ diverticula, strictures, and megaesophagus.

The esophagus is not visible in its physiologic state as it has the same opacity as the surrounding soft tissue. A mildly air-filled esophagus or small "pockets" of air can be present due to physiologic transient dilation, aerophagia (anxiety, dyspnea) and during sedation/anesthesia. Both left and right lateral radiographic views might be necessary in some cases to diagnose esophageal dilation.

Megaesophagus is characterized radiographically via visualization of a dilated, enlarged, air-filled esophagus (sometimes also filled with fluid or ingesta). The trachea can show some ventral deviation. The caudodorsal thorax might appear hyperlucent.

If plain radiographs are inconclusive, contrast studies (esophagrams) can be helpful. They should not be performed if the cause of regurgitation is already clear on the plain radiographs. The use of barium sulfate in cases where perforation cannot be excluded/is suspected (pneumomediastinum) or where the risk of immediate regurgitation is high should be avoided. Ideally, contrast studies of the esophagus should be limited to the use of iodine-containing media.

Immediately after oral administration of contrast (10–20 mL/animal at a time), a few longitudinal parallel esophageal folds outlined by barium can be visible in the normal canine esophagus, while cats show additional transverse mucosal folds in the caudal third of the esophagus (so-called "herringbone" pattern). To assess subtle motility disorders limited to the passage of solid food,

contrast can be mixed with food and the radiographs can be repeated.

To diagnose functional cricopharyngeal and esophageal dysmotilities that do not lead to dilation (achalasia, cricopharyngeal bars), a sliding hiatal hernia (type I) or GERD, contrast-enhanced videofluoroscopic esophagography (fluoroscopy) is the imaging modality of choice, as it provides continuous, dynamic and real-time assessment of the entire swallowing process. Conscious animals are placed in lateral or sternal position. Neat liquid barium, barium paste, barium mixed with canned food (all administered via syringe) or barium-soaked kibble (in animals willing to eat) can be used. Three to five swallows are observed in real time with at least one followed all the way into the stomach.

Esophagoscopy is rarely useful to investigate functional dysphagia as esophageal motility cannot be assessed under general anesthesia, but it can be performed to remove esophageal foreign bodies, detect esophagitis/GERD, esophageal tumors or hiatal hernias. Esophageal mucosal biopsies can be useful in the diagnosis of GERD, esophagitis, and neoplasia, but can be difficult to retrieve due to the firmness of the mucosa and the difficulty in achieving an oblique or 90° angle.

Esophageal manometry allows assessment of the intraesophageal pressure generated by peristalsis and provides clinically important information on esophageal motor function. Recently, high-resolution impedance manometry has become the standard for the evaluation of esophageal function in humans. This technique has recently been used in dogs (Figure 53.1) and while technically demanding and limited to a research setting at the moment, it gives an overall highly informative assessment of esophageal motility.

Treatment of Esophageal Motility Disorders

Medical treatment of esophageal dysmotility in dogs qnd cats is typically unrewarding. Management of megaesophagus is directed towards treating the inciting cause (e.g., use of pyrido- or neostigmine in myasthenia gravis) and based on the optimization of feeding regimens. Feeding from an elevated position, sometimes aided by using specialized feeding chairs, and the attempt to avoid complications like aspiration pneumonia are the most important measures. The ideal type of food (kibbles, gruel, homogenized food, etc.) for individual patients has to be found in a "trial-and-error" fashion. If an underlying disease process is suspected, empirical treatment is often initiated until test results (e.g., AchRA titer) are available. Aspiration pneumonia has to be treated aggressively, usually with intravenous fluids and antibiotics, coupage, and potentially secretolytics. If esophagitis is suspected or proven, oral sucralfate suspension and proton pump inhibitors (to avoid GERD) should be prescribed.

Motility Disorders of the Stomach

Gastric motility is a highly coordinated process involving neuromuscular and hormonal signals and is triggered as a response to either the presence of food in the stomach or a range of different local (mechanical or functional) or systemic diseases. There are three separate types of gastric motility disorders: accelerated gastric emptying, retrograde transit (reflux), and delayed gastric emptying.

Physiology of Gastric Motility and Emptying

Functionally, the stomach can be divided into the proximal (consisting of cardia, fundus, first third of the corpus) and distal (distal two thirds of the corpus and antrum) compartments. The proximal compartment is responsible for the accommodation of food and liquids and characterized by slow tonic contractions. The distal compartment is characterized by phasic propagating contractions generated by pacemaker cells (interstitial cells of Cajal [ICC]) that lead to mechanical milling of gastric contents (called trituration) and their final expulsion through the pylorus. Pressure and amplitude of these contractions increase in an aboral direction.

Digestive motility resulting in gastric emptying occurs in three consecutive phases:

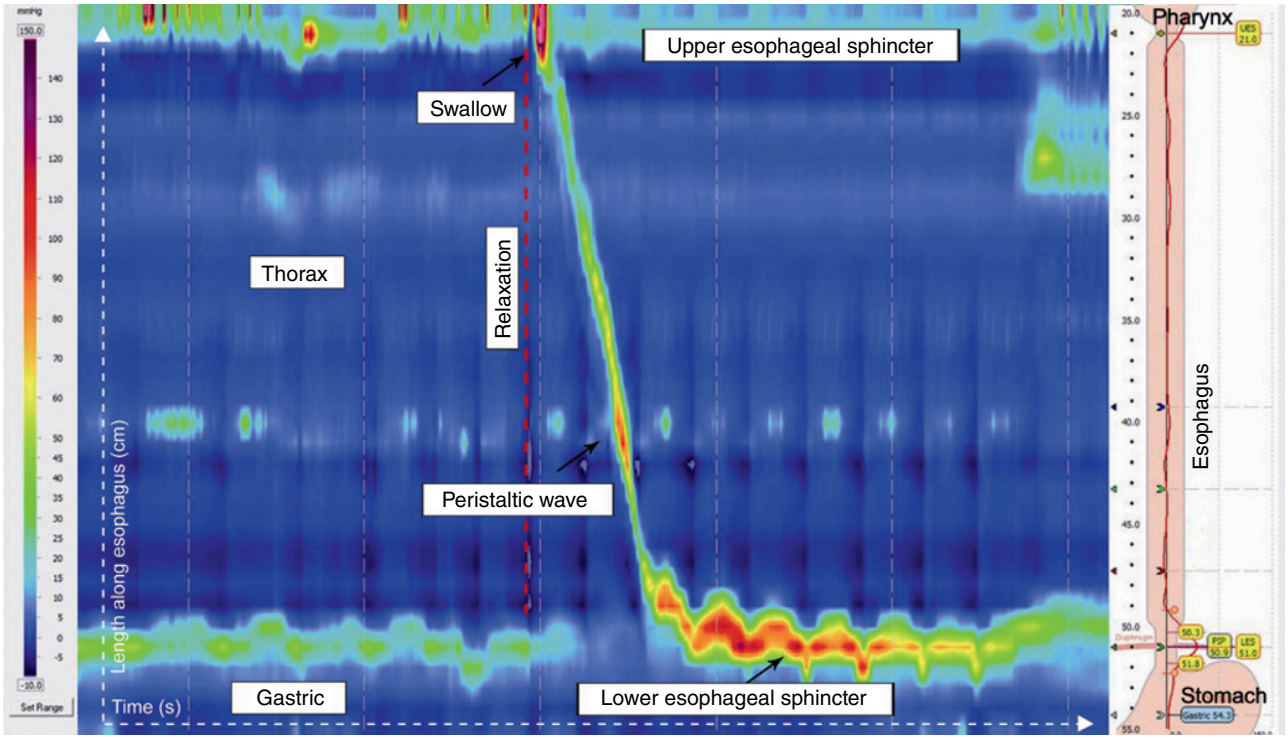
1) propulsion (proximal part of the antrum contracts)
2) emptying and mixing (pylorus opens partially and duodenal peristalsis is momentarily halted while particles up to 2 mm pass the pylorus)
3) retropulsion (larger particles are propelled back into the corpus).

Interdigestive motility occurs to empty nondigestible food particles/foreign bodies, swallowed saliva, and small amounts of mucus and cellular debris. In the dog, this motility pattern is called the migrating motor complex (MMC) and starts with intense contractile activity in an aboral direction ("clean sweep") followed by a period of relative quiescence and a short phase of irregular undirectional contractions. Interdigestive motility in the cat is uniquely associated with long fused migrating spike burst contractions interspersed with short periods of irregular activity.

Clinical Signs of Gastric Dysmotility

In dogs with delayed gastric emptying, clinical signs can include gastric distension and vomiting of undigested or partially digested food >8 h after feeding (when the stomach should be empty). In cats, the importance of gastric emptying disorders remains unclear. Clinical signs include anorexia, vomiting, regurgitation, and weight loss.

(a)



(b)



Figure 53.1 (a) Physiologic swallow pressure topography of a healthy dog extending from the pharynx to the stomach. The colors reflect the intensity of the pressures; red stands for high and blue for low pressure (color scale on the left). The upper and lower esophageal sphincters are clearly detectable as high-pressure zones. There is a relaxation of both sphincters following a swallow. (b) Dog with esophageal manometer catheter in place. *Source:* Courtesy of Jennifer Kempf and Peter Kook, Vetsuisse Faculty, University of Zurich, Switzerland.

Gastroesophageal reflux disease is detected more frequently in dogs than cats. It can occur spontaneously or be related to general anesthesia. In both species, it can result in ptyalism, retching, regurgitation or vomiting, pain when swallowing and dysphagia (see Esophageal Dysmotility, earlier). Occasionally, excessive grass eating and cough are also reported in dogs.

The frequency of duodenogastric reflux in dogs is unclear. However, it has been proposed to lead to bilious vomiting syndrome (BVS), which is characterized by vomiting of bile and mucus after a prolonged fasting period.

Accelerated gastric emptying is rarely a problem leading to clinical signs in dogs, but is hypothesized to be the cause of vomiting in hyperthyroid cats. Acute infectious or obstructive diseases of the gastrointestinal tract can also lead to secondary hyperperistalsis of the stomach, but hypoperistalsis, vomiting/retching, and diarrhea are more frequent presenting complaints.

Other signs of gastric dysmotility or its underlying causes can include anorexia, belching, pica, weight loss or abdominal pain. In animals with dysautonomia, gastric hypomotility is one of many problems due to denervation of the autonomous nervous system. Hence, other clinical signs typically associated with this disease, such as dry eyes and nose, mydriasis, regurgitation, and constipation, are often predominant.

Physical examination findings can range from no detectable abnormalities to the presence of an enlarged abdomen (gastric distension), decreased or increased bowel sounds, and nonspecific/cranial abdominal pain. Rarely, neuromuscular abnormalities may also be observed if severe metabolic or systemic derangements (electrolyte abnormalities, dysautonomia) are present.

Causes of Gastric Dysmotility

Delayed Gastric Emptying

Delayed gastric emptying is probably underdiagnosed in both dogs and cats, especially in cases where no obvious obstruction of gastric outflow is present. Mechanical obstructions (gastric neoplasia, hyperplasia, polyps, foreign material) are usually easy to diagnose based on history, physical examination and diagnostic imaging procedures and are not further discussed in this chapter. However, diagnosis of functional problems (due to either local or systemic disorders) is not as straightforward.

A number of primary causes of functional gastric stasis have been described in the dog, including infectious and/or inflammatory diseases, peptic ulcers, and following surgical procedures. Systemic disorders suspected to affect gastric motility include electrolyte disturbances (especially hypercalcemia, hyper- or hypokalemia), disorders of acid–base balance, septicemia, pancreatitis, peritonitis, systemic inflammatory response syndrome (SIRS), dysautonomia, and metabolic diseases such as diabetes mellitus

Gastric dilation-volvulus (GDV) in large and giant dog breeds has been speculated to be caused by delayed gastric emptying, but evidence for the influence of size or weight on gastric emptying times and the presence of gastric dysmotility in dogs with GDV is controversial.

Diseases of the large intestine (e.g., colitis, constipation) can potentially also delay gastric emptying via reflex mechanisms.

The clinical importance of gastric emptying disorders in the cat is unknown. There are a few case reports of delayed gastric emptying in cats with rare conditions such as pylorospasm, hyperplastic gastropathy, and dysautonomia. Delayed or dysfunctional gastric emptying is suspected in conjunction with conditions like diabetes mellitus, pancreatitis, and inflammatory bowel disease (IBD) but specific investigations into these diseases as causes of gastric dysmotility in cats are lacking.

Retrograde Transit

Gastroesophageal reflux disease and duodenogastric reflux are retrograde transit disorders. Neither of these conditions has been extensively investigated in small animals. GERD is more often associated with diseases of the esophagus or the distal esophageal sphincter, and occurs most commonly during or after general anesthesia.

Duodenogastric reflux can lead to BVS (also called fasting vomiting) in dogs. Clinical signs of BVS improve in most cases by changing the feeding regimen (frequent feeding of small meals) and administration of prokinetics and gastroprotectants. This suggests an underlying abnormality in gastrointestinal motility, but no further investigations have been performed to date. No reports exist of duodenogastric reflux in cats apart from its occurrence with experimental devascularization and ulceration of the stomach.

Accelerated Gastric Emptying

Accelerated gastric emptying (for example, in acute infectious or obstructive disease) is usually associated with hypermotility of the entire GI tract; hence diarrhea can be the predominant problem, or occur alongside other clinical signs. Isolated hypermotility of the stomach has not been reported in dogs.

Diagnostic Tests to Assess Gastric Motility and Emptying

Several methods have been used to assess gastric motility – especially gastric emptying times – in small animals. Their diagnostic usefulness and availability for the practitioner are summarized in Table 53.1.

Table 53.1 Methods to assess gastric emptying in small animals and their diagnostic usefulness and availability to the practitioner

Technique	Information gained	Availability in pets
Plain radiographs	+	+++
Contrast radiographs (barium)	++	+++
Contrast radiographs (BIPS)	+	++
Ultrasonography	+	++/+++
Endoscopy	(+)	++/+++
^{13}C-based breath tests	++	+ /++ (referral /research)
Blood tracers (paracetamol)	Unknown	+ (if reference method to measure paracetamol is available)
Scintigraphy	+++	+ (referral/research)
CT or MRI	–	++
Manometry	++	+ (referral/ research)
Wireless motility capsule	+++	+ (referral/ research)
Surface electrical resistance	(+)	– (research)

BIPS, barium-impregnated polyethylene spheres; CT, computed tomography; MRI, magnetic resonance imaging.

Diagnostic Imaging for Gastric Motility Disorders in Routine Veterinary Practice

Plain abdominal radiographs showing liquid or solid gastric contents after a fasting period of >6–8 hours in the dog and >4 hours in the cat should raise the suspicion of delayed gastric emptying. If no obvious cause can be identified, serial radiographic imaging after oral administration of contrast media (i.e., liquid barium sulfate, iodinated contrast) can be performed (for the full protocol see section on small intestinal dysmotility later).

This method only evaluates emptying of liquid contents, which is less relevant, and can appear normal even though emptying of solids is impaired. Liquids (including neat barium) should be emptied from the stomach within three hours in dogs and within 60 minutes in cats (50–70% of cats have an empty stomach at 15 and 30 minutes, respectively). Completion of gastric emptying when barium is mixed with food can be variable in both dogs and cats (4–16h), and barium can separate from the food, making this method unreliable to assess solid-phase gastric emptying in small animals.

Barium-impregnated polyethylene spheres (BIPS) were originally designed to mimic solid-phase gastric emptying and to detect GI obstructions. They are commercially available in two sizes (1.5 and 5 mm diameter), with the smaller theoretically being emptied with digestive contractions and the larger with interdigestive motility. Attempts have been made to assess gastric emptying times using BIPS in both dogs and cats, but the data are not reliable. In one study using dogs, the time to emptying of half the administered BIPS from the stomach was nearly twice as long as that of simultaneously administered, radiolabeled food. In cats, gastric emptying of 1.5 mm BIPS also did not parallel "true" gastric emptying of a solid radiolabeled meal, but rather assessed interdigestive motility. Therefore, interpretation of solid-phase gastric emptying with BIPS cannot be recommended in small animals.

Technologic advances have facilitated the availability and feasibility of using abdominal ultrasonography to assess gastric emptying. Even though gastric motility can be visualized with ultrasound and the frequency of antral contractions has been reported in healthy dogs (4–6/min during emptying), no standardized protocol to assess gastric emptying is available. Also, as this method is based on the estimated change in antral volume, it might not accurately reflect gastric emptying if antral contents are moved into the fundus by the antral contractions. This procedure requires a skilled operator and the administration of a test meal or liquid of a defined volume, which can be challenging in veterinary patients. At this stage, ultrasound cannot be recommended to assess gastric emptying in a routine setting.

Diagnostic Tests Currently Restricted to Referral Centers or Research Facilities

Radioscintigraphy is considered the gold standard method to assess gastric emptying and has been used in a number of studies to determine physiologic gastric emptying times and validate new tests. Due to the need for special facilities and equipment, this technique is not often applied in small animal patients. Most commonly, ^{99m}technetium bound to tracer substances to avoid GI absorption (i.e., albumin colloid) is used. "Dual isotope" methods where solid- and liquid-phase gastric emptying are assessed simultaneously (using both ^{99m}technetium

and ^{111}indium) have also been described. Typical gastric half-emptying times when using canned food are around 70 minutes in dogs and 2–4 hours in cats.

Magnetic resonance imaging (MRI) and computed tomography (CT) imaging have so far not been used in veterinary patients to assess gastric emptying, although these modalities have been used in human patients. One complicating factor might be the need for sedation or general anesthesia, which can influence GI motility. Some protocols for sedation have been evaluated regarding their influence on gastric emptying, but the results are inconsistent, especially in cats. In dogs, a combination of acepromazine and butorphanol was shown to significantly prolong GI tract emptying times and decrease motility.

Noninvasive methods to detect smooth muscle contractions based on measurement of changes in electrical resistance across the epigastric region after ingestion of a test meal using standard ECG electrodes have been assessed in dogs. Because of the sensitivity of these methods to artifacts induced by even slight body movements, their future application in dogs and cats is probably confined to research purposes.

Methods that might have potential to be used in a routine clinical setting involve plasma or breath tracers. The paracetamol (acetaminophen) absorption test has been described for assessment of liquid- and solid-phase gastric emptying. Plasma drug concentrations are measured in serial blood samples after ingestion of paracetamol in solution, and the rate of gastric emptying is related to the appearance of paracetamol in the blood, as it is poorly absorbed from the stomach but rapidly from the duodenum. However, this test has so far only been used in a research setting and not been validated against scintigraphy.

Breath tests have been studied comparatively well to assess gastric emptying in dogs and to a lesser degree in cats. These tests involve the ingestion of a stable ^{13}C-labeled substrate which is rapidly absorbed (e.g., octanoic acid or sodium acetate) and metabolized to $^{13}CO_2$, which is then detectable in exhaled breath. The test protocol is simple, labelled tracers are comparably cheap and no special equipment or expertise is required. Breath samples can be collected from animals with a facemask, which does not involve excessive restraint. Samples can be stored for up to 60 days in sealed containers and can be sent to the laboratory for analysis, where the ^{13}C:^{12}C ratio is determined by infrared or mass spectrometry. From these data plotted against time, gastric emptying times and coefficients can be calculated. Normal gastric half-emptying times determined by breath test are around 2.7–3.4 hours in dogs and four hours in cats. ^{13}C-breath tests show acceptable to good correlation to scintigraphy and ultrasonography, respectively, in dogs and good correlation compared to scintigraphy in cats.

Treatment of Gastric Dysmotility

No guidelines for the appropriate indication, combination, and duration of motility-modifying therapies for gastric emptying disorders are available. Due to the diagnostic challenges discussed above, correct assessment of most gastric motility disorders or any therapeutic effect is difficult. It is important to investigate, diagnose, and treat any underlying disease leading to dysmotility before motility-modifying drugs are administered (Table 53.2).

Motility Disorders of the Small Intestine

Small intestinal (SI) motility ensures the efficient absorption of nutrients (mixing of chyme with digestive enzymes, optimal contact of ingesta with the intestinal mucosa) and orderly aboral movement of content, including indigestible residues. Motility is also critical in preventing bacterial translocation, which is achieved by constant net aboral flow of luminal contents and the unidirectional "valve" function of the ileocecal junction, preventing backflow of cecal contents.

Physiology of Small Intestinal Motility

Similar to gastric motility, physiologic motility of the SI in dogs consists of digestive contractions (uncoordinated circular segmentation and highly coordinated propulsive peristalsis) and interdigestive motility (interdigestive migrating motility complexes [IDMMCs]). In cats, IDMMCs do not exist; instead, they show migrating spike complexes that are less vigorous than the canine counterpart.

Dogs have been extensively used to understand the physiology of intestinal motility, the importance of neurotransmitters, hormones, and other polypeptides and the effect of different dietary components on GI transit times. Very little of the information gained from experimental studies in dogs can be directly translated into veterinary practice.

There is evidence for breed and/or size differences in GI transit times in dogs, with larger breeds showing longer transit times compared to miniature breeds. This might be partially due to the relative size of the GI tract compared to body weights: the GI tract of dogs >60 kg comprises 2.8% of their total body weight, compared to 7% in small-breed dogs (<5 kg). Hence, breed and age characteristics must be taken into account when assessing SI or total GI transit times.

Clinical Signs of Hypo- and Hypermotility of the Small Intestine

Clinical signs of small intestinal dysmotility can be variable, and heavily depend on the underlying cause. Assessing the animal's signalment and taking a thorough history including any drug administration, potential for accidental ingestion of medication(s), toxins or foreign material, vaccination status, contact with other animals, recent surgical procedures, etc. can help to initially classify the possible problem.

Local diseases (within the abdominal cavity or the GI tract) are more likely to cause clinical signs obviously associated with intraabdominal organs, ileus or GI obstruction (abdominal pain, vomiting, diarrhea, but also anorexia, constipation) whereas systemic diseases can present with a variety of signs not necessarily immediately associated with the GI tract (e.g., mydriasis, dry nose and eyes, and prolapse of the third eyelid in dysautonomia or generalized neuromuscular signs in muscular dystrophy).

Physical examination in patients with signs of GI dysmotility can be variable and depend on the underlying problem. Signs can be unspecific (lethargy, poor body condition), point towards a local intraabdominal process (nausea, abdominal pain, distension, mass, fluid-filled intestines) or be suggestive of a more generalized systemic problem (generalized weakness, neurologic abnormalities). Depending on the severity of fluid losses through vomiting and/or diarrhea, clinical signs can also be dominated by dehydration or hypovolemia (circulatory shock) or even SIRS.

Diseases Associated with Dysmotility of the Small Intestine

Most reports regarding SI motility focus on functional or mechanical GI ileus. Ileus is defined as the inhibition of propulsive bowel activity, irrespective of the pathogenic mechanism.

In small animals, SI ileus due to a primary (systemic or local) neuropathy or neuromuscular disease is much less common than secondary ileus, for which the causes are multiple.

Dysautonomia and Other Neuromuscular Diseases

Dysautonomia is a generalized neuropathy first described in cats in the United Kingdom. Subsequently, this disease has been documented worldwide in dogs and cats. It is characterized by generalized autonomic dysfunction with megaesophagus/esophageal hypomotility, gastric and small intestinal distension/hypomotility, and urinary bladder distension. Degenerative lesions are found in autonomic ganglia, the spinal cord and axons, but the cause for these changes is unknown. Diagnosis is based on typical clinical signs, ophthalmic pilocarpine test and (postmortem) histopathology. Supportive care (with or without chronic topical piloacarpine) is the only treatment option. Prognosis is grave in most cases.

Muscular dystrophy has been described in the golden retriever (X-linked genetic disorder), rarely other dog breeds and cats, and is primarily characterized by progressive muscular weakness. It is typically caused by mutations in the dystrophin gene responsible for muscle structure and metabolism. Affected dogs and cats show hypertrophy of skeletal musculature, tongue, diaphragm, esophagus and sartorius muscle and atrophy of others. Clinical signs apart from muscle weakness and tremor include dysphagia, gastroparesis, abdominal pain, and intestinal distension. In one postmortem canine study, petechial hemorrhages, ecchymosis, and ulceration of the gastric mucosa and generally dilated intestinal loops were described, which was suggested to be indicative of decreased intestinal transit. Most dogs die of cardiac or respiratory failure within 8–9 months.

One case of visceral myopathy in a 6-month-old domestic shorthair kitten with a six-day history of anorexia, vomiting, and diarrhea has been reported. Severely dilated loops of hypomotile intestine were found and 20 cm of jejunum was resected. On histopathology, the distal jejunum showed a markedly atrophic longitudinal muscle layer with focal degeneration, calcification, loss of myocytes, and replacement by fibroblasts. The cat was alive and doing well 20 months after surgery.

Postoperative Ileus and Short Bowel Syndrome

Postoperative ileus, defined as "ileus that develops following abdominal surgery, typically resolving spontaneously with 2–3 days," is more frequent in humans than dogs and has not been reported in cats. Laparotomy and manipulation of the viscera are the main postulated etiologies but other factors, such as anesthetic agents or postoperative opioid administration, can contribute. Diagnosis can be based on clinical signs such as nausea, vomiting, intestinal distension and abdominal pain and via the exclusion of other causes of functional ileus (e.g., metabolic disorders, renal injury, septic peritonitis, pancreatitis, obstruction) postoperatively. Treatment consists of intermittent orogastric or permanent nasogastric tube placement to empty the stomach of excess fluid and gas, early postoperative ("trickle") feeding, as this might stimulate coordinated propulsive activity of the GI tract, and the administration of prokinetics. Prognosis is generally good to excellent.

Short bowel syndrome is defined as malabsorption due to insufficient intestinal surface area to an extent that fluid and nutrients to sustain life cannot be absorbed without specific nutritional support. There is evidence of

dysmotility of the remaining parts of the GI tract, with reduction of slow waves and disappearance of interdigestive motility. Clinical signs usually consist of watery diarrhea, steatorrhea, polyphagia, and weight loss. Total parenteral nutrition and aggressive medical management are often necessary in the early postoperative period, until oral feeding can counterbalance the nutritional needs. Stabilization of intestinal function should start within 1–3 months after surgery. Complete recovery occurs within 3–12 months, but depends on the extent of surgical removal of intestinal segments, with early reports demonstrating a poor prognosis in some cases with massive resections (74–88%).

Intestinal Pseudoobstruction

Intestinal pseudoobstruction or functional paralytic ileus is characterized by the presence of chronic intestinal dilation and dys- or amotility in the absence of mechanical obstruction. Only 12 cases of chronic intestinal pseudoobstruction have been reported in small animals (10 dogs and two cats) that showed clinical signs of chronic intestinal disease (anorexia, intermittent vomiting, diarrhea). Diagnosis was based on abdominal imaging with radiographs showing generalized intestinal dilation but no evidence of mechanical obstruction. Histopathology showed some recurrent common features in dogs such as atrophy or complete loss of smooth muscle fibers (n = 10), moderate to severe lymphoplasmacytic or mixed inflammation of the muscular layers (n = 7) with predominantly T cells being present (n = 4), and varying degrees of fibrosis/sclerosis (n = 6). In one dog, severely hyperplastic smooth muscle of the lamina propria and thickening of the muscularis mucosae were reported. In cats, the histologic picture was somewhat different: even though muscle atrophy was present, this was true only for the longitudinal muscle layers in certain segments of the jejunum in one cat. Seven out of the 10 dogs were euthanized due to progressive disease within days to five weeks after diagnosis.

Secondary Small Intestinal Hypomotility

Dogs and cats frequently suffer from obstructive intestinal diseases (foreign bodies, bezoars, neoplasia, volvulus), hence these conditions – together with neoplasia and intussusceptions – should always be considered as potential cause of dysmotility.

Few large-scale reports examining clinical abnormalities, causes, prognostic factors, and outcome in small animals with mechanical ileus are available. Of 704 examined cases, the average age was 4 years for dogs and 3 years for cats, with 60% being male. Mean duration of illness before presentation was four days and most common symptoms included inappetence, vomiting, lack of defecation, and abdominal pain. Mechanical ileus due to a solitary foreign body obstruction (plastic balls, stones, textiles) was the most common cause (69 cats and 338 dogs) followed by a linear foreign body (35 cats, 43 dogs) and neoplasia (24 cats, 195 dogs). Less common causes were intussusception, ileal obstipation, intraabdominal inflammatory or neoplastic adhesions, volvulus, incarcerations of intestinal loops, idiopathic intestinal paralysis, intestinal diverticula, and parasitic infections.

Diagnosis (history of foreign body ingestion, physical examination revealing abnormal intestinal palpation, diagnostic imaging confirming the suspicion of obstruction/ileus) is usually straightforward and the optimum treatment depends on the localization, size, material or underlying cause (i.e., neoplastic) of the obstruction. In most cases (>90%), surgical intervention is necessary. Long-term-survival can be achieved in >80% of patients. A longer duration of clinical signs, presence of a linear foreign body (as opposed to a discrete one), multiple surgical procedures/incisions of the intestine and intestinal perforation have been associated with increased mortality, whereas neither the degree of obstruction (partial or complete) nor the location of the foreign body had an effect on survival.

Obstruction due to neoplasia carries a much graver prognosis, with median survival times of six months for dogs and seven days for cats.

Intussusception is frequently found in young animals and often associated with parvoviral enteritis or other forms of acute gastroenteritis. There is some evidence for a breed predisposition in the German shepherd dog and pure-breed/pedigree cats. Prognosis is good if surgical reposition or resection is successful.

Functional SI dysmotility can be secondary to any type of infection or inflammation of the GI tract or within the abdominal cavity. Both hypo- and hyperperistalsis can occur, but reports of hyperperistalsis are scarce.

Parvoviral enteritis is the classic example of functional ileus secondary to infection. Generalized atony of the intestinal tract with distended and fluid-filled intestinal loops is a frequent finding on ultrasonography (75%) and weak peristaltic contractions indicative of functional ileus were observed in most of the remaining cases.

Sepsis or other serious medical illnesses requiring hospitalization in the intensive care unit (ICU) are known to be associated with gastrointestinal dysfunction in people. Both gastric and small intestinal motility is delayed in human ICU patients, which may lead to intolerance of enteral nutrition and increased risk of aspiration. Additionally, acute stress-induced gastropathy and ischemic colitis (both associated with risk of hemorrhage) is a common finding in human ICU patients. In the authors' experience, similar syndromes and complications also exist in small animals admitted to the ICU. We routinely and regularly assess the grade of gastric

filling in our ICU patients (especially patients with sepsis, SIRS, on mechanical ventilation, and those with increased risk of aspiration pneumonia) semiquantitatively via ultrasonography. If there is sufficient suspicion of GI hypomotility (gastric distension), prokinetic drugs like prucalopride or erythromycin are administered early. If oral medication is not tolerated, rectal administration can be tried. Even though the authors subjectively think this type of management decreases the risk of aspiration pneumonia and other complications, there is at this time no objective evidence that these interventions influence outcome of small animal ICU patients.

Acute pancreatitis causes substantial damage to the GI tract in people and rodent models. Usually, this is associated with acute necrosis, ischemia, and bleeding, but varying degrees of dysmotility have also been documented, likely due to cytokines being produced as part of the local inflammatory process. In dogs, the typical clinical signs associated with acute pancreatitis (vomiting) and the severity of abdominal inflammation in some patients suggest that GI dysmotility or ileus is commonly present. However, no data regarding GI dysmotility in pancreatitis in small animals are available.

There is some evidence that both acute kidney injury (e.g., in leptospirosis) and chronic kidney disease have an inhibitory function on orderly intestinal motility. In other conditions, GI dysmotility is suspected but not proven. One example is diabetes mellitus, where altered levels of neuropeptides have been documented in experimental animals. However, even in humans, the exact mechanism for small intestinal dysmotility in this endocrinopathy is not well understood. So far, no consistent correlation between changes in enteric neurotransmitters, numbers of ICCs (decreased markedly in one neuroanatomic human case report) and manometric or transit observations has been detected.

It is likely that (gastro)intestinal dysmotility is also present in other chronic conditions such as IBD, canine idiopathic large bowel diarrhea (CILBD), hepatitis/hepatopathies, etc. Unfortunately, no study investigating GI motility in these conditions in dogs and cats is available.

Iatrogenic and Toxic Causes of Gastrointestinal Ileus

Intestinal dysfunction is a common side-effect when opioid mu- and delta-agonists are administered as analgesics. Most commonly, constipation and vomiting are observed. This can occur immediately after the first dose and persist for the duration of therapy. In most cases, discontinuation of opioid treatment is sufficient to improve intestinal function. Occasionally, laxatives and other therapies may be used additionally to treat constipation.

A variety of toxins (e.g., mercury, thallium, lead), pharmaceuticals (antibiotics like lasalocid, nitrofurantoin, salinomycin), pesticides (e.g., organophosphates), organic solvents and other chemicals (e.g., acrylamide, hexacarbons) have been reported to cause peripheral neuropathies, which might include ileus or other forms of dysmotility of the GI tract (i.e., megaesophagus, etc.) although these are infrequently seen and poorly documented.

Diagnostic Tests to Assess Small Intestinal Motility or Transit Times

The outcome of SI motor activity depends on the patterning of contractions in both space and time; that is, where and when do the contractions occur with respect to each other? Methods to assess these relationships must address substantial technical challenges to gather functionally relevant information.

Diagnostic Imaging Procedures for Small Intestinal Transit Studies

Contrast studies of the SI are the most commonly used method to assess transit time or to search for intestinal obstruction in small animals. Neat liquid barium sulfate, ionic or nonionic organic iodine contrast media or, less frequently, contrast mixed with semisolid food is administered orally. The recommended dosage for liquid barium is 6–16 mL/kg body weight, with the high end of the dose range for cats and small dogs and the lower end for large dogs. The protocol for performing a contrast study of the GI tract in dogs and cats is summarized in Box 53.1. Usually, the final radiograph is taken after 12 hours to check the complete gastric and SI evacuation of contrast.

Barium-impregnated polyethylene spheres (see above) have also been used for SI transit studies. The sensitivity and specificity of this method, however, is low.

Contrast fluoroscopy is used in human medicine to detect mucosal disease and stenoses that may induce secondary changes in motility, transit, and absorption. However, this technique is insensitive for the direct detection of abnormal transit times. Observation times are limited (radiation exposure) and once the majority of contrast has entered the small intestine, overlying loops of bowel hinder the interpretation. Fluoroscopy has not been reported for assessment of small bowel transit in small animals.

Ultrasonographic assessment of small intestinal motility is challenging due to observer variability, interference from intraluminal gas and the difficulty of finding objective measures to assess contractions. Even though two studies found that Doppler ultrasound techniques (pulsed-wave and duplex Doppler, respectively) allow graphic visualization and qualitative and quantitative

Box 53.1 Guidelines for performing a contrast passage of the gastrointestinal tract

Preparation	24 h fast or immediately if foreign body or perforation is suspected No sedation or general anesthesia
Type of contrast media	1) Liquid barium sulfate (used at a concentration of 30% weight/volume, which may require dilution. Higher concentrations are too opaque, especially with digital systems) • Preferred option 2) Water-soluble iodine-containing contrast (diluted 1 part to 2–3 parts water) • Indicated if rupture of parts of the alimentary tract cannot be excluded or if endoscopy is necessary afterwards • As these media are hypertonic, they osmotically attract water to the gastrointestinal lumen which can exacerbate dehydration and leads to dilution of contrast 3) Mixture of 1. or 2. with food • Does not always correlate with solid-phase transit time (contrast can separate from food) • Admixed food particles cannot always be distinguished from pathologic filling defects of the gastrointestinal tube
Dosage of contrast media	Either 10–12 mL/kg BM or Medium-sized to large dog: 5–7 mL/kg BM Small dog and cat: 10–15 mL/kg BM • Administer via syringe or gastric tube if necessary • The stomach has to considerably fill with contrast media • There should not be an interruption of visualization/filling of the entire gastrointestinal tract, as this might cause false interpretation of radiographs
Timing of radiographs (always both lateral and ventrodorsal views)	Dog • Immediately before and after contrast media administration • Additionally at 15, 30, and 60 min; then every 15–60 min until barium reaches rectum • Later radiograph times must be adjusted for every patient; a "standard" protocol is just a starting point and will probably need to be modified • If transit is quick, radiographs at 10–15-min intervals may be required • Depending on pictures so far, late additional radiographs after 12 and 24 h (until stomach has completely emptied and all contrast media has reached the colon) • If an abnormalitiy is suspected, it is best to obtain multiple radiographs close together to confirm persistence of the lesion (with iodine-containing media: half the above-mentioned time-points) Cat • Immediately before and after contrast media administration • Additionally at 5, 20, 30, 40, 60 and 120 min • Late additional radiographs after 6 and 12 h (with iodine-containing media: identical time-points) BEWARE: Do NOT omit any of the radiographs or "only" perform radiographs at the late time-points (6–24 h after administration) as important subtle changes or evidence of partial obstructions can be missed!
Tips for practical execution and overall interpretation	• Rule of thumb: at the end of the examination the stomach has emptied completely and all contrast is in the large intestine • The above-mentioned times are guidelines. For individual cases they might vary depending on passage timings • Fluoroscopy can be helpful for initial orientation, but is not routinely necessary, increases radiation exposure and is not always available • Have a stop-watch handy as well as a time indicator that can be placed on the radiograph film • Make sure enough staff are available at the necessary time-points

analysis of intestinal motion in dogs, these procedures are rarely used in routine practice.

Scintigraphy can potentially be used to assess small intestinal transit times. However, unless the test substance is delivered past the pylorus, this technique also includes gastric emptying. Therefore, scintigraphy is usually imprecise about actual small intestinal transit time and more accurately assesses orocecal transit time. In small animals, scintigraphy has rarely been used for assessing small bowel transit alone. Dual-scintigraphy (using ^{99m}technetium and ^{111}indium) can be used to assess whole-bowel transit times. More recently, scintigraphy has been used to assess GI motility in comparison to a wireless motility capsule, which gives accurate information about whole-intestinal transit times and their respective subsets.

Recording of Small Intestinal Muscle Contractions

These procedures are usually of an invasive nature (implanted strain gauges or luminal manometers) or can be used *ex vivo* only. As far as the authors are aware, no attempts at noninvasive detection of electrical potentials created by intestinal muscle contractions (as done with moderate success for gastric emptying) have been reported in small animals. It can be assumed, however, that they are extremely prone to artifacts created by patient movement.

Breath Tests and Other Tracer Tests

The lactulose or hydrogen breath test, which is the breath test most widely used to assess SI transit in humans, has also been applied to dogs. Nonabsorbable lactulose is fermented, yielding H_2 on reaching the colon. This hydrogen gas is rapidly absorbed and exhaled. Interpretation of hydrogen breath test results can be complicated if carbohydrate malabsorption is present. Additionally, the effect of diet is not entirely clear, hence this test is not currently recommended for routine use.

Salicylazosulfapyridine has been administered orally, intraduodenally or intracecally in experimental dogs as a SI tracer substance; the detection of its metabolite sulfapyridine in plasma correlates with SI transit time. Apart from drug metabolism studies, this tracer has not been used in a clinical setting or in dogs with GI diseases.

Treatment of Small Intestinal Dysmotility

Treatment of small bowel dysmotility is usually targeted to the specific etiology. Intestinal obstruction should be relieved surgically as soon as the patient is stable enough for general anesthesia. If infection, inflammation or sepsis is suspected, a search for the underlying cause, depending on the predominant clinical signs, followed by appropriate treatment should be initiated. If intestinal hypomotility is suspected to be drug induced, any medication with the potential to adversely affect GI motility should be discontinued.

Supportive treatment is mandatory to maintain fluid and electrolyte balance and perfusion of vital organs. Prokinetics (Table 53.2) should be used cautiously and only if elimination of the inciting cause and supportive treatment is not sufficient to restore SI motility. Especially in severe infectious enteritis, prokinetics are not recommended, as they might increase the risk for intussusception or volvulus. In postoperative ileus, however, or in patients requiring long-term intensive care, prokinetic agents have a place to decrease hospitalization time and co-morbidities such as aspiration pneumonia. Intestinal stasis in severely ill patients increases the risk of intestinal bacterial translocation, hence cautious feeding of small energy-dense meals (depending on what the primary condition is and what the patient tolerates) and prokinetic treatment can aid in maintaining small bowel function.

Motility Disorders of the Large Intestine

Physiology of Large Intestinal Motility

The large intestine is mainly responsible for the absorption of water and electrolytes, and storage of intestinal content, as feces enter the colon in a liquid state. There are three prominent patterns of colonic motility:

- segmentation contractions which separate and mix the ingesta, increasing the contact time with the mucosa for absorption
- antiperistaltic contractions propagating ingesta back toward the ileum, again slowing down intestinal transit and allowing additional time for absorption
- mass movements, which are unique to the large intestine. Also known as giant migrating contractions (GMCs), the mass movement consists of strong and prolonged peristaltic aboral contractions, which evacuate the entire large intestinal content.

In contrast to the interdigestive phases, when the colon shows no considerable motility, colonic contractions increase significantly following a meal. These so-called gastrocolic and duodenocolic reflexes are controlled by the enteric nervous system and ensure coordinated movement and orderly evacuation of the GI tract with the ingestion of a "new" meal.

Clinical Signs of Hypomotility and Hypermotility of the Large Intestine

Large intestinal (LI) diarrhea is a manifestation of colonic hypermotility and hypersecretion, typically characterized

Table 53.2 Mechanism and site of action, dosages and important clinical information for drugs with prokinetic actions in small animals

Class	Site of action	Dose	Other properties	Comments
Serotonergic 5-HT_4 agonists				
Cisapride	GES, stomach, intestine, colon, CRTZ	0.1–0.5 mg/kg PO TID-BID	5-HT_3 antagonist 5-HT_2 antagonist 5-HT_1 agonist	Removed from the human market due to severe cardiac arrhythmias; in some canine studies no effect on gastric emptying; in high doses (3 mg/kg) decreases gastric motility
Mosapride	Stomach, colon	0.25–2 mg/kg PO BID; 5 mg/cat BID	None	
Prucalopride	Stomach, small and large intestine	Dog: 0.01–0.16 mg/kg SID stimulates gastric emptying 0.6 mg/kg SID stimulates GI peristalsis 1–1.25 mg/kg SID induces migrating motor complexes (defecation) Dosages up to 2 mg/kg SID described Cat: 0.24–0.5 mg/kg SID	None	Can be administered rectally as well if oral administration is not considered safe (risk of aspiration) or gastric motility is severely impaired
Tegaserod	Small and large intestine	0.05–0.1 mg/kg PO or IV BID	5-HT_1 antagonist	Not currently on the market (allegedly increased risk of cardiovascular disease in people)
Motilin-like substances				
Erythromycin	GES, stomach, small and large intestine	0.5–1 mg/kg PO or IV BID	5-HT_1 antagonist	Induces interdigestive motility, which might lead to "dumping" of gastric contents into the duodenum before appropriate digestion can take place
Acetylcholinesterase inhibitors				
Ranitidine	Stomach, colon	1–2 mg/kg PO BID-TID or slow IV/CRI	H2-histaminergic antagonist	Probably only mild to no prokinetic effects
Nizatidine	Stomach, colon	1 mg/kg IV BID; 2.5 mg/kg PO SID–BID	H2-histaminergic antagonist	Probably even less effective than ranitidine
Others/Miscellaneous				
Bethanechol	Esophagus	5–15 mg/dog PO TID	Cholinomimetic substance	
Mirtazapine	Stomach, others unknown	0.6 mg/kg PO SID In experimental dogs: 2 mg/kg SID	Noradrenergic and specific serotonergic tricyclic antidepressant	Limited clinical data available, but at 2 mg/kg SID showed accelerated gastric emptying times in experimental fistulated dogs

Source: Modified from Washabau and Day (2013). Reproduced with permission of Elsevier.
BID, twice a day (*bis in die*); CRI, continuous rate infusion; CRTZ, chemoreceptor trigger zone; GES, gastroesophageal sphincter; GI, gastrointestinal; IV, intravenous; PO, by mouth (*per os*); SID, once a day (*semel in die*); TID, three times a day (*ter in die*).

by increased defecation frequency, decreased fecal volume per defecation, tenesmus, increased fecal mucus, and the occurrence of fresh blood (hematochezia).

Large intestinal hypomotility results in constipation, which is defined as absent, infrequent or difficult defecation (tenesmus). In its most severe form, constipation leads to obstipation where impacted, hard and dry feces make normal defecation impossible. Typically owners observe frequent attempts to defecate, tenesmus and dyschezia (difficult or painful defecation) with little or

no feces produced. Animals might vocalize during attempts at defecation. Other possible signs are anorexia, lethargy, vomiting, and an abnormal stance (hunched up). Infrequent passage of watery material and mucus, which has bypassed the impacted feces, might be wrongly interpreted as diarrhea.

Animals with LI diarrhea will frequently be normal on physical examination, even though in some cases rectal palpation might reveal irregular mucosal surface or rectal masses. Impacted feces and, depending on the severity of the problem, dehydration, abdominal pain, and debilitation are findings in animals with decreased colonic motility or obstruction resulting in constipation, obstipation or even megacolon.

Diseases Associated with Dysmotility of the Large Intestine

Increased Large Intestinal Motility

As increased LI motility is part of the manifestation of every type of "colitis" (acute or chronic), the number of underlying diseases is manifold. In dogs, this includes infectious (e.g., *Trichuris vulpis*, toxins from *Clostridium perfringens* infection, *Prototheca zopfii*) and noninfectious (e.g., food hypersensitivity) causes, diseases with inflammatory (IBD, granulomatous colitis [GC] of boxers and bulldogs) or neoplastic infiltration of the colonic wall, as well as a number of "idiopathic" disorders where hypermotility is implicated as a primary cause; these include fiber-responsive colitis and CILBD. The latter is also often called irritable bowel syndrome (IBS), spastic colon, nervous/stress-induced colitis or mucoid colitis. In these dogs, inciting stressors can sometimes be identified (travel, changes in daily routine, loss of other pets or family members). They can show submissive or anxious behavior (urination, separation anxiety, fear of noise), but tend not to be aggressive.

Canine idiopathic large bowel diarrhea is defined by colonic dysfunction in the absence of identifiable structural, biochemical, or microbiologic abnormalities and thus is a diagnosis of exclusion. While no studies have shown a pathophysiologic mechanism in dogs, abnormal myoelectrical activity leading to abnormal LI motility is likely part of this disease in humans, in combination with psychosocial factors, altered pain, and visceral reception. The prevalence of CILBD ranges from as low as 5% to 26% in dogs. It is more commonly found in large breeds and those under stress (police/customs, guide dog for the blind, herding) or dogs that are easily overexcited.

Decreased Large Intestinal Motility

Constipation can be due to intestinal or systemic problems. Intestinal causes are mostly obstructive (intraluminal [stricture, fecolith, tumor] or extraluminal [prostatomegaly, pelvic fracture, perianal tumor, pseudocoprostasis]) or dietary (foreign material [bone, stones, garbage, hair]) in origin. Systemic problems can be caused by external factors (long inactivity, confinement [hospitalization]), drugs (opioids, barium, sucralfate, calcium channel blocker, anticholinergic) or be part of metabolic problems (dehydration, hypokalemia, hypercalcemia). Finally, neuromuscular dysfunction may also result in decreased LI motility. Here, colonic hypomotility is frequently associated with lumbosacral spinal cord problems (Manx cat deformity, neoplasia, degenerative disease, injury) and feline idiopathic megacolon, and less frequently with ganglioneuritis (one dog reported), dysautonomy (Key–Gaskell syndrome), and canine hypothyroidism.

Megacolon is more commonly seen in cats than dogs. It is defined as persistently increased large bowel diameter, often as an end-result of chronic constipation. Idiopathic megacolon accounts for about two-thirds of all feline cases of constipation. Its etiopathogenesis is incompletely understood, but dilation of the colon appears to be due to functional disturbances of the colonic smooth muscle cells. Lesions seem to begin in the descending colon and then progress to involve the ascending colon. Affected cats are usually middle-aged (mean 5–6 years) with males (70%) more commonly affected. Repeated episodes of obstipation are often reported. Diagnosis is reached when all other causes (mechanical obstruction, inflammation, neoplasia) have been excluded and typically involves neurologic assessment, diagnostic imaging studies (with and without contrast), and histopathology.

Assessment of Large Intestinal Motility or Transit Times

Real-time assessment of LI motility is difficult to perform and thus complete GI or orocecal transit times are usually investigated.

Diagnostic Imaging Procedures Available in Routine Practice

On survey radiographs, size and opacity of the LI are extremely variable and formed feces are of a heterogeneous opacity. Nevertheless, a ratio of the maximal diameter of the colon to L5 length >1.48 is a good indicator of feline megacolon (sensitivity 77%, specificity 85%). Contrast radiographs after rectal administration of positive (barium) or negative (air) contrast media or their combination (double contrast studies) might be indicated in animals with LI diarrhea or constipation to exclude an obstruction but they do not show true LI motility. The LI should not be assessed on a SI contrast study as LI filling is incomplete and there is overlap with

parts of the SI. LI contrast studies should also not be done two hours after a cleansing enema, 6–12 hours after colonoscopy and 3–4 days after full-thickness colonic biopsies. Ultrasound has so far not been investigated to evaluate LI motility.

Measurement of Gastrointestinal Transit Times

Different ways to assess LI motility or whole-intestinal transit have been employed, but are so far limited to research purposes or require special equipment. The simplest way to assess oroanal transit time is to feed plastic markers of different colors and recover them from the feces. Different radiopaque markers have been used in healthy dogs as well. Similar to assessment of gastric emptying (see earlier), radioscintigraphy has also been used to determine LI motility (e.g., with ^{111}In). Recently, total GI transit times and LI transit times were measured with a wireless motility capsule system in dogs. Other tests used in human medicine, such as colonic manometry or MRI, have so far only been used in experimental dogs to assess LI motility and are not useful for routine diagnostics.

Treatment of Large Intestinal Dysmotility

Treatment of Idiopathic Colitis and CILBD

Treatment of LI dysmotility secondary to infectious or inflammatory colitis, neoplasia or mechanical impairment is directed towards the underlying cause. Treatments for IBD with LI involvement, food hypersensitivity, fiber-responsive colitis and CILBD overlap frequently, as all involve some form of dietary modification (see later). This also explains why definitive diagnosis and accurate separation of these disease entities can be difficult.

Dietary modifications often include the change to a novel protein (and possibly carbohydrate) source or a hydrolyzed protein diet. Alternatively, increasing the amount of dietary fiber or adding bulk-forming agents (e.g., a commercial high-fiber diet or the addition of psyllium 1–3 tbsp/day or unprocessed wheat bran 1–5 tbsp/day) to the food also frequently leads to clinical improvement.

Antibiotics usually have no place in treating "idiopathic" colitis. However, the authors have noticed that some dogs improve with the administration of metronidazole or tylosin, similar to antibiotic-responsive chronic enteropathy/IBD, even if constipation or LI diarrhea are the only presenting complaints.

Antiinflammatories can aid in controlling LI symptoms in some dogs. As in small intestinal forms of IBD, this might include the administration of steroids (if all other causes of clinical signs, especially infectious diseases, have been excluded), for example prednisolone (1–2 mg/kg SID to BID) or budesonide (0.05–1 mg/kg/day with the total dose not exceeding 3 mg q8h). Alternatively, sulfasalazine (15–30 mg/kg BID to TID, maximum 6 g/day) has been particularly useful in controlling idiopathic colitis in some dogs. However, this is usually done on an empirical basis, and the decision regarding which dogs can or need to be treated with either of those antiinflammatory compounds is often arbitrary.

When CILBD is suspected (and all other causes of colitis have been ruled out), treatment should start with dietary modifications (fiber supplementation; see earlier). The remainder of treatment depends on the nature of clinical signs (intermittent, alternation between constipation and diarrhea, abdominal pain/cramping) and their suspected inciting cause. Different types of bulking agents (psyllium, kaolin, pectin) can help in times of diarrhea. Alternatively, motility modifiers or antispasmodics may be tried (Table 53.3). Antispasmodic drugs might relieve some pain and sedatives reduce stress effects. Most dogs only require treatment for a day to two weeks, with some requiring long-term treatment. Stressors should be avoided and behavioral therapy can be considered. Drugs modifying behavior, including amitriptyline, can be tried in refractory cases of CILBD (see Table 53.3). The prognosis of CILBD is good, particularly for dogs that respond to fiber supplementation.

Treatment of Constipation

Management of constipation depends on the severity and the underlying cause, which should be addressed first (mechanical obstruction, pelvic fracture, neurologic disorder, etc.). If possible, drugs that may cause constipation (opioids, diuretics, antispasmodics, anticonvulsants, sucralfate, NSAIDs) should be minimized or discontinued. In overweight animals, weight loss should be encouraged and their activity increased. Cat litter boxes should always be kept clean, to encourage defecation, and water intake should be increased (availability of water bowls, addition of water to food).

In addition, or as sole treatment in mild cases, dietary modification is recommended. This can again consist of bulk-forming agents (high-fiber diet, added psyllium or bran) or the administration of lactulose or other laxatives (see Table 53.3). A single enema or rectal suppository on an outpatient basis can also be considered.

In more severe or refractory cases, manual removal of impacted feces and several warm water enemas (in many cases requiring general anesthesia) are necessary. Adequate amounts of intravenous fluids need to be administered to correct dehydration and possible electrolyte abnormalities and to prevent worsening of obstipation. Constipation is most commonly a recurring problem and long-term prophylactic measures (dietary

Table 53.3 Treatments for chronic idiopathic large bowel disease (CILBD)

Class	Name	Dose	Comment
Fiber	Psyllium	Daily dose: ½ tablespoon for toy breeds 1 tablespoon for small-breed dogs 2 tablespoons for medium-breed dogs 3 tablespoons for large-breed dogs	Median dose was 1.3 g/kg/day in one study
	Canned pumpkin	1–4 tablespoons mixed with food per day	
	Coarse wheat bran	1–4 tablespoons mixed with food per day	
	Commercially available diets with high fiber contents	Feeding recommendation by weight/the manufacturer	Available from reputable pet food manufacturers
Motility-modifying agents	Loperamide	0.04–0.2 mg/kg PO q8–12h	Not for prolonged use
	Diphenoxylate	0.05–0.1 mg/kg PO q6–8h	Often in combined preparations with atropine sulfate
Laxatives	Lactulose	1 mL per 4.5 kg PO BID–TID	Hyperosmotic
	Bisacodyl	5–20 mg per dog PO SID	Stimulant/prokinetic
Antispasmodics (neurotropic)	Chloriazepoxide (5 mg) and clidinium bromide (2.5 mg)	0.1–0.25 mg/kg clidiniium PO BID–TID for a few days	Librax®. Can be given prophylactically or metaphylactically as well as therapeutically
	Propantheline	0.25 mg/kg PO TID (round dose to nearest 3.75 mg)	Do not use for longer than 48–72 h
	Hyoscyamine	0.003–0.006 mg/kg PO BID–TID	Not for prolonged use
	Butylscopolamine/hyoscin	0.5–0.8 mg/kg PO SC IM or IV SID–TID	Inhibits M1 muscarinic acetylcholine receptors in the GI and urinary tract, does not cross blood–brain barrier. Often in combination with metamizole
	Dicyclomine	0.15 mg/kg BID–TID	
Antispasmodics (musculotropic)	Mebeverine	2.5–5 mg/kg PO BID	
	Pinaverium	1 mg/kg PO BID	
	Trimebutine	0.33 mg/kg PO TID	
Behavior-modifiying agents	Amitriptyline	1–2 mg/kg PO SID–BID	The atypical tricyclic antidepressant clomipramine exists as an authorized preparation for use in dogs and is claimed to have better anticompulsive properties. Amitriptyline is bitter/distasteful. Some caution and careful monitoring are warranted in patients with cardiac or renal disease
	Selegiline	0.5–1 mg/kg PO SID	Dopamine agonist. Dose can be increased to 2 mg/kg SID if no response after 2 months
	Clomipramine	1–2 mg/kg PO BID	Tricyclic antidepressant. Increase gradually up to 3 mg/kg PO BID if necessary after 14 days

Source: Modified from Lecoindre and Gaschen (2011). Reproduced with permission of Elsevier.
BID, twice a day (*bis in die*); IM, intramuscular; IV, intravenous; PO, by mouth (*per os*); SC, subcutaneous; SID, once a day (*semel in die*); TID, three times a day (*ter in die*).

adjustment and laxative therapy) are often needed permanently.

Chronic treatment of constipation and idiopathic megacolon might require prokinetic treatment. Drugs that show some effect on colonic motility include cisapride and prucalopride. The influence of H2 receptor antagonists on colonic motility is not entirely clear. Newer drugs that might have some positive effect on colonic motility in dogs (lubiprostone, mirtazapine) have not been thoroughly tested in clinical cases.

Subtotal colectomy should be considered in cases of feline idiopathic megacolon refractory to conventional (diet, laxatives) and prokinetic treatment.

Prokinetics

Prokinetic drugs are divided into serotonergic 5-HT_4 agonists, motilin-like drugs, dopaminergic D2 antagonists, H2-receptor antagonists, and novel compounds (see Table 53.2).

5-HT_4 Agonists

Drugs acting on gastrointestinal 5-hydroxytryptamine (5-HT_4 or serotonin) receptors have potent prokinetic effects. Of the various 5-HT_4 agonists, cisapride has been most extensively studied, but was withdrawn from most of the European and US markets due to lethal cardiac side-effects (torsade de pointes tachycardia) seen in humans. Other 5-HT_4 agonists include mosapride (available in Japan), prucalopride (available in the USA and Europe), and tegaserod (also removed from the market for similar reasons as cisapride).

The gastric prokinetic properties of cisapride have been documented in many experimental settings, but in some studies, no effect on gastric emptying in dogs was observed. In high doses (3 mg/kg), it can even slow emptying of solids.

Mosapride has been shown to restore gastric motility in dogs with vincristine- or prednisolone-induced gastric hypomotility in healthy experimental dogs, but seems to have no effect on the distal intestinal tract.

Prucalopride stimulated gastric emptying in a dose-dependent manner at relatively low doses (0.01–0.16 mg/kg), stimulates physiologic gastrointestinal peristalsis/defecation at higher doses (approximately 0.6 mg/kg) and induces MMCs at still greater doses (around 1 mg/kg) in dogs.

Naronapride (ATI-7505) is marketed as a selective 5-HT_4 agonist without the cardiac side-effects in humans, but only one study has assessed its gastric prokinetic properties in dogs so far. It was found to be orally bioavailable in dogs with an increase in coordinated antral and small bowel contractility but little effect on colonic motor activity.

Motilin-Like Drugs

The antibiotic drug erythromycin accelerates gastric emptying by inducing phase III contractions of the interdigestive MMCs, even when used in a subantibiotic dosage. These contractions are similar to those induced by the endogenous gastrointestinal hormone motilin. Several synthetic erythromycin derivates have been developed; for example, EM574, which is 250 times more potent than erythromycin itself in inducing MMCs and has no antibacterial properties. Similarly, mitemcinal (GM-611) has been shown to accelerate gastric emptying in healthy dogs as well as to improve delayed gastric emptying in a canine model of diabetic gastroparesis. Another synthetic erythromycin derivative, ABT-229, accelerates gastric emptying, motility index, and gastroduodenal coordination in a dose-dependent manner. This compound is around 40-fold more potent than erythromycin.

One potential complication that can arise from the stimulation of interdigestive motility is that it can lead to "dumping" of gastric contents into the duodenum before they have been acidified and denatured appropriately. This can then lead to inadequate absorption of nutrients and osmotic diarrhea.

Dopaminergic D2 Antagonists

There is no convincing evidence that dopaminergic D2 antagonists like metoclopramide and domperidone have prokinetic effects on the canine stomach, even though metoclopramide in particular has been advocated for this purpose for years. Consequently, these drugs should not be used solely for this indication in dogs.

Metoclopramide has no effect on complete gastric emptying times or corporeal contractions in experimental dogs. Regarding its effects on MMC disruption or inhibition as well as antral contractions, study results are inconsistent. When emptying of solid and liquid contents were assessed separately, metoclopramide slowed solid gastric emptying (cooked liver), while accelerating emptying of liquids (5% dextrose). There is some potential evidence from several studies that metoclopramide might improve antropyloroduodenal coordination and the frequency of pyloric and duodenal contractions in experimental settings, possibly by enhancing acetylcholine effects. However, there was no acceleration of gastric emptying in dogs after GDV surgery. Effects of metoclopramide might be dose dependent, as the standard dose

(0.2–0.4 mg/kg) did not reduce gastroesophageal reflux; however, a high dose (1 mg/kg followed by a CRI with 1 mg/kg/h) reduced reflux. Thus, metoclopramide might not be harmful in a dog with suspected gastric hypomotility, especially as nausea and vomiting might also be present and its antiemetic effects via 5-HT_3 antagonism are undisputed, but metoclopramide cannot induce a strong prokinetic effect, particularly in cases with complete gastric atony.

Domperidone decreases the frequency of corporeal, pyloric, and duodenal contractions and deteriorates antropyloroduodenal coordination by decreasing the frequency of contractions spreading from the antrum or pylorus to the duodenum. It is therefore not indicated as a prokinetic agent in the dog.

Itopride (Ganaton®, Abbott) is used to treat functional dyspepsia in people. It is a prokinetic benzamide derivate, unlike metoclopramide and domperidone. This drug has both antidopaminergic and antiacetylcholinesterase actions. Its gastroprokinetic dose, when administered intraduodenally in healthy experimental dogs, was 1–3 mg/kg while at doses of 10–100 mg/kg it inhibited apomorphine-induced vomiting. It seems to have similar prokinetic effects to cisapride and mospride when given orally.

Histamine H_2-Receptor Antagonists

Some H_2-receptor antagonists (ranitidine and nizatidine, but not cimetidine or famotidine) have prokinetic effects mediated by cholinergic mechanisms, especially on gastric smooth muscle or, in the case of ranitidine, also on isolated small intestine.

The gastric prokinetic properties of ranitidine have been assessed in both rodents and humans. However, neither in healthy subjects nor in various diseases (gastric stasis in intensive care patients, peptic ulcers, and others) have the effects on gastric emptying, gastric volume/retention or pH been consistent. Some studies suggest acceleration of liquid gastric emptying times as well as faster passage of a motility capsule, possibly based on an increase in phase III motor activity. Other studies show no effect on gastric motility, and two studies even demonstrate a dose-dependent delay in gastric emptying. In dogs, only a few studies are available assessing the effect of ranitidine of gastroesophageal reflux during anaesthesia (where it had no apparent effect) or on GI transit times using a wireless motility capsule (also no effect).

Nizatidine has also been studied extensively regarding its gastric prokinetic properties in experimental rodents and humans. Most studies seem to agree that it has more consistent gastroprokinetic effects than ranitidine or famotidine. In addition, it also enhances colonic peristalsis in humans. In experimental dog models, it was as potent as cisapride in accelerating solid-phase gastric emptying, but clinical studies or extensive *in vivo* studies in dogs are lacking.

Novel Prokinetic Compounds

Several new drugs and compounds have been tested for their prokinetic properties in dogs. Some have a defined mechanism of action, some are herbal extracts where the principal component is not identified. This includes DA-9701 (marketed as Motilone® in Korea), which is an extract from *Corydalis* tubers (a genus of plants in the Papaveraceae family with about 470 species, also sometimes known as Chinese poppy) and *Pharbitis* seeds (plants belonging to the Convulvulaceae family and often used synonymously to morning glory, which is another genus [*Ipomoea*]of this family). This substance lead to improvement of gastric accommodation and increased postprandial volume in healthy experimental dogs, but the effects on gastric emptying are unclear.

Lubiprostone (Amitiza®, Mallinckrodt) is used in the management of chronic idiopathic constipation or inflammatory bowel disease with constipation in humans. It is a selective type-2 chloride channel (ClC-2) activator and hence increases chloride ion transport and fluid secretion into the intestinal lumen. This compound has been shown to accelerate gastric emptying in healthy experimental dogs, as well as small bowel and colon transit and interdigestive motility.

Mirtazapine (several brand names) is a noradrenergic and serotonergic antidepressant used in small animals as appetite stimulant. One study in healthy experimental dogs has shown that it can accelerate gastric emptying times when given at a high dose, but it is unclear if this translates to a clinical setting yet.

To the authors' knowledge, none of the drugs mentioned above have been used outside a research setting or in spontaneously occurring disease in dogs.

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54

Exocrine Pancreatic Insufficiency in Dogs and Cats

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Exocrine pancreatic insufficiency (EPI) results from an inadequate production of pancreatic enzymes from pancreatic acinar cells, leading to maldigestion and clinical signs of weight loss, polyphagia, and diarrhea. There are currently no studies estimating the prevalence of EPI in the general canine and feline population, but EPI is considered the second most common disease of the exocrine pancreas in small animals (after pancreatitis). Although EPI is considerably more common in dogs than in cats, in the past few years EPI has been diagnosed with increasing frequency in the feline population, likely due to increased awareness of this condition in cats and the availability of better tests for its diagnosis.

Pathogenesis

In humans, it has been estimated that EPI occurs when more than 90% of the exocrine pancreas (i.e., pancreatic acinar cells) is destroyed. When that happens, the functional capacity of the remaining exocrine pancreas is inadequate for the production and secretion of sufficient amounts of:

- enzymes for the digestion of protein, fat, and carbohydrate
- bicarbonate for neutralization of gastric acid entering the duodenum
- pancreatic intrinsic factor for the absorption of cobalamin in the ileum
- antimicrobial proteins for regulation of small intestinal microbiota.

Therefore, EPI has multiple consequences.

The main consequence of EPI is deficient intraluminal digestion of nutrients. This is mainly the result of insufficient production and secretion of pancreatic proenzymes and enzymes by an inadequate number of pancreatic acinar cells. However, this is not the only mechanism leading to nutrient maldigestion and malabsorption in EPI. Studies have shown that there is also altered activity of intestinal mucosal enzymes and impaired intestinal function. In some cases, these functional abnormalities are accompanied by mucosal pathology. Although the exact reason for these abnormalities is unknown, it is speculated that the lack of trophic influence of pancreatic secretions, as well as bacterial overgrowth in the small intestine, may play a role. In addition, acid injury of the intestinal mucosa may occur, as a result of lack of neutralization of gastric acid entering the duodenum.

Another major consequence of EPI is related to cobalamin absorption. The exocrine pancreas is a major source of intrinsic factor in the dog and the main one in the cat. Therefore, EPI leads to a significant reduction in or even total absence of intrinsic factor in the intestinal lumen, which in turn leads to cobalamin malabsorption and cobalamin deficiency at both the intracellular and extracellular level. Overgrowth of cobalamin-binding bacteria in the small intestine may also be a contributing factor. Severe cobalamin deficiency is typically recognized by low serum cobalamin concentrations. Cobalamin deficiency has been shown to have major biochemical implications (e.g., defective amino acid metabolism and DNA synthesis) and has also been shown to be a negative prognostic factor in animals with gastrointestinal diseases, including EPI.

Alterations in the intestinal bacteria and small intestinal bacterial overgrowth are likely common in animals with EPI due to the lack of antibacterial properties of pancreatic secretions. Intestinal dysbiosis is believed to contribute to clinical signs of EPI and might often be a reason for treatment failure, especially when proper antibiotic treatment is not used.

Etiology

Current studies on the etiology of EPI in dogs have investigated specific canine breeds predisposed to developing this disease. Therefore, information from those studies

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involves certain breeds and may or may not hold true for other breeds.

Most studies available to date have investigated the etiology and pathogenesis of EPI in German shepherd dogs (GSD) and rough-coated collies, and in those breeds EPI is most commonly the result of pancreatic acinar atrophy (PAA). In those breeds, PAA likely is the result of an immune-mediated condition resulting in atrophic lymphocytic pancreatitis, as evidenced by histopathology of the pancreas in dogs during the development of PAA. Eventually, this chronic inflammation, which is limited to the exocrine portion of the pancreas, leads to total destruction of pancreatic acinar tissue and PAA. In those breeds, PAA is most likely acquired and almost certainly has a genetic basis. The earlier belief that EPI in these breeds has an autosomal recessive mode of inheritance has been largely abandoned, and a polygenic inheritance pattern is currently suggested. Genome-wide association studies in GSD have failed to identify any specific genes or major loci associated with EPI, suggesting that EPI in this breed might have several different genetic causes or might be the result of multiple loci with small effects. Further studies are required to identify the genes involved in the development of PAA in GSD and other dog breeds. In addition, the roles that various environmental factors might play in association with a predisposing genetic background have not been investigated.

Pancreatic acinar atrophy is typically considered to be by far the most common etiology of EPI in the overall canine population. Although PAA can be the cause of EPI in any canine breed, other etiologies might be more common in certain breeds. End-stage chronic pancreatitis leading to pancreatic fibrosis is likely the most important etiology after PAA, and it has been reported as a cause of EPI in several studies. Chronic pancreatitis can be especially difficult to diagnose in dogs and cats and, therefore, in most cases a diagnosis of chronic pancreatitis has not been reached by the time EPI is diagnosed. In chronic pancreatitis, both endocrine and exocrine pancreatic cells may be destroyed and therefore EPI may be accompanied by diabetes mellitus in some cases.

Recently, isolated pancreatic lipase deficiency has been reported as a cause of EPI in dogs. In these cases, all other pancreatic enzymes and proenzymes are synthesized and secreted normally. Isolated pancreatic lipase deficiency causes severe lipid maldigestion and malabsorption, leading to the typical signs of EPI despite the fact that there is no deficiency in other pancreatic enzymes. The cause of isolated pancreatic lipase deficiency in dogs is unknown.

Other possible causes of EPI in dogs include pancreatic duct obstruction, pancreatic hypoplasia or aplasia, and pancreatic neoplasia. All of these are extremely rare causes of EPI in dogs.

Chronic pancreatitis is believed to be the most common cause of EPI in cats. PAA has been reported in three cats with EPI and is therefore believed to be a considerably less common cause of EPI in this species compared to dogs. Other causes of EPI in cats may include pancreatic aplasia or hypoplasia, pancreatic tumors, isolated deficiencies of pancreatic enzymes, and pancreatic duct obstruction (for example, as a result of neoplasia, *Eurytrema procyonis* infestation, and complications from cholecystoduodenostomy surgery).

Signalment

Dogs and cats of any breed can develop EPI. However, certain groups are clearly predisposed. The most well-described breed predisposition for EPI involves the GSD. Studies in North America and Europe have shown that GSDs have increased prevalence of EPI, with this breed representing approximately 60% of all cases of EPI. Other breeds predisposed to EPI include rough-coated collies, Cavalier King Charles spaniels, cocker spaniels, West Highland white terriers, and chow chows. No breed predispositions have been described for cats.

Dogs of almost any age can develop EPI, with a reported age range extending from 3 months to 17 years. When considering all dogs with EPI, the disease more commonly appears in young adult dogs (median age 3 years). However, within the group of dogs with EPI, there are subgroups that have different ages of onset. Specifically, the onset of the disease might be at an earlier age in certain breeds (median 18 months for chow chows; median 3 years for GSDs and rough-coated collies) compared to other breeds (median 7 years for Cavalier King Charles spaniels). These differences may in part reflect differences in the etiology of EPI; for example, EPI as a result of PAA typically develops in young adult dogs (usually by the age of 5 years). EPI that develops in older dogs (such as Cavalier King Charles spaniels) might be more likely to be the result of chronic pancreatitis rather than PAA, because more time is believed to be required until pancreatic acinar cells are destroyed as a result of chronic low-grade inflammation.

Cats of any age can develop EPI, with some cats diagnosed at less than 1 year of age. However, EPI is more commonly diagnosed in middle-aged to older cats, with a mean age of 8 years.

Exocrine pancreatic insufficiency can occur in both male and female dogs. Most studies agree that females are slightly predisposed compared to males. No sex predilection has been reported for cats.

Clinical Features

The classic and most common presentation of dogs with EPI involves a chronic history of weight loss (Figure 54.1), a normal or increased appetite, and diarrhea, which is



Figure 54.1 This dog presented with significant weight loss due to EPI. The dog had lost 10 kg during the last few months. This is a common clinical presentation of dogs with EPI although weight loss is often not as severe.

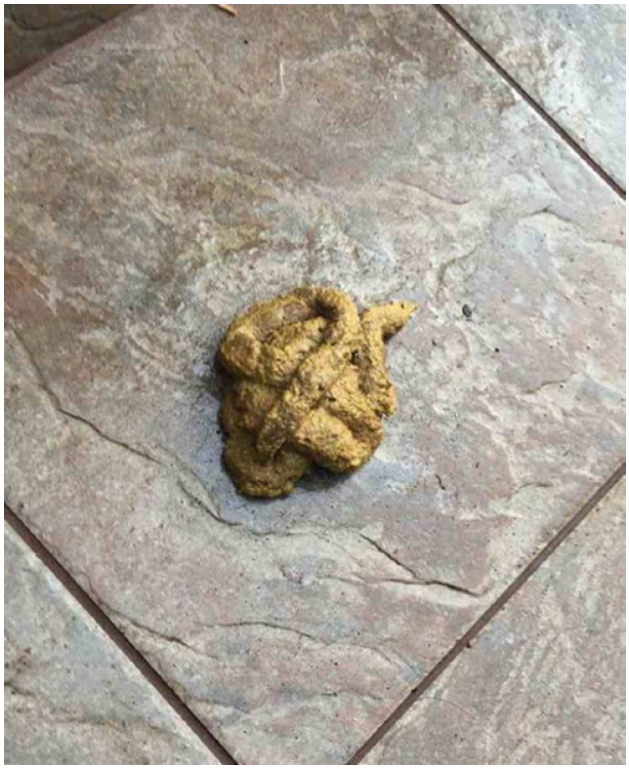


Figure 54.2 The feces from the dog in Picture 1. The feces are large in volume and semi-formed. This is a common finding in dogs with EPI.

usually characterized by passage of large volumes of semiformed feces (Figure 54.2). However, it is not uncommon for some dogs with EPI to present with a clinical picture that deviates from the classic presentation. In those cases, periods of anorexia, absence of diarrhea, and occasionally watery diarrhea or vomiting might be seen. Other possible clinical signs include coprophagia, borborygmus, flatulence, abdominal discomfort, and a poor hair coat. In some cases, EPI may be subclinical and those cases can only be diagnosed with appropriate laboratory testing (see section on Trypsin-Like Immunoreactivity). Dogs may remain in the subclinical phase for years or sometimes for life.

Cats with EPI have a similar presentation to dogs. In a retrospective study of 150 cases of feline EPI, the most common clinical sign was weight loss (which was often the only clinical sign), followed by loose stools, poor hair coat, anorexia, increased appetite, depression, watery diarrhea, and vomiting. It is likely that many of these clinical signs reflect concurrent diseases such as chronic pancreatitis and inflammatory bowel disease. In cases where chronic pancreatitis is the cause of EPI, polyuria and polydipsia may be seen as a result of concurrent diabetes mellitus.

Diagnosis

The diagnostic evaluation of animals suspected of having EPI should always take into consideration the clinical presentation, general clinicopathologic findings, and the results of diagnostic modalities used to specifically assess pancreatic structure, function, and pathology.

Routine Clinical Pathology

Findings of complete blood count (CBC), chemistry profile, and urinalysis are typically unremarkable in animals with EPI. When present, routine blood test abnormalities (e.g., increased hepatic enzyme activities, hypoalbuminemia, hyperglycemia) reflect concurrent diseases such as inflammatory bowel disease and diabetes mellitus.

Trypsin-like Immunoreactivity

Trypsin-like immunoreactivity (TLI) measures serum concentrations of trypsin and trypsinogen and is the test of choice for the diagnosis of EPI in dogs. This test is highly sensitive and specific for the diagnosis of EPI. Animals with EPI produce and secrete lower than normal amounts of trypsinogen in serum and therefore a subnormal TLI concentration (usually defined as <2.5 µg/L) in an animal with compatible clinical signs is sufficient to make a diagnosis of EPI. A TLI result well within the reference range is sufficient for excluding EPI in the vast majority of cases, and a normal TLI result should direct clinicians towards the investigation of other disorders as the cause of the observed clinical signs.

One exception to this rule is the case of isolated pancreatic lipase deficiency, where the patient has EPI but

secretion of trypsin and trypsinogen is normal and therefore serum TLI concentrations are also normal. In these cases, the diagnosis of EPI is quite challenging. The current assays for the measurement of pancreatic lipase concentration (i.e., Spec-cPL) are not suitable for the accurate measurement of pancreatic lipase concentrations at very low concentrations, and therefore isolated pancreatic lipase deficiency cannot be diagnosed using these assays. Although epidemiologic studies are lacking, isolated pancreatic lipase deficiency in dogs is considered to be an uncommon cause of EPI.

Single TLI results within the equivocal range (usually between 2.5 and 5.7 µg/L) in dogs with clinical signs of gastrointestinal disease need to be interpreted with caution. In these patients, subsequent retesting of serum TLI may show either a normal concentration or progression to EPI. Therefore, patients with canine TLI (cTLI) results in the equivocal range should be investigated for chronic intestinal disease, while cTLI concentrations should also be measured a few weeks later.

Some dogs with no clinical signs characteristic of EPI have repeatedly subnormal (<5.7 µg/L) cTLI concentrations. These dogs have been shown to have subclinical EPI and some, but not all, are expected to develop clinical EPI in the future. The time of progression from the subclinical to the clinical disease varies greatly and might be from a few months to years. Thus, these patients should be closely monitored for the development of clinical signs of EPI and cTLI testing should be repeated periodically. It should be noted that a single serum cTLI concentration is not sufficient for diagnosing subclinical EPI.

Because renal disease might increase serum cTLI concentrations and obscure a diagnosis of EPI, reevaluation of nondiagnostic serum cTLI concentrations in azotemic dogs suspected of having EPI is recommended. Similarly, concurrent pancreatitis might falsely increase the serum cTLI concentration.

Due to the fact that EPI appears to be less common in cats than in dogs, diagnosis of this disease has been less well investigated and is more challenging in this species. Similar to dogs, the feline TLI (fTLI) test appears to be the most reliable test for the diagnosis of EPI in cats with a specificity of at least 85%. The sensitivity of this assay for the diagnosis of feline EPI has not been evaluated to date. Although there are currently two assays that measure fTLI in serum (one radioimmunoassay that is available in the USA and one ELISA available in Europe), only one of those assays (the radioimmunoassay) has been reported to be analytically validated; this test is available through the Gastrointestinal Laboratory at Texas A&M University. Similar to dogs, it can be recommended that nondiagnostic serum fTLI concentrations in azotemic cats suspected of having EPI be reevaluated, because renal disease might falsely increase serum fTLI concentrations. The same is true for cats with concurrently increased serum feline pancreatic lipase (fPLI, Spec-fPL) concentrations indicating pancreatitis.

Trypsin-like immunoreactivity testing can be performed in animals that are already on enzyme supplementation without this affecting the results. TLI assays are species specific and do not measure trypsinogen and trypsin of other species.

Pancreatic Fecal Elastase

An ELISA for the measurement of pancreatic elastase in feces is commercially available and is marketed in Europe (Shebo Biotech, Germany) for the diagnosis of canine EPI. It is considered to be specific for EPI, although a recent study reported false-positive results in 23.1% of cases and the sensitivity of this test has not been sufficiently evaluated. The fact that this test is easy and quick to perform might make it a reasonable initial approach for dogs with suspected EPI, but a positive test result must be verified by measurement of a serum TLI concentration. This test might also be useful for EPI cases that are due to pancreatic duct obstruction. However, to date such cases have only been anecdotally reported in the veterinary literature.

Other Tests

Serum amylase and lipase activities have been shown to have no value in the diagnosis of EPI in either dogs or cats. Canine pancreatic lipase immunoreactivity concentrations are low or undetectable in most dogs with EPI, but commercial assays for the measurement of serum PLI concentration (Spec-cPL and Spec-fPL) are not useful for the diagnosis of EPI in dogs and cats, respectively, because they have been optimized to detect changes in the higher levels of their respective working ranges.

Measurement of the fecal proteolytic activity has been used in the past for the diagnosis of EPI in dogs and cats. A plethora of other tests, including microscopic examination of feces and the bentiromide absorption (BT-PABA) test, have also been used for the diagnosis of EPI. These tests often give false-positive and/or false-negative results, and many of them are impractical, expensive or of limited availability, and thus are not recommended for the diagnosis of canine or feline EPI. However, these tests may be useful in special cases where serum TLI concentration is in the normal range (e.g., EPI due to pancreatic duct obstruction) but EPI is heavily suspected based on the clinical picture.

Histopathology

Exocrine pancreative insufficiency is a functional and not a histopathologic diagnosis, and thus histopathology

is not indicated for the diagnosis of EPI in dogs and cats. While it is believed that more than 90% of the pancreatic parenchyma needs to be destroyed in order for clinical signs of EPI to develop, it is almost impossible to accurately determine the extent of pancreatic atrophy either grossly or histopathologically, and thus whether acinar cell loss is leading to EPI. The utility of histopathology is limited to determination of the underlying cause of EPI (PAA or pancreatitis). Even then, in dog breeds that have been shown to be predisposed to EPI due to acinar atrophy (i.e., German shepherds, rough-coated collies), histopathology is redundant. Therefore, histopathology should only be used in atypical cases where the cause of EPI needs to be determined.

Treatment

The vast majority of animals with EPI require lifelong treatment with pancreatic enzyme supplementation, with or without other treatments. Although pancreatic enzymes are essential for digestion, alternative pathways for digestion of some nutrients do exist and therefore rare animals may compensate for the loss of pancreatic enzymes and display only minimal clinical signs without treatment.

Table 54.1 summarizes the treatment options for dogs and cats with EPI.

Pancreatic Enzyme Supplementation

Pancreatic enzyme supplementation is the cornerstone of EPI treatment in the vast majority of cases. There are several different types of products that can be used for the management of EPI in animals and differences in efficacy may exist among them. Options generally include enteric-coated preparations, uncoated enzyme powder (as powder or in capsules), and raw pancreas. Most commercially available products contain pancreatic enzymes and proenzymes that are derived from porcine pancreas (in the form of dried extracts), while raw pancreas (which also contains pancreatic enzymes and proenzymes) is usually obtained from cattle or pigs.

Only a small proportion of the orally administered pancreatic enzymes remains functionally intact by the time they reach the small intestine. It has been reported that up to 85% of pancreatic enzyme activity can be lost in the stomach due to the acid pH and/or the action of gastric pepsins. Therefore, enteric-coated preparations have been developed to protect the enzymes from degradation in the stomach. There has been considerable discussion regarding the comparative efficacy of different products for the treatment of EPI. To add to the confusion, results of available studies have been conflicting. An early study suggested that enteric-coated preparations were less effective than uncoated preparations, while a more recent study suggested that there was no

Table 54.1 Treatment options for dogs and cats with exocrine pancreative insufficiency (EPI)

	Dosage regimen		
Medication	**Dog**	**Cat**	**Comments**
Pancreatic enzymes			
Powder	1–2 teaspoon per 10 kg in each meal	0.5–1 tsp per meal	Mix with food just prior to feeding (powder) or give with food (enteric-coated formulations)
Enteric-coated formulations			Titrate to the minimum effective dose when clinical signs are in remission
Raw pancreas	50–100 g per meal, mixed with food	30–90 g per meal, mixed with food	Rarely, may cause oral bleeding and irritation. In these cases dose reduction is indicated
Antibacterials			
Tylosin	10–25 mg/kg q12h	10–25 mg/kg q12h	Treat for a minimum of 4 weeks
Metronidazole	10–15 mg/kg q12h	10–25 mg/kg q12h	The benefits of antibacterial treatment are uncertain in cats with EPI
Vitamin supplements			
Cobalamin (in the form or cyanocobalamin or hydroxycobalamin)	250–1000 μg, SC, weekly for 6–8 weeks or orally, daily for 8 weeks	250 μg, SC, weekly for 6–8 weeks, or orally, daily for 8 weeks	Measure serum cobalamin concentrations every 3–6 months after initial supplementation and treat as necessary with additional supplementation
Acid suppression medications			Not generally indicated

difference between coated and uncoated products. However, these studies were retrospective and uncontrolled. A more recent blinded, randomized, controlled trial showed that dogs receiving an enteric-coated pancreatic enzyme product responded better to treatment compared to dogs receiving identical but uncoated product. Therefore, enteric coating seems to be beneficial, although the results of this study may not be applicable to all preparations of enteric-coated pancreatic enzymes. In a recent retrospective study of 150 cats with EPI, there was no difference in the efficacy of different pancreatic enzyme products suggesting that all products might be similarly effective.

Fresh raw pancreas contains pancreatic enzymes and can be used to effectively manage animals with EPI. Raw pancreas should be fresh-frozen in aliquots, and each aliquot should be used with one meal. Raw pancreas is likely the most economical option for pancreatic enzyme supplementation but it is also associated with certain limitations. First, it can be difficult to obtain and inconvenient for most owners to process raw pancreas. More importantly, raw animal tissues might be contaminated with important pathogens (e.g., *Salmonella* spp., *Campylobacter* spp.) and may pose a risk for infection to both humans and animals. For these reasons, raw pancreas is not commonly used for the treatment of EPI in animals.

All dogs and cats with clinical EPI should receive pancreatic enzymes. Regardless of the product used, pancreatic enzymes are added to each meal. Preincubation of the food with pancreatic enzymes is not necessary. The starting dose varies depending on the manufacturer but is usually titrated to individual patients after initial treatment and resolution of clinical signs. In many animals, doses can be significantly reduced long term to the lowest effective dose. Enzyme supplementation therapy is required for the rest of the animal's life. Side-effects from pancreatic enzyme use are rare but may include oral bleeding and irritation that typically resolve with dose reduction.

Antibacterials

Some animals with EPI do not respond to pancreatic enzyme replacement therapy alone. In a large percentage of animals with EPI, this is believed to be partially due to small intestinal dysbiosis and/or bacterial overgrowth (SIBO), which might be present as a result of loss of the bacteriostatic effects of pancreatic secretions and the presence of excess undigested substrates that can be used by intestinal bacteria. However, studies of antibacterial use in dogs with EPI have not shown improved treatment response or prognosis consistently. In addition, no studies have compared the efficacy of different antimicrobial agents in the treatment of dogs and cats with EPI.

Because small intestinal dysbiosis/SIBO is believed to be common in dogs with EPI and is notoriously difficult to confidently diagnose, antimicrobials are usually used in conjunction with pancreatic enzyme supplementation at the beginning of EPI treatment. Alternatively, antimicrobials can be added to the treatment regimen if there is poor response to treatment with pancreatic enzymes alone. Antimicrobials commonly used include metronidazole, tylosin, and oxytetracycline, and are typically used for a minimum of 2–4 weeks (see Table 54.1). Some animals might need multiple courses of antibiotics throughout their lives. The role of intestinal bacteria and dysbiosis is much less clearly defined in feline EPI. Choices for antibacterial treatment in this species are similar to those in dogs, and can be used in cases that do not respond to treatment with pancreatic enzyme and cobalamin supplementation (see Table 54.1).

Cobalamin Supplementation

As mentioned previously, hypocobalaminemia and cobalamin deficiency are especially common (>80% of cases) in dogs and cats with EPI. Therefore, serum cobalamin concentrations should be measured in all animals with EPI. Cobalamin deficiency can lead to various gastrointestinal and systemic complications, and severe hypocobalaminemia has been reported to be a negative prognostic factor in dogs with EPI and cats with chronic gastrointestinal disease, that often co-exists with EPI in this species. Cats with cobalamin deficiency have been shown to have abnormalities in amino acid metabolism. In a recent publication reviewing 150 cats with EPI, cobalamin supplementation favorably affected the response to treatment, even in cats with normal serum cobalamin concentrations. Therefore, correction of cobalamin deficiency is important in both dogs and cats with EPI.

Because cobalamin deficiency can lead to cobalamin malabsorption, oral supplementation of cobalamin was considered not to be effective in dogs and cats with EPI. However, recent evidence suggests that oral supplementation of cobalamin might be equally effective in these cases. Cobalamin should be administered subcutaneously using the following dosage regimen: 250–1250 µg (depending on the size of the animal) once a week for six weeks, followed by an injection one month after that. Oral cobalamin should be administered at 250 µg (cats) or 250–1250 µg (dogs, depending on the size), daily, for 8 weeks. Serum cobalamin concentrations should

be checked one month after the last dose and then monitored periodically (e.g., every six months) as some animals may require repeated cycles or life-long cobalamin supplementation.

Dietary Modification

There are two major dietary factors believed to be important in the management of dogs with EPI: the fat content of the diet and the amount and type of dietary fiber. Historically, it has been suggested that a fat-restricted diet should be offered to dogs with EPI because adequate fat digestion and subsequent resolution of clinical signs may not be achieved with enzyme replacement therapy alone. One of the problems encountered with the use of low-fat diets in dogs with EPI is that weight gain could be difficult and slow to achieve, especially in large-breed and cachectic dogs. In addition, low-fat diets may contribute to deficiencies of fat-soluble vitamins given the fact that fat digestibility does not normalize after enzyme supplementation.

Studies in dogs with EPI failed to show a clear benefit of any diet (including low-fat diets) over another. In fact, different diets appeared to be more suitable for different dogs, suggesting that several diets should be tried in patients with EPI until the most appropriate one for a specific animal is identified. Therefore, the routine and exclusive use of fat-restricted diets in all dogs with EPI is not currently recommended. High-fat diets should probably be avoided, however, at least during the initial stabilization phase. In some cases, there might be no need to change the animal's original diet, if it is complete and balanced. The type of fat (e.g., long-chain vs medium-chain triglycerides) also does not seem to play a crucial role in the response to treatment.

It has been suggested by some authors that high-fiber diets should be used in dogs with EPI. However, there is no convincing evidence in the literature for such recommendation. High-fiber diets might prohibit weight gain in hyporexic animals as a result of low caloric density. In addition, certain types of fiber can impair the activity of pancreatic and brush border enzymes, potentially leading to reduced digestibility of nutrients. Therefore, high-fiber diets are currently not recommended in dogs with EPI.

No studies have evaluated the use of specific diets in cats with EPI. Therefore, dietary recommendations are based mainly on clinical experience and extrapolation from clinical experience with dogs. Fat-restricted diets should be avoided if possible, for the same reasons mentioned above for dogs. In addition, cats are strict carnivores and protein and fat are their main energy sources, while carbohydrates (which are often increased in fat-restricted diets) should be generally kept at low levels. As in dogs, high-fiber diets should probably be avoided in cats with EPI.

Histamine-2 Receptor Antagonists and Proton Pump Inhibitors

Histamine-2 receptor (H2 receptor) antagonists and proton pump inhibitors (PPIs) have been recommended by some as adjunctive treatment in animals with EPI. A large proportion of pancreatic enzymes, especially lipase, is inactivated in the stomach due to low pH. It has been hypothesized that acid-suppressing medications may reduce the hydrolysis of pancreatic enzyme supplements in the stomach through the increase of gastric pH, thus increasing efficacy. Obviously, this applies only to uncoated enzyme supplements and raw pancreas. However, no studies have evaluated the efficacy of acid suppression in the treatment of EPI in dogs and cats, and therefore their usefulness is questionable. In addition, the potential problem of reduced efficacy of enzyme supplements due to hydrolysis in the stomach could be overcome by increasing the dose of enzymes or by using products with enteric coating. Therefore, the routine use of acid suppression medications is currently not recommended.

Prognosis

Although clinical improvement is noted in the vast majority of dogs and cats treated appropriately for EPI, a percentage do not respond well to treatment for reasons that have not been clearly defined. Good initial response to treatment is seen in approximately 60% of dogs and cats with EPI, with the remaining animals showing either partial (~20%) or poor (~20%) response. Partial or poor response is usually indicated by the animals remaining underweight or having soft stools.

Median survival time for dogs with EPI has been reported to be approximately five years. The most important parameter that affects survival seems to be initial response to treatment, with animals that have a good initial response surviving on average almost eight times longer than those with poor response. Therefore, animals that respond well to initial treatment seem to survive for long periods. As mentioned above, hypocobalaminemia has been shown to be a negative prognostic factor, and animals with severe hypocobalaminemia survive half as long as animals without severe hypocobalaminemia. The nature and severity of clinical signs, signalment, and different therapeutic interventions do not seem to have important prognostic significance. No data are available for survival and prognosis in cats with EPI.

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55

Pancreatitis in the Dog

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Etiology/Pathophysiology

Pancreatitis in the dog includes an array of presentations, from low-grade inflammation incidentally discovered to animals with severe, life-threatening systemic disease. Clinically, veterinarians often use the term chronic pancreatitis (CP) to describe instances where the clinical signs are mild, whereas acute pancreatitis (AP) is the term used when there is greater severity and a rapid onset of clinical signs. This clinical classification, however, does not always correlate with the histologic classification.

Histologically, AP is defined as neutrophilic inflammation, without fibrosis or exocrine atrophy, which is usually present within the body of the pancreas and/or peripancreatic fat. There have been extensive experimental studies, predominantly in rodent models, of initiating events of AP. In essence, AP develops when inert zymogens (precursors of digestive enzymes) are activated within pancreatic acinar cells rather than within the duodenal lumen. If this occurs at a low level, safeguards such as pancreatic secretory trypsin inhibitor (PSTI) come into play and mop up the activated pancreatic enzymes within the body of the pancreas. Once PSTI is overwhelmed, there is an influx of proinflammatory cytokines (especially interleukin-8) and neutrophils. Other inflammatory pathways are then also stimulated including the complement, kallin-kallikrein, and nitric oxide pathways. Circulating anti-inflammatory mediators (such as alpha-macroglobulins) can initially counteract this inflammatory state, but in many situations are themselves overwhelmed. When pro-inflammatory pathways overcome defences, there is reduced pancreatic microcirculation, as well as ongoing inflammation and necrosis within the pancreas due to neutrophil migration and adherence. This inflammation and necrosis theoretically therefore starts in the pancreatic acinar cells, but when severe spills out into the peripancreatic fat.

Although some dogs with AP may have self-limiting disease or mild clinical severity (mild abdominal pain, vomiting), others develop systemic complications due to activation of the multiple inflammatory cascades. The cause of abdominal pain is considered to be distension of the pancreatic capsule, or via stimulation of mesenteric pain receptors by inflammatory exudate. The pathophysiology of pain is quite complex: the nociceptive (ascending) pathway travels via the dorsal horn, and is mediated by amino acid (glutamate and aspartate) and neuropeptide (substance P, neurokinin A, and calcitonin gene-related peptide) release. If there is ongoing nociceptive input, activation of N-methyl-D-aspartate (NMDA) receptors may occur, which is considered a key step in the development for central sensitization. Vomiting occurs due to both central and peripheral stimulation of vomiting pathways, but the exact mechanism has not been confirmed for AP. Systemic effects of AP relate both to the clinical signs (hypovolemia, etc.) and the presence of circulating proinflammatory mediators.

There are many potential factors that may initiate or trigger the initial activation of pancreatic zymogens within the acinar cells. Experimentally, it has been shown that co-localization of lysosomal granules and zymogen granules leads to zymogen activation. This effect appears to be amplified by a reduction in acinar cell pH, and is considered to be the mechanism by which activation occurs in people with sudden increases in intracellular calcium (as can occur during cardiopulmonary bypass). In dogs, the most commonly implicated causes of AP include dietary indiscretion, drugs, trauma, and unknown (or idiopathic). High-fat, low-protein diets in particular are clearly implicated in causing AP in dogs and rodent models; clinically this is typically in association with long-term feeding of urolithiasis diets. There is a large list of drugs that may cause idiosyncratic pancreatitis, but the most frequently implicated drugs include azathioprine, potassium

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bromide, and organophosphates. Onset of pancreatitis can occur immediately after starting these medications. In some cases, there is delayed onset of drug-induced pancreatitis, particularly in humans; this would make the link more difficult to prove in dogs. Trauma is also well recognized as a cause of AP but the pancreatic trauma is usually one of a constellation of abnormalities. Often, no inciting cause is identified; however, unobserved dietary indiscretion may still occur in these cases.

Chronic pancreatitis (CP) is defined histologically as lymphocytic-plasmacytic inflammation of the pancreas and peripancreatic area with presence of concurrent fibrosis. Although pancreatic function is generally preserved, dogs with CP can develop diabetes mellitus or exocrine pancreatic insufficiency associated with the fibrosis. The etiology of CP is poorly understood in dogs. The currently accepted rationale for CP in humans is called the sentinel acute pancreatitis event (SAPE) hypothesis. With the SAPE hypothesis, pancreatic acinar cells initially come under some type of oxidative stress (e.g., fats, alcohol, oxidative products in the bile), but do not develop any inflammation or fibrosis. When the acinar cells are sufficiently stimulated by the oxidative stress, a pro-inflammatory response occurs (the acute pancreatitis event). If the oxidative stresses are removed at this point, the pancreas generally heals with no ongoing consequences. However, if there is perpetuation of low-grade inflammation in response to continued oxidative stresses, stellate cells that migrate to the pancreas in response to secretion of proinflammatory cytokines are stimulated, leading to periacinar fibrosis. It is not certain if SAPE occurs in dogs, as many or most of the oxidative stressors do not generally occur chronically in the canine population, but the rationale appears logical to apply.

There are also multiple genetic abnormalities that predispose humans to CP, including mutations of cationic trypsinogen, which cause spontaneous production of trypsin in the acinar cells. To date, no similar genetic mutation has been identified in dogs, although investigations are still ongoing. Additionally, autoimmune disease is strongly suspected to occur in cocker spaniels, and may be similar to the autoimmune form of pancreatitis identified in people. Obstructive causes of CP are not common in dogs, and dietary indiscretion is not thought to be as important a trigger for CP as it is for AP.

Epidemiology

The true incidence of pancreatitis is difficult to determine, as definitive antemortem diagnosis is often problematic. In one study assessing dogs submitted for postmortem at a first opinion practice, the prevalence of CP was 34%, with over half of those classified as having moderate or marked pancreatic inflammation. Similarly, inflammation or fibrosis was identified in approximately 50% of dogs in a postmortem study at a referral institution. There appears to be a breed predisposition for spaniel breeds, particularly cocker spaniels. This may reflect the dog population in the study region, but anecdotal evidence would support this statement to hold in a wider dog population. These prevalence studies raise two major points. Firstly, CP is probably grossly underrecognized due to the difficulties in diagnosing the condition antemortem. Secondly, histologic changes may not be clinically important, and postmortem studies may actually overemphasize the importance of CP or the sensitivity of various tests.

The incidence of AP is similarly difficult to determine, although it is a condition that occurs worldwide. Anecdotal reports would suggest that AP is the most commonly diagnosed emergency presentation of the gastrointestinal system in dogs. In most reports, middle-aged, overweight dogs appear to be predisposed.

History and Clinical Signs

Acute Pancreatitis

The clinical presentation of AP is initially related to the development of gastrointestinal clinical signs: vomiting, anorexia, and abdominal pain. Abdominal pain may be subtle or difficult to determine initially but can be manifested as severe (e.g. crouching in prayer position and excessive restlessness). The severity of these clinical signs along with the duration of onset also determines the findings. Animals may be weak or obtunded and in hypovolemic shock if there is a rapid reduction in circulating blood volume and vasoconstriction due to systemic inflammation. This spectrum of clinical signs is incorporated in Table 55.1. Rectal temperature can be increased (due to inflammation) or decreased (due to shock), and some dogs may also present with neurologic signs. Roughly one-third of dogs will also reportedly have diarrhea or melena.

Co-morbidities such as diabetic ketoacidosis (DKA) may be present. It is considered probable that DKA develops secondary to overwhelming destruction of the pancreatic tissue; however, it is also possible that the acidotic state in DKA leads to pancreatitis. However, with preexisting or undiagnosed diabetes, dogs can be expected to also have a history of polyuria/polydipsia and weight loss.

The systemic nature of severe inflammation also means that animals may have respiratory signs (due to development of acute lung injury and/or pleural effusion), neurologic abnormalities (due to thromboembolic

Table 55.1 Classification of clinical signs into severity categories

Severity of presentation	Mild	Moderate	Severe
Gastrointestinal signs	Vomiting 1–2 times/past 12 hours	Vomiting 4–6 times/past 12 hours; occasional regurgitation; melena; hematochezia; no gut sounds auscultated in 24-hour period	Vomiting or regurgitation 6 times/past 12 hours, or for longer than 36 hours; no food for >3 days; plus any of the following: melena, absent gut sounds 24 hours, hematochezia
Dehydration	Skin tent	Skin tent, weak pulses	Marked skin turgor, prolonged capillary fill time, injected mucous membranes, tachycardia, weak/thready pulses
Abdominal pain	May be unsettled and respond when abdomen palpated	Decreased response to surroundings, stretches and looks around at abdomen, flinches or snaps on abdominal palpation	Non-responsive to stimuli, screams, cries or snaps when moving or abdomen palpated
Heart rate (HR)	Tachycardia with no pulse deficits	Occasional ventricular premature complexes or sustained HR >180/min	Paroxysmal or sustained ventricular tachycardia
Respiratory rate	Normal	Dyspnea or tachypnea (>40 breaths/min)	Signs consistent with pneumonia, pleural effusion
Vascular forces	Normal systolic blood pressure (BP) and albumin >18 g/L	Systolic BP <60 or >180 mm Hg or albumin <18 g/L	Systolic BP <60 and >180 mmHg and serum albumin <18 g/L

Source: Adapted from Mansfield et al. (2008).

disease), cardiac arrhythmias, and signs associated with renal failure (oliguria, obtundation).

Local complications can also occur, such as extrahepatic bile duct obstruction (EHBDO); EHBDO may develop due to physical obstruction of the bile duct by an enlarged and inflamed pancreas, or due to decreased motility of the bile duct mediated by local peritonitis. Regardless, dogs with EHBDO are jaundiced, although as a complication it generally occurs late in the progress of disease and often the dog appears to be recovering. Another local complication is the development of fluid-filled regions within the pancreas, often associated with necrosis (Figure 55.1). These acute fluid collections may be incidental findings, but often are associated with a sudden increase in abdominal pain. True pancreatic abscessation is extremely unlikely in dogs, and pseudocysts develop weeks following an acute episode of pancreatitis.

Chronic Pancreatitis

Chronic pancreatitis is generally a milder presentation than AP. In some circumstances, there may be no associated detectable clinical signs. In other dogs, there may be a single episode or waxing and waning loss of appetite, mild vomiting, and abdominal pain. Diabetes mellitus may occur in conjunction with CP, and so flares of pancreatic inflammation may coincide with periods of insulin resistance. Similarly, CP may be concurrent with exocrine pancreatic insufficiency and the clinical signs of the latter may predominate.

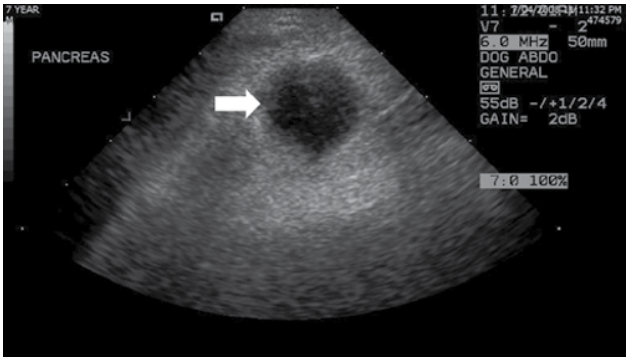
Diagnosis

Routine Laboratory Tests

Routine hematology is fairly nonspecific in pancreatitis, although a stress leukogram is usually present. As AP is a systemic inflammatory condition, there may also be changes in other white blood cell concentrations.

Biochemical changes reflect the degree of dehydration and hypovolemia present (increased total protein, azotemia, electrolyte derangements, etc.) but are not pathognomonic for pancreatitis. Total lipase and amylase activities can be markedly increased in AP, but can also be normal in severe AP and increased with nonpancreatic disease. Both renal disease and administration of dexamethasone can increase serum lipase and/or amylase activities, without primary pancreatitis being present. Due to the inherent issues with sensitivity of routine lipase assays, a catalytic assay utilizing a more selective lipase substrate (1,2-o-dilauryl-rac-glycero-3-glutaric acid-{6′-methylresorufin} ester [DGGR]) has been recently assessed. The DGGR assay appears to have higher sensitivity than routine lipase assays, and has similar findings to ELISA-based measurements of specific pancreatic lipase concentrations (details of this test are given later). Often dogs with AP have grossly lipemic serum, and although this may be a consequence of fat saponification during the disease, fasting serum cholesterol and triglycerides should be measured 1–2 weeks after recovery to ensure that hyperlipidemia is not an inciting factor.

(a)



(b)

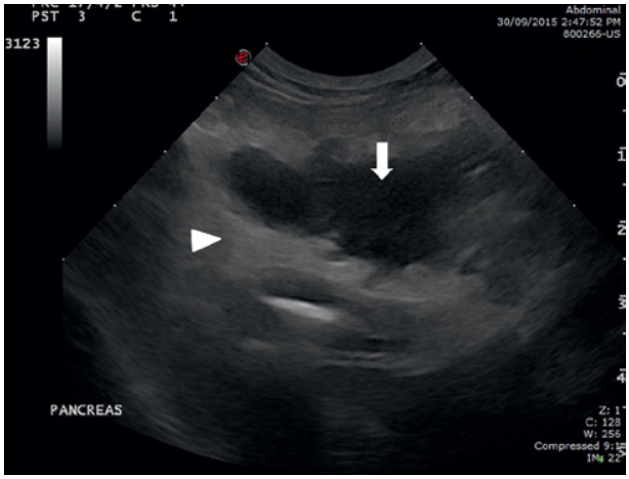


Figure 55.1 (a) Ultrasound image of pancreas with large fluid-filled lesion (*white arrow*). (b) Irregular and ill-defined fluid collection (*white arrow*) surrounded by hyperechoic fat (*arrowhead*). If either of these were present in a dog with increasing levels of pain, then percutaneous drainage should be recommended.

Pancreas-Specific Biochemistry

Until the past decade, pancreas-specific enzymes such as trypsin-like immunoreactivity or trypsinogen activation peptide have not been considered useful in diagnosing either AP or CP. Canine pancreatic lipase (cPL) has been developed into a commercially available ELISA test (Spec-cPL), and is now used widely in veterinary practice. It is thought that cPL is only produced in the pancreas, and is affected less by non-pancreatic disease than total lipase. There have been some studies that show clearance of cPL is not affected by acute or chronic reductions in glomerular filtration. The reference interval for the laboratory ELISA is <200 µg/L in healthy dogs, with results >400 µg/L considered consistent with a diagnosis of pancreatitis in dogs with compatible clinical signs. There is also an in-clinic rapid semiquantitative assay (SNAP-cPL™, Idexx Laboratories) that shows good alignment and reproducibility with the laboratory-based ELISA.

There have been a number of studies evaluating cPL for the diagnosis of pancreatitis (Table 55.2). Overall, cPL should be considered highly specific for pancreatitis. Sensitivity of the cPL assay appears to be high in animals with AP, but less so for CP. When interpreting cPL, it should be remembered that pancreatic inflammation may be present, but not be the cause of the clinical presentation. The most relevant application of this is when there are duodenal foreign bodies or septic peritonitis that can cause "bystander" pancreatic inflammation. Misdiagnosis in this situation could fail to identify that surgical correction is required.

Pancreatic elastase (PE-1) is another enzyme considered to be pancreas specific. There is a commercially available canine PE-1 (cPE-1) ELISA (ScheBo·Elastase 1-Canine, ScheBo Biotech AG, Giessen, Germany). It appears that PE-1 has wide variation in healthy dogs, and similar sensitivity and specificity to cPL when assessing dogs with severe AP (see Table 55.2). However, this premise should be tested in a larger cohort of dogs.

Diagnostic Imaging

Diagnostic imaging is an important component of the investigation of dogs presenting with signs of abdominal disease. The major indication for abdominal radiographs is to rule out the presence of surgical disease such as intestinal obstruction or gallbladder rupture. The changes associated with AP are nonspecific on radiographs and include loss of detail in the cranial abdomen, and on the VD view, pushing of the proximal duodenum laterally (Figures 55.2 and 55.3).

Ultrasound is generally accepted as the most useful diagnostic imaging modality to evaluate the pancreas in clinical practice. Full abdominal ultrasound is recommended to assess for the presence of free fluid or other diseases. Changes described in CP are fairly vague, and it is considered that this diagnosis is difficult to make definitively via ultrasound. Pathognomonic signs of AP include an enlarged, hypoechoic pancreas surrounded by bright, hyperechoic fat and mesentery (Figure 55.4).

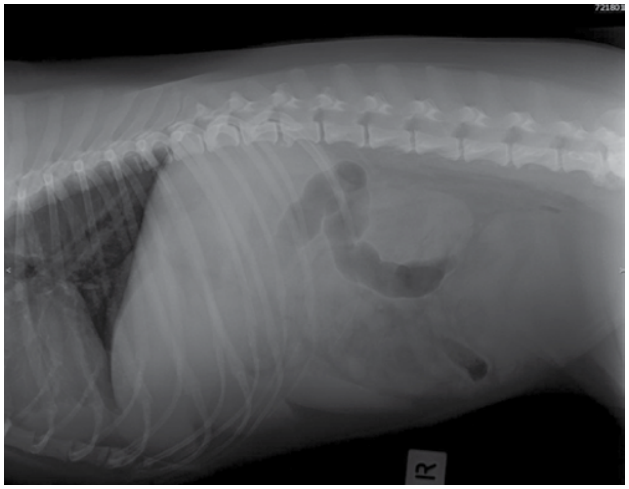
To date, more advanced imaging modalities such as magnetic resonance imaging (MRI) or computed tomography (CT) are infrequently performed in dogs with AP, due to the prolonged anesthesia required and the accepted sensitivity of ultrasound. The use of CT imaging in people is more frequently done, and can identify infected necrosis and other changes with a high degree of sensitivity.

Table 55.2 Summary of sensitivity and specificity for various laboratory testing in dogs from various studies

Study	Number of dogs	Method of diagnosis	Analyte assessed	Sensitivity (%)	Specificity (%)
Haworth *et al. J Vet Emerg Crit Care* 2014;24(2):135–43	n = 38 AP = 11 Non AP = 26	Clinical evaluation of dogs presenting with acute abdominal disease	SNAP-cPL	82	59
			Spec-cPL >400 µg/L	70	77
Chartier *et al. Vet J* 2014;201:385–9	n= 14 AP n = 19 non-AP (11 pure/ modified transudate, 1 septic exudate, 2 nonseptic exudate and 5 hemorrhagic effusion)	Clinical evaluation	Peritoneal CPL >500 µg/L	100	94.7
			Peritoneal amylase >1050 U/L	71.4	84.2
			Peritoneal total lipase >500 U/L	92.9	94.7
McCord *et al. J Vet Intern Med* 2012;26:888–96	n = 84 AP = 57 Non-AP = 27	Combination of clinical and imaging results	Spec-cPL >400 µg/L	71.7–77.8	80.5–88
			Lipase	43.4–53.6	89.3–92.5
			Amylase	52.4–56	76.7–80.6
Mansfield *et al. J Vet Diag Invest* 2012;24:312–18	n = 32 Minimal/no inflammation = 20	Histology	Spec-cPL >400 µg/L	NA	90
Trivedi *et al. J Vet Intern Med* 2011;25:1241–7	n = 70 Mild AP = 56 Moderate-severe AP = 7 Normal pancreas = 7	Histology	Spec-cPL >400 µg/L	21 (mild) 71 (mod-severe)	100
			TLI	30 (mild) 29 (mod-severe)	100
			Lipase	54 (mild) 71 (mod-severe)	43
			Amylase	7 (mild) 14 (mod-severe)	100
Mansfield *et al. J Vet Diag Invest* 2011;23:691–7	n = 61 AP = 41 CP = 3 Pancreatic carcinoma = 5 Nonpancreatitis = 12	Histology	CPE-1 >17.24 ng/mL	61.4 (all) 66 (AP) 78 (severe AP)	91.7
Neilson-Carley *et al. Am J Vet Res* 2011;72:302–7	n = 64 AP = 20 Other disease = 17 Healthy = 27	Histology	Spec-cPL >400 µg/L	NA	95%
Steiner *et al. Vet Ther* 2008;9:263–73	n = 22	Gross evidence at postmortem	Spec-cPL >400 µg/L	63.6	NA
			Lipase	31.8	NA
			Amylase	40.9	NA
Steiner *et al. J Vet Intern Med* 2001;15:274	n = 11 (Severe AP)	Clinical findings and histology	Spec-cPL >400 µg/L	88	NA
Mansfield and Jones *Aust Vet J* 2000;78:416–22	n = 42 AP = 15 Non-AP = 27	Clinical findings and histology	Lipase >3 × RI	63.6	54.6
			Amylase >3 × RI	22.7	78.1
			TLI >100 µ/L	37.5	89.3

Source: Adapted from Mansfield (2013).
AP, acute pancreatitis; CP, chronic pancreatitis; CPE-1, serum canine pancreatic-elastase-1; cPL, canine pancreatic lipase (or canine pancreatic lipase immunoreactivity in earlier studies); NA, not assessed; RI, reference interval; TLI, trypsin-like immunoreactivity.

(a)



(b)

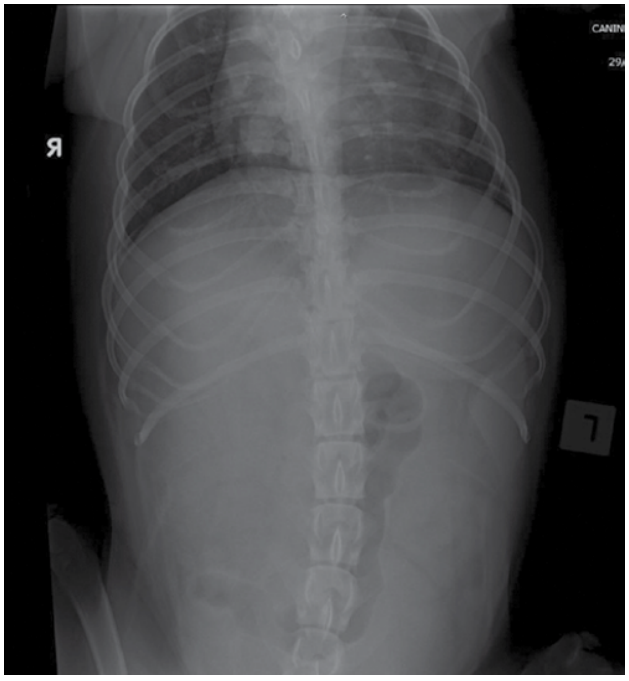


Figure 55.2 Abdominal radiographs of a dog with free fluid (lateral (a) and VD (b)). The cause of the effusion cannot be determined by radiographs alone. Fluid analysis and further imaging is required.

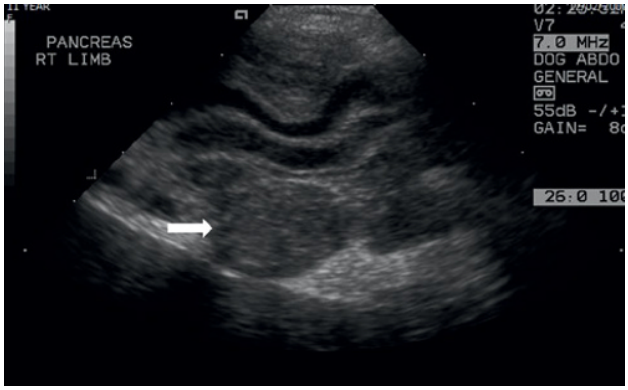
Cytology and Histology

Cytology is not used frequently in evaluating dogs with AP. However, abdominal fluid analysis should form part of the work-up to ensure that a septic or neoplastic process is not missed. Dogs with AP will generally have a suppurative, non-septic exudate present. A recent study in a small number of dogs with AP determined that measurement of cPL in peritoneal fluid had a sensitivity of 100% when using a cut-off value >500 µg/L. Caution



Figure 55.3 VD radiograph of a dog with acute pancreatitis. The descending duodenum is pushed laterally (*arrow*) and there is decreased contrast in the cranial abdomen.

(a)



(b)

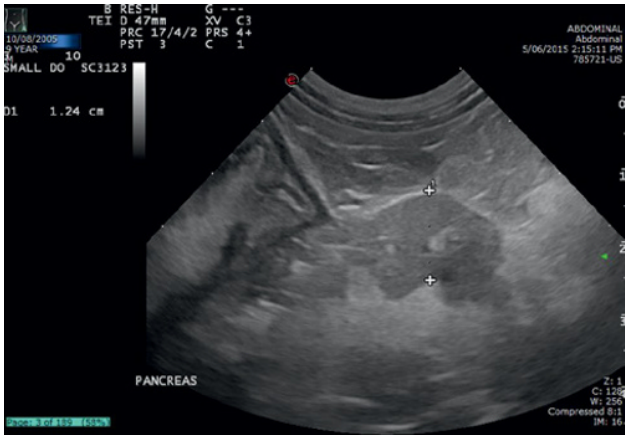


Figure 55.4 (a) Ultrasound image of enlarged hypoechoic right pancreatic limb (*arrow*). (b) In this ultrasound image, the pancreas is larger and more heterogeneous in appearance, with hyperechoic speckling of surrounding fat.

should be applied before relying extensively on this, as the study had only a few dogs with inflammatory/septic exudates as comparison.

Aspiration of fluid-filled collections within the pancreas may have a therapeutic benefit (described later). Fine needle aspirates (using a 25 G needle) can safely be obtained from the pancreas and may be beneficial in some cases of CP. Cytology is generally considered of marginal utility in AP, as there is often such a large degree of necrosis and inflammation that the samples are nondiagnostic and/or cellular criteria overlap with malignancy.

Histologic evaluation of pancreatic biopsy is considered the gold standard for diagnosis of pancreatic pathology. This is seldom obtained in dogs with AP, due to the morbidity associated with this procedure. The most common finding in dogs with AP is widespread necrosis of pancreatic and peripancreatic tissue. In dogs with milder, more intermittent clinical signs, exploratory laparotomy is more commonly indicated. The stomach, intestines (distal and proximal small intestine), mesenteric lymph nodes, and liver should all be sampled in addition to the pancreas.

A summary of the diagnostic approach recommended when dogs present with severe signs compatible with AP is shown in Figure 55.5.

Therapy

Acute Pancreatitis

Treatment of AP is generally supportive and nonspecific. The major "triad" of treatment is IV fluids, analgesia, and nutritional support. Fluid therapy should be tailored to the individual dog, with correction of electrolyte losses and restoration of circulating blood volume and acid–base balance being of the utmost importance. A recent study in humans suggested that using alkalinizing fluids (Hartmann's solution) produced a better response than acidifying solutions (saline) and so extrapolation would suggest that this (or alternatively, lactated Ringer's solution) would be a good first-line fluid choice in dogs. The volume of IV fluids required to correct blood volume may be higher than can be tolerated, and potentially lead to pulmonary edema or other signs of volume overload. In those circumstances, the use of colloid therapy may be of benefit. There is little to no evidence that using plasma will be beneficial in dogs with AP unless they have overt coagulation disorders.

Analgesia is essential in dogs that have AP, even if little pain is observed. Abdominal pain can be categorized as mild, moderate or severe (see Table 55.1). The principle behind analgesia in these situations is to start with the maximal combination/dose considered necessary for the level of pain and then titrate down (rather than starting low and titrating up if ineffective). Ideally, analgesic protocols in AP should avoid the use of drugs such as fentanyl that dramatically reduce gastrointestinal motility. However, if pain is not controlled by the recommended protocols, then using fentanyl as a constant rate infusion (CRI) should be considered. The addition of methylnaltrexone may mitigate the decreased GI motility in those circumstances.

A partial mu-agonist such as buprenorphine or full mu-agonist such as methadone should be considered as the baseline therapy (starting at maximum doses and intervals: 10–40 µg/kg q6–8h and 0.1–0.5 mg/kg q4–6h respectively, then tapering down). If pain is moderate then ketamine (5–20 µg/kg/min) and lidocaine (25–50 µg/kg/min) CRIs should be started at the higher dosage end. Once pain is well controlled, the ketamine should be reduced first, followed by lidocaine and then tapering of the opioid. With severe pain, epidural morphine (0.1 mg/kg q12–24h) or a fentanyl CRI (0.2–0.8 µg/kg/min) should be given, along with the lidocaine and ketamine as above. Once pain is controlled, the epidural/CRI is swapped for intermittent opioid, then all are tapered as previously described.

If possible, oral gabapentin (10 mg/kg q12–24h) could also be administered. If there is a sudden relapse of pain, the pancreas should be reexamined via ultrasound for the presence of a fluid collection. In people, aspiration of fluid collections is recommended when they are sterile, in preference to surgical debridement. Even in infected necrosis, control with antibiotics is undertaken before any surgical procedures. As virtually all the fluid collections in dogs will be sterile, and pancreatic surgery is associated with high morbidity and mortality rates, percutaneous drainage of fluid-filled areas is advocated for dogs as well. This can be performed using mild sedation and fine needle aspiration.

Nutritional support is the third major component of management. In people and dogs with critical illness, lack of enteral nutrition has been shown to perpetuate systemic inflammation as well as leading to mucosal atrophy and other changes. In mild-to-moderate cases of AP, the current rationale is to start enteral feeding if there has been no/little enteral nutrition for more than five days. In severe cases of AP, the earliest possible enteral nutrition is advocated. Dogs with severe AP can tolerate esophageal tube feeding, and so surgery or prolonged anesthesia to insert jejunostomy tubes is not essential. If the animal is moribund or unable to withstand a general anesthesia, then nasoesophageal tube feeding should be started as soon as possible. Once they are able to have GA safely, then an esophageal (E) tube should be inserted. Dogs can still be offered food by

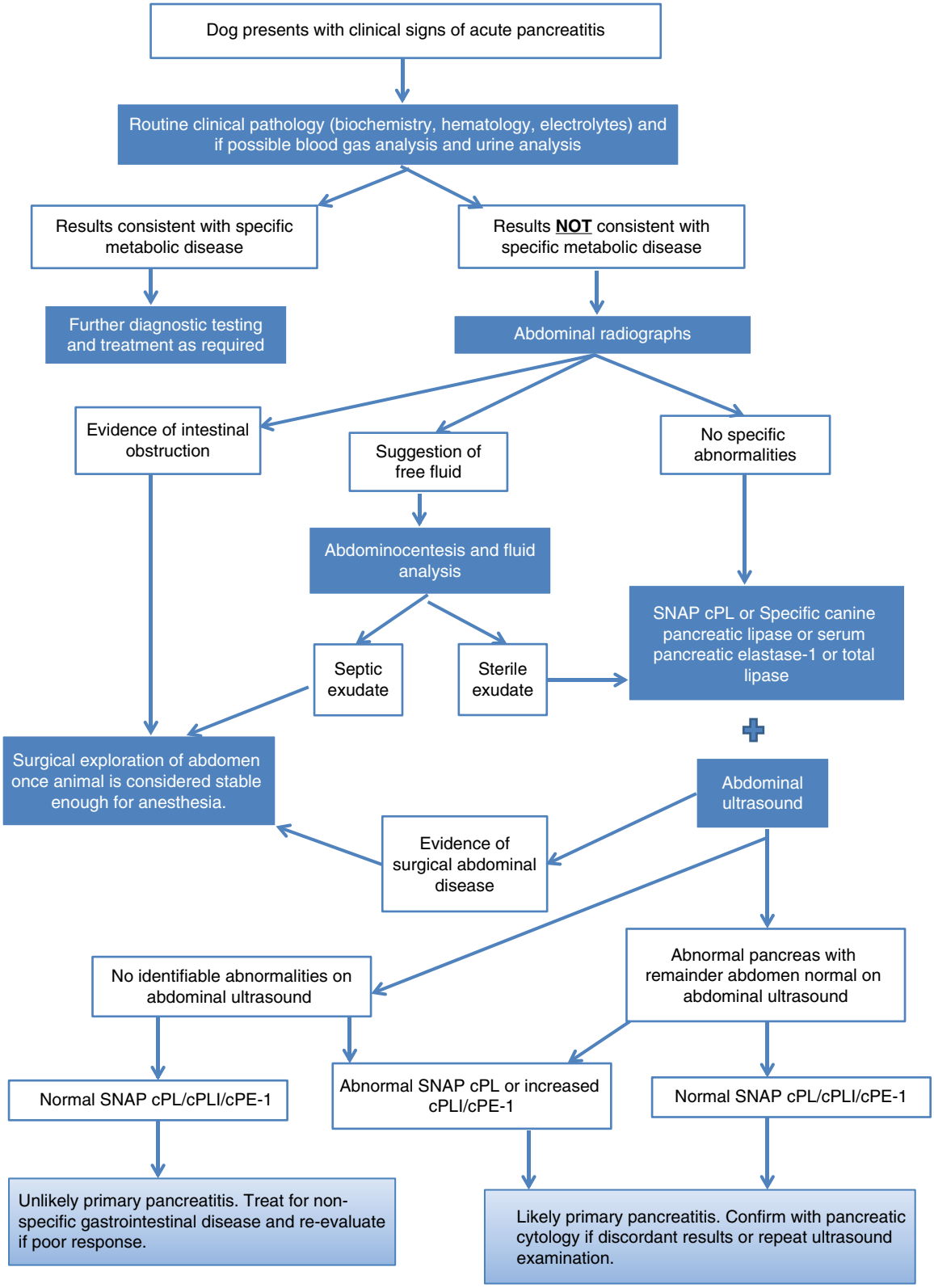


Figure 55.5 A diagnostic algorithm for the diagnosis of acute pancreatitis in the dog. *Source:* Mansfield (2013). Reproduced with permission of Elsevier.

mouth, and can be sent home with an E tube in place if necessary.

The biggest complications associated with interventional enteral nutrition are aspiration pneumonia and tube site infection. Close attention should be paid to the tube site to avoid the latter. To avoid regurgitation and development of aspiration pneumonia, it is not recommended to feed full resting energy requirements (RER) unless the feeding is extremely well tolerated. Rather, the first 24 hours should be 25% RER and titrate up slowly each day. Similarly, there is no evidence that a specific diet will result in improved outcome or speed of recovery, and as such any balanced convalescent diet for dogs is generally well tolerated.

Another important aspect of management of AP is to reduce vomiting and control nausea. Due to the role of substance P in mediating abdominal pain and vomiting, maropitant should be considered a first-line antiemetic drug. If vomiting is poorly controlled, or the dog appears to have severe nausea, then additional medications such as ondansetron (0.5 mg/kg IV then q12–24h) can be added. There is a theoretical disadvantage in using metoclopramide as it inhibits dopamine in rodent models. Due to the potential prokinetic benefits of metoclopramide a CRI should still be considered if decreased GI motility is thought to be contributing to nausea/inappetence.

There is little to no evidence that administering gastric acid suppressants does anything to reduce morbidity of AP in dogs. However, if there is melena or hematemesis then use of a proton pump inhibitor should be considered. The presence of any systemic complications such as pleural effusion or ventricular tachycardia should be assessed and treated as required. Antibiotics are not necessary unless bacterial translocation is considered likely.

The area most likely to undergo investigation in the future is targeted antiinflammatory therapies and analgesic agents. Similarly, the use of corticosteroids may be further evaluated, particularly when hypotension appears to be nonresponsive to fluid therapy.

Follow-Up

If an inciting cause (such as drug or food) is known, then this should be removed. Dogs can be discharged with feeding tubes in place if required, and a low-fat diet is currently recommended. This should generally be fed for 1–2 weeks and then the dog should be reevaluated and fasting serum triglyceride and cholesterol concentration measured. If these are high, investigations should be undertaken for underlying causes of hyperlipidemia and treatment, including diet, continued as appropriate. If there is no hyperlipidemia, dogs can be transitioned back to their regular diet. Analgesia may be necessary in the early stages following hospitalization, and medication such as tramadol or gabapentin dispensed.

Anecdotally, tramadol may cause inappetence and so gabapentin may be a better alternative. In people, after a bout of severe AP subclinical EPI exists for approximately four weeks following resolution. It is not certain if this occurs in dogs, but it may be therapeutically useful to supplement pancreatic enzymes for a short period after discharge. Animals should not be discharged if they still need antiemetic therapy.

Chronic Pancreatitis

Unfortunately, treatment options for CP are poorly explored, and the benefit of proposed treatments is unsupported. It does make sense to look for underlying causes of CP that can be corrected, such as hyperlipidemia. If there is hyperlipidemia, then an underlying endocrinopathy should be considered, particularly hypothyroidism. If both triglycerides and cholesterol are increased, then an inherent defect in lipid metabolism is more likely. In the absence of an endocrinopathy, treatment should initially consist of feeding a low-fat diet, with <15% dry matter as fat. Other treatments such as omega-3 fatty acid supplementation (20–30 mg/kg day) can also be used, but should be gradually introduced as they can cause gastrointestinal signs in their own right. If triglycerides (TG) alone are high and do not decrease with dietary management then gemfibrosil (7.5–10 mg/kg PO q12h) may be used. Other less well-established treatments such as chitin (binds lipids in the diet) and niacin (to reduce liver TG synthesis) may also be beneficial. For treatment of high cholesterol (with normal TG) when dietary treatment is ineffective, a statin (HMG CoA-reductase inhibitors) may be used. Safety margins are high for this group of drugs in dogs, and a dosage of 10–20 mg PO once daily is currently recommended for lovastatin. If the animal is not hyperlipidemic, there is no evidence for benefit from feeding a low-fat diet. However, this is frequently done in practice and if the diet is well balanced, long-term feeding of it is unlikely to cause harm.

If no underlying cause is diagnosed and CP is confirmed or strongly suspected, then the dilemma is whether to treat with analgesia alone or with additional antiinflammatory/immune suppression. Ideally, immune suppression should be used only when there is histologic confirmation of lymphocytic inflammation within the pancreas. If the dog is not diabetic, prednisolone is the drug of choice for both immune suppression and to treat inflammation/fibrosis, albeit at different dosages for the different effects. Prednisolone has been removed from the register of drugs that can potentially cause

pancreatitis in people, and studies have shown that glucocorticoids do not cause any histologic changes in dogs. If the dog is diabetic, it is not appropriate to use prednisolone due to increased insulin resistance. Ciclosporin is a viable treatment option for CP in diabetic dogs, but it is expensive in medium to larger breeds. Azathioprine has been implicated as causing pancreatitis in dogs, but this is a weak association. More importantly, it has not been shown that dogs with preexisting idiopathic or dietary-induced pancreatitis are more likely to develop reactions to azathioprine.

The pathogenesis of pain in CP is complex and multifactorial. Studies in humans have shown that the degree of fibrosis is not related to the degree of pain, and that interaction between the nervous system and inflammatory process is crucial. Major mediators of pain in CP appear to be calcitonin gene-related peptide (CGRP) and substance P, acting through the neurokinin-1 receptor. Therefore, during acute bouts of inflammation, treatment with a NK1 receptor antagonist such as maropitant may be of benefit in multiple ways (antiemetic, reducing pain and potentially directly attenuating the systemic inflammatory response). Additionally, the concept of neuronal plasticity suggests that the longer inflammation has been present, the more severe the pain associated with it will be. The most effective method of long-term analgesia that can be administered at home in dogs is probably tramadol, and/or gabapentin.

Prognosis

The reported mortality rate for AP in dogs ranges from 27% to 58%. This reported rate may not reflect the mortality in general veterinary practice, as the reports originate from referral centers, and euthanasia for non-medical reasons (i.e., financial) may also exert an influence. Even taking these factors into account, there apparently is a higher mortality rate in dogs with AP than the 5–15% reported in human studies. Chronic pancreatitis is unlikely to carry a high mortality rate if it occurs in isolation, but as a co-morbidity it may exert a negative prognosis on other co-existing diseases.

Conclusion

The pancreas should be considered in a similar light to the liver, in that many intraabdominal diseases can cause secondary inflammation and changes within the pancreas. To attribute clinical signs in a dog to pancreatitis, all other abdominal diseases such as septic peritonitis or intestinal foreign body obstruction, for instance, should be excluded. Treatment of acute and chronic pancreatitis is nonspecific and supportive. This too suggests that exclusion and management of concurrent or primary disease are often more important than a definitive diagnosis of pancreatitis in itself.

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56

Pancreatitis in the Cat

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In the veterinary profession, attitudes to pancreatitis in cats have undergone a massive shift in relatively recent times. From an earlier perspective that pancreatitis was an uncommon disease in the cat, recent findings and the introduction of new diagnostic testing modalities have led to the understanding that pancreatitis is actually common in the feline patient. Pancreatitis may actually be one of the most common diseases of the domestic cat, and is often an important co-morbidity with other diseases. This is particularly true of diseases of the gastrointestinal tract and liver. The actual importance of pancreatitis in the overall health of the domestic cat remains somewhat unclear, in part due to the very different pathology of most cases of pancreatitis in this species and the markedly different way in which cats tend to manifest this disease when compared to dogs.

In large part, this relatively recent change in attitudes to feline pancreatitis has arisen with the development and ready availability of much more sensitive and specific diagnostic tests for this disease. Advances in the resolution and availability of ultrasound imaging, new noninvasive diagnostic tests for specific markers of pancreatic tissue integrity and increased willingness to obtain pancreatic biopsies and histopathologic assessment have all been extremely valuable in advancing our knowledge of this disease.

The purpose of this chapter is to provide an overview of the presenting signs and histories, diagnostic approach to, and current recommendations for the management of pancreatitis in the domestic cat.

Clinical Signs and Symptoms of Pancreatitis in Cats

History and Physical Examination Findings

A quite remarkable difference between companion animal species is seen in the way that pancreatitis manifests. While specific reporting of clinical signs seen in cats with either suspected or actually confirmed pancreatic disease is uncommon in the veterinary literature, aggregation of results from several studies has provided data on clinical signs and owner complaints in 136 cats; these findings are summarized in Table 56.1.

One remarkable observation from the aggregated data in Table 56.1 is that the most common clinical sign in cats with pancreatitis, across a variety of studies spanning several decades, is decreased appetite, followed closely by lethargy. Vomiting and abdominal pain, both frequent clinical signs of pancreatitis in dogs, were reported in less than 50% of feline patients. The actual case outcomes and severities of clinical presentations in the cats aggregated for Table 56.1 range from mild disease with "incidental" findings of pancreatic disease through to objectively severe, life-threatening or terminal disease. Based on clinical signs alone, there is no way to distinguish the severity of pancreatic disease or predict the histopathologic findings if biopsies are to be taken. While some authors have suggested that chronic pancreatitis in the cat is a less severe disease, this is probably an unfounded belief; cats with chronic pancreatitis can present with objectively severe presenting signs (most likely associated with an acute worsening of their disease, or an "acute on chronic" disease presentation).

Given that both decreased appetite and lethargy are nonspecific signs, and are also common reasons for presentations of feline patients for veterinary care, it is not surprising that pancreatitis is becoming a much more common diagnosis in feline medicine. In light of these data, pancreatitis should be considered a reasonable and important differential diagnosis for any cat presenting with vague, nonspecific clinical signs.

Physical examination findings in cats with pancreatitis are also often unrewarding. Clinical signs such as cranial abdominal pain and guarding, commonly encountered in canine patients, are uncommon in cats with diagnoses

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Table 56.1 Historical and clinical findings in cats with confirmed pancreatic inflammatory disease

Clinical sign	Frequency (#cats/ total cases reported)	Frequency (% of cats)
Reduced appetite	113/136	83
Lethargy	105/136	77
Dehydration	88/136	65
Vomiting	58/136	43
Abdominal pain	27/73	36
Icterus	40/136	29
Weight loss	22/96	16

of pancreatitis. This may be due to the tendency of feline patients to "hide" clinical signs, the relatively subtle nature of pain manifestation in many cats, and a tendency to interpret struggling or resisting examination as a normal response on the part of feline patients. Often, the most important findings on physical examination in feline patients with pancreatitis are signs and symptoms of co-morbid disease (palpably thickened gastrointestinal tract, icterus, poor body condition), or findings that are important in the assessment of the overall state of health of the patient (state of hydration, presence of free abdominal fluid, alterations in body temperature). As with the histories of cats with pancreatitis, these vague, diffuse, and nonspecific findings in most cats with pancreatic inflammatory disease mean that pancreatic disease is a reasonable differential diagnosis in essentially any cat that presents unwell.

Characterization of Pancreatitis in the Cat

Typically, pancreatitis has been divided into acute and chronic diseases, based on histologic differences in human and canine patients. Generally speaking, "acute pancreatitis" is either neutrophilic or hemorrhagic and is associated with rapid onset of severe symptoms, marked abdominal pain and potentially life-threatening acid–base and electrolyte disturbances. By comparison, "chronic pancreatitis" is typically associated with fibrous replacement of pancreatic tissue and the presence of a lymphocytic inflammatory infiltrate. Although chronic pancreatitis is being recognized more frequently in canine patients, most clinicians consider acute pancreatitis to be the most common form of the disease in dogs.

In cats, chronic pancreatitis is the most commonly diagnosed disease following histologic assessment of pancreatic biopsies. As in humans and dogs, this diagnosis is based on the presence of lymphocytic or plasmacytic cellular infiltrates and, typically, some degree of fibrosis. In some studies, >80% of cats with pancreatic disease show this form of pancreatic infiltrate. Remarkably, at least one necropsy-based study of cat pancreata has suggested that signs of pancreatic inflammation, including lymphocytic-plasmacytic infiltration and fibrotic change, are common in cats with no history suggestive of pancreatic disease.

One problem with the terminology of pancreatitis, particularly the distinction of acute vs chronic pancreatitis, is the implication of differing chronologies of the disease. This is particularly problematic in the feline patient. While it is generally safe to assume that cats with longer histories of recurrent clinical signs such as lethargy, decreased appetite, and recurrent vomiting do indeed have chronic pancreatitis, the converse is not necessarily true. Given the subtle nature of clinical signs and historical complaints in many cats with pancreatic disease, and the waxing/waning nature of clinical signs in most chronic lympho-plasmacytic diseases, it is not valid to assume that a cat with a new presentation of relatively acute clinical signs actually has "acute pancreatitis" as defined histologically. As discussed earlier, there is no reliable way to distinguish necrotizing or hemorrhagic pancreatitis from lympho-plasmacytic disease in feline patients. Therapeutic decision making should be based on assessment of the overall state of health of the patient on presentation, rather than assumptions that a patient may or may not have a particular form of the disease.

Noninvasive Diagnostics for Feline Pancreatitis

Routine Clinical Chemistries

Routine clinical chemistry and complete blood count (CBC) evaluations are a critical part of the approach to any unwell feline patient. In the context of cats with a suspicion of pancreatitis, the most important aspect of the routine chemistry panel and CBC is the assessment of the overall physiology of the patient. There are very few to no findings on routine clinical pathology panels that can be considered highly sensitive or specific for pancreatitis in the cat. One exception to this would be the "pancreas-specific lipase" assays that are beginning to be promoted more heavily in some routine chemistry panels, and are discussed in more detail later.

In the dog and human patients, traditionally we have relied on the measurement of serum amylase and lipase activities to establish a diagnosis of pancreatitis, with the expectation that these activities will be markedly elevated. While these tests are admittedly low sensitivity and specificity in both dogs and people, marked elevations in patients with compatible clinical signs are at least strongly supportive of the clinical suspicion of pancreatitis.

In the cat, a long-standing belief in veterinary medicine is that amylase and lipase activities have essentially no diagnostic utility, with unacceptably low sensitivity and specificity in this species. While there is a large element of truth to these assertions, these opinions are based on a limited number of publications that assessed a small number of cats, and all dated from a period before the veterinary profession came to truly appreciate the very different manifestations of this disease in the cat. The low specificity reported for these tests may owe as much to false-negative diagnoses based on an incorrect understanding of the way in which this disease presents in the cat.

Common clinical pathology abnormalities encountered in cats are related to organ systems that are commonly compromised or involved in co-morbid diseases. Abnormalities in liver enzyme activities (both alanine aminotransferase [ALT] and alkaline phosphatase [ALKP], suggesting both hepatocellular compromise and cholestasis), azotemia, alterations in acid–base status, hypocalcemia, and inflammatory leukograms (typically left-shift neutrophilia) are all encountered relatively commonly. Some studies have suggested that marked hypocalcemia is a negative prognostic factor, likely due to sequestration of calcium in saponified abdominal fat, a phenomenon that tends to accompany hemorrhagic and necrotizing pancreatic pathology.

Specialty Diagnostic Tests

Noninvasive diagnostic testing relies on the use of marker compounds, detectable in the serum or some other sample such as urine, that are specific to the organ of interest and are altered in disease states of that organ. Ideally, the marker compound will be altered with disease of the primary organ, but unaltered by changes in other organ systems or by concurrent medical therapy. In the case of pancreatic disease, these marker compounds are usually digestive enzymes of some type. The use of typical amylase and lipase activity assays has already been discussed. More recent diagnostic tests that have been investigated include serum concentrations of trypsin-like immunoreactivity (fTLI), feline pancreatic lipase (now offered as the Spec-fPL™ assay), and activity tests using more "pancreas-specific" lipase substrates, particularly DGGR-lipase activity.

While trypsinogen/fTLI is pancreas specific, and is released in conditions of pancreatic disease, the peak changes in this enzyme are relatively short and soon after the onset of disease, and some other diseases (specifically small intestinal disease and severe azotemia) can be associated with elevations in fTLI without histologic evidence of pancreatic disease. This combination of transient changes in serum concentrations and minor alterations with other, nonpancreatic diseases results in fTLI testing having only moderate sensitivity and specificity for the diagnosis of pancreatitis in the cat. The greatest utility of fTLI testing lies in the ruling in or out of exocrine pancreatic insufficiency in feline patients (see Complications of Pancreatitis in Cats, later).

Serum concentrations of feline pancreatic lipase (Spec-fPL) and lipase activity assays using more highly selective assay substrates both show greater utility than routine amylase/lipase activities and the fTLI test; these tests are discussed in greater detail later.

Specific Pancreatic Lipase Test

Feline-specific pancreatic lipase (fPLI) refers to a particular protein, a lipase enzyme, synthesized and released solely by the pancreas in cats. This particular enzyme's concentration in serum is measured using the serum Spec-fPL assay, available either as a "cage-side" SNAP test or via specialty clinical pathology testing. This assay relies on monoclonal antibodies directed against the feline protein which are highly species specific. The use of canine PLI tests with feline samples can result in a false-negative rule-out of pancreatic disease in the cat.

As the fPLI protein is specifically and exclusively synthesized in the exocrine pancreatic tissue, the concentrations in the serum are dependent on the rate of synthesis and the "leakage" of the protein into the interstitial space and then the circulation. Conditions associated with increased cellular leakage (generally, some form of pancreatitis) are associated with increased serum concentrations of this protein, so the detection of increased circulating fPLI protein (i.e., a high Spec-fPL test result) is suggestive of pancreatic disease, particularly in cats with compatible clinical signs.

The sensitivity and specificity of fPLI testing have been investigated in several studies. Reported sensitivities and specificities for this test are 67–100% and 67–82%, respectively. In one moderately large study (n = 182 cats) using the Spec-fPL assay, the overall sensitivity for this test was 79%, with a specificity of 82%, for detection of pancreatitis in this group. Overall, the Spec-fPL has the highest reported sensitivity and specificity (at the time of writing) of any diagnostic modality for the detection of pancreatitis in the cat.

The use of Spec-fPL measurement as a prognostic marker and monitoring parameter for recovery has also received some attention. Marked elevation of Spec-fPL (values >20 µg/L) has been associated with a poorer prognosis in cats hospitalized with pancreatitis. There are no data in the literature suggesting that greater elevations in Spec-fPL are associated with poorer response to therapy in cats with chronic pancreatitis, assuming adequate management of co-morbidities. A much greater factor influencing response to chronic pancreatitis in cats is adequate management of chronic enteropathy and

the identification and treatment, if present, of cobalamin deficiency in these cats.

Pancreas-Specific Lipase Assays

The lipase activity assays used in most commercial laboratories and bench-top analytic systems rely on lipase within the serum sample cleaving a substrate of some sort; this cleavage then results in a change in the test solution (such as changing pH or color) that can be measured, giving a value for lipase activity. There is a large number of lipase activity substrates that can be used, and the substrates typically used by high-throughput commercial laboratories are different from those used in the bench-top systems. Even within bench-top systems, there are differences in substrates between differing manufacturers. For this reason, the comparison of lipase activity assays between two different systems is generally fruitless and does not yield any useful data.

Many tissues in the body contain quite high amounts of lipase. Obviously, the exocrine pancreas is very rich in these enzymes but other organs, including the liver, gastric mucosa, and duodenal mucosa, contain lipase activity. These lipases can be released from these other organs in disease states, and contribute to the total circulating lipase activity. The specificity of a lipase assay for detection of pancreatic disease thus depends on the specificity of the substrate used for pancreatic lipase. This substrate specificity varies markedly between substrate types.

One substrate with greater specificity for pancreatic lipase that has undergone some investigation in cats is 1-2-o-Dilauryl-rac-glycero-3-glutaric acid-(6'-methylresorufin) ester (DGGR). A DGGR-based clinical chemistry assay has been validated for use in feline serum samples, and the sensitivity and specificity of the test compared with the use of both Spec-fPL testing and abdominal ultrasonography. The DGGR-based assay had similar, if slightly lower, sensitivity and specificity to the Spec-fPL assay in the assessment of cats with clinical signs compatible with pancreatitis. In a similar follow-up study, the DGGR-based assay was found to show the best agreement with both Spec-fPL and abdominal ultrasonography in cats with hypo- or mixed-echoic pancreatic parenchyma, findings that are generally considered consistent with acute pancreatic disease.

Overall, DGGR-based lipase activity assays likely have clinical utility in feline patients, and an elevated activity value in an unwell feline patient should prompt further assessment for the presence of pancreatic disease. However, this approach is reliant on the use of this specific substrate in whichever analytic system is being employed. Information regarding the actual substrates used by the various reference laboratories and in-house chemistry systems commonly found in veterinary practice is not readily available at this time.

Pancreatic Biopsy and Histology

Pancreatic biopsy and histologic examination is generally considered the "gold standard" for the detection of pancreatic disease, including pancreatitis. Unfortunately, pancreatic biopsy is still a relatively uncommon part of the approach to feline patients, for a variety of reasons. Chief among these is likely cost to the client and the invasive nature of celiotomy to obtain biopsies. Recently, however, the use of laparotomy and laparoscopy-assisted biopsy techniques has provided a lower cost, less invasive method for obtaining pancreatic biopsies, usually in concert with liver and intestinal biopsy procedures.

Surgical biopsy of the feline pancreas has been shown to have a low risk for complications such as postsurgical pancreatitis, assuming that the patient is adequately hydrated and hemodynamically stable at the time of surgery. Side-effects and postsurgical morbidity are uncommon in cats undergoing surgical biopsy of the pancreas using punch biopsy instruments or crush-fracture techniques using hemostats. Pancreatic biopsy, particularly in cats undergoing assessment for gastrointestinal disease, is justified in many cases and should be considered part of the routine samples collected during exploratory celiotomy or laparoscopic exploratory procedures.

While biopsy samples are rightly considered the most effective way of assessing pancreatic disease, a number of shortfalls of this technique must be recognized. Even with laparoscopic procedures, the collection and assessment of histologic samples are still more expensive and have higher risk to the patient than the use of noninvasive testing such as clinical chemistries. In addition, pathology within the pancreas is often heterogeneous in distribution, and differing areas may show differing cellular infiltrates or levels of activity. This may lead to incorrect diagnosis of the overall state of the pancreas when only a single sample is taken, as is often the case with laparoscopic biopsies of the pancreas in the cat. Finally, there is a well-recognized variability between individual pathologists with respect to assessment and description of pancreatic samples. Histologic scoring systems for pancreatic disease have been proposed and published, including for the cat, but the use of these systems is generally limited to research publications and retrospective case series descriptions. It is uncommon for histopathologists to report pancreatic biopsy samples using these scoring systems in veterinary medicine.

Interpretation of Specialized Tests

Interpretation of the specialized tests used for the diagnosis of pancreatic disease in cats is sometimes complicated, particularly if the test is part of a broad-ranging panel used in the initial assessment of a patient if there is no clear initial diagnosis being assessed. Part of the

difficulty of assessing these tests comes from the observation that we do not truly know the prevalence of pancreatic disease in the feline population. While at least one study suggests that pancreatic pathology is quite common in the feline population (approximately 60% of cases necropsied, where the patient was *not* suspected to have pancreatic disease), one caveat about this study is that these were still, largely speaking, unwell cats that were necropsied. If the true prevalence of pancreatic disease in the feline population is as high as 60%, then an unexpected finding of a high Spec-fPL concentration or DGGR-lipase activity on sentinel chemistry panels may be a true indication of pancreatic disease. While the pancreatic disease present may not be an important *clinical* finding, this does not mean that this is an incorrect *diagnostic* finding. This is particularly true when the clinical chemistry panel is being run on an apparently healthy patient as part of a health monitoring or wellness program.

An additional important factor in the interpretation of these tests is the very variable, and often subtle, clinical signs and histories of this disease, as previously discussed. When clinical chemistry panels and Spec-fPL tests are being run as part of a broad-ranging assessment in a cat that is known to be unwell, but with no clear initial indication of why, abnormalities in these tests are a strong indication of likely *clinically significant* disease. It is inappropriate to discount these findings in these patients, and important to consider that pancreatic disease is, to all indications, common in the sick cat population and also a common co-morbid condition with other diseases.

Diagnostic Imaging

Along with the specialized noninvasive testing methods discussed above, diagnostic imaging is commonly used in the assessment of pancreatic disease in the cat. Of the various methodologies available, high-resolution abdominal ultrasonography typically has the greatest diagnostic yield. It also allows further assessment of other abdominal organs that may be involved in co-morbid diseases, such as the hepatic parenchyma, biliary tree, and intestinal walls.

Plain abdominal radiography, while commonly used in cats with suspected abdominal disease, has a very low diagnostic yield in cats with pancreatitis. The pancreas is not visible on plain abdominal radiographs, and changes commonly seen in dogs with pancreatitis ("ground glass" appearance, loss of local contrast, widening pyloric angle) are infrequent in cats due to the differing underlying pathology in most cases. While abdominal radiography has some possible advantages in terms of lower cost and greater availability, the very low diagnostic yield is a contraindication for its use in most cases.

The increasing availability of high-resolution abdominal ultrasonography in companion animal practice has dramatically improved the use of diagnostic imaging to characterize pancreatic disease in the cat. Observation of pancreatic enlargement, hyperechoic mesentery and abdominal fat, altered parenchymal echogenicity (most commonly hypoechogenicity or a mixed pattern), abdominal effusions, pancreatic cysts or pseudocysts, corrugation of the duodenum, and dilation of the pancreatic duct are all considered consistent with pancreatitis in cats with consistent clinical signs. These findings are specific indicators of the presence of pancreatic pathology, but their sensitivity for accurate diagnosis in cats with histologically confirmed pancreatitis is quite variable, with reported sensitivities ranging from ~11% to 80%. Sensitivity of abdominal ultrasound for the detection of feline pancreatic disease is highly dependent on operator skill and equipment resolution. Given the variable and often low sensitivity of abdominal ultrasound examination in the diagnosis of pancreatitis in cats, this modality cannot be reliably used as a "rule-out" test for this disease. However, significant additional information useful for management of these cases is often obtained, particularly when screening for co-morbid conditions such as cholangitis/cholangiohepatitis or the presence of extrapancreatic disease that could explain the clinical signs. Therefore, abdominal ultrasonography, carried out by a well-trained and experienced operator, is recommended in all cats where there is a clinical suspicion of pancreatitis.

In humans, the use of abdominal computed tomography (CT) examination is considered highly useful in the assessment of pancreatic disease. This modality allows the assessment of pancreatic architecture, presence and severity of fibrotic change and detection of both common inciting causes for pancreatitis in humans (such as gallstones) and other co-morbid diseases. The utility of abdominal CT for the assessment of feline pancreatic disease is much lower than in humans. This is due to the much smaller mass of pancreatic tissue in the cat, and less common presence of severe architectural distortions due to fibrosis. Additionally, abdominal CT examination of cats typically requires general anesthesia, which may be contraindicated in severely unwell cats and also leads to significant additional cost. CT examination has been reported in cats in a small number of publications; the overall sensitivity and specificity were not higher than those seen with less invasive testing such as Spec-fPL or abdominal ultrasonography, and thus abdominal CT cannot be recommended as a part of the diagnostic approach to pancreatic disease in the cat at this time.

Approaches to Management of Pancreatitis in Cats

Care of Cats Hospitalized for Pancreatitis

As previously discussed, it is not possible to distinguish so-called "acute necrotizing" pancreatitis from chronic lymphocytic-plasmacytic pancreatitis in the cat, regardless of presenting clinical signs, history or chemical findings. The approach to the management of cats with this disease is determined by the overall degree of health of the patient as assessed by initial examination and screening chemistries. Cats presenting with a suspicion of pancreatitis that are showing other signs of systemic illness, marked abdominal pain, systemic inflammatory response syndrome (pyrexia, tachycardia, tachypnea), hypothermia or hypotension should be considered to have severe disease, and immediate hospitalization and aggressive stabilization therapy are recommended. If multiple abnormalities are detected on routine chemistry panels, particularly if hypoalbuminemia and/or hypocalcemia are present, this is a strong indication of severe disease associated with significant risk of in-hospital mortality.

Cats with severe disease require careful monitoring, appropriate fluid therapy, and effective analgesia. In humans and dogs, severe pancreatic disease is inarguably painful, and while cats may not show as many overt signs of pain, such as vocalization or abdominal guarding, there is no reason to suspect that this disease is not painful in cats as well. Many of the clinical signs at presentation of severe cases, such as tachypnea and tachycardia, resolve rapidly with effective pain control interventions.

Initial screening chemistry panels are important to assess for other co-morbid or complicating diseases, particularly extrahepatic biliary duct obstruction, hepatic lipidosis, and diabetes mellitus (which may proceed to diabetic ketoacidosis). Samples should also be drawn for special diagnostic testing (i.e. Spec-fPL assay or DGGR-lipase). If available, patient-side SNAP tests for Spec-fPL can give initial support to a clinical suspicion of pancreatitis, but these tests should not be relied on to rule out the disease, and measurement of a quantitated value through a reference laboratory is recommended as soon as possible. Pending results of specialized diagnostics, the management of these cases follows typical management protocols for acute abdomen/septic shock patients.

The initial aims of therapy are to replace circulating fluid volumes, restore end-organ perfusion, and maintain organ function. Obtaining effective perfusion of the pancreas is particularly important, as pancreatic ischemia is a significant inciting cause for the development of necrotizing pancreatitis. With the combination of aggressive fluid therapy and increased endothelial "leakiness," it is critical to monitor total protein and, if necessary, restore and maintain plasma colloid oncotic pressure. Colloid fluids, such as synthetic hydroxyethyl starches, are often highly beneficial in the initial resuscitation of these cases. Fresh-frozen feline plasma can also be considered, and likely provides oncotic support while replenishing coagulation cascade proteins; however, there is little information in the veterinary literature regarding use of plasma in severe feline pancreatitis cases. Substantial electrolyte abnormalities, particularly hypokalemia and hypocalcemia, should be anticipated in these cats. Supplemental potassium is administered in combination with crystalloid fluids following routine guidelines for concentrations based on serial determination of serum potassium concentrations, typically every eight hours during the initial resuscitation phase.

Drug Therapy in Feline Pancreatitis

Effective analgesia and control of vomiting are important aspects of management of severe pancreatitis in all species. A selection of medications that are often useful in the management of pancreatitis in the cat is summarized in Table 56.2.

Narcotic pain control is typically indicated in cats with sufficiently severe pancreatitis to warrant hospitalization. Transdermal fentanyl patches (25 µg/h) can be very effective for longer term (up to 72 h) analgesia without the need for frequent handling and injection in these patients, but initial therapy with an injectable or sublingual agent (commonly buprenorphine) is necessary as it can take up to 12 hours for therapeutic fentanyl concentrations to be reached. Maropitant, a neurokinin-1 receptor antagonist, is both an effective antiemetic and may have antinociceptive effects in the viscera. The combination of maropitant with a 5-HT_3 receptor antagonist, such as ondansetron or dolasetron, often provides effective control of vomiting and nausea in these patients with minimal need for repeated handling during the day. Together, obtaining adequate analgesia and control of nausea/vomiting are important for the overall well-being of the patient, and increase the likelihood of an early return to voluntary eating.

Early Nutritional Management

Long-standing dogma for the management of severe pancreatitis in humans and canine patients has been that these patients should be maintained *nil per os* for some period, with introduction of food occurring only after cessation of vomiting for a minimum of 12 hours, and often 24 hours or more. This attitude is being supplanted by early enteral nutrition strategies in both humans and, more recently, dogs. Preliminary evidence suggests that early enteral nutrition in these species is

Table 56.2 Medications commonly used in the management of severe pancreatitis in the feline patient

Class	Drug	Mechanism	Main indication	Dose and route
Analgesic	Buprenorphine	Opioid	Acute, severe	0.01–0.02 mg/kg SC, IM, IV, TM
	Fentanyl	Opioid	Acute, severe	25 µg/h patch, 5 µg/kg IV bolus, CRI 2–4 µg/kg/h
	Butorphanol	Opioid	Acute, severe	0.1–0.5 mg/kg SC, IM, IV
Antiemetic Antinausea	Maropitant	Neurokinin-1 receptor antagonist	Acute, severe chronic	1 mg/kg SC q24h, 2 mg/kg PO q24h
	Dolasetron or ondansetron	5-HT_3 receptor antagonist	Acute, severe	0.8–1.0 mg/kg IV q24h
	Metoclopramide	Dopamine D2 receptor antagonist	Acute, severe	0.2–0.5 mg/kg PO, SC, IM q6–8h, 1–2 mg/kg/24h CRI
Antacid	Omeprazole	Proton pump inhibitor	Acute, severe	1.0–1.3 mg/kg PO q12h
	Pantoprazole	Proton pump inhibitor	Acute, severe	0.7–1.0 mg/kg IV q12h
	Ranitidine	Histamine H2 receptor antagonist	Acute, severe	0.5 mg/kg PO q12h

CRI, constant rate infusion; IM, intramuscular; IV, intravenous; PO, by mouth (*per os*); SC, subcutaneous.

associated with shorter ICU and hospital stays, lower total costs of care, and fewer complications during initial management. With cats, the potential for development of hepatic lipidosis as a complication of severe pancreatitis and inadequate caloric intake must also be considered. While currently there is limited information in the veterinary literature regarding the use of early enteral nutrition in cats with severe pancreatitis, the author uses this modality regularly, and quite aggressively. In many cats, assisted feeding devices such as esophagostomy tubes are placed during the first 24–36 hours of hospitalization to achieve early return to feeding. For both hepatic lipidosis and diabetic ketoacidosis, a return to caloric intake is critical to their successful management, and the presence of pancreatitis (either as an inciting disease or a complication) does not alter the importance of a return to positive caloric balance in these diseases.

Outpatient Management of Cats with Chronic Pancreatitis

Cats presenting with less severe clinical signs, perhaps with histories of vomiting, weight loss or other gastrointestinal signs but without significant abnormalities on screening biochemical panels, can typically be treated on an outpatient basis. In these patients, collection of samples for specialized testing (Spec-fPL) is recommended, but there is less utility to the patient-side testing, as these patients will be treated on an outpatient basis in the same manner regardless of the initial patient-side test result. Cats that had originally presented with a suspicion of severe pancreatitis should also transition to this more chronic management approach once they are eating voluntarily and are able to be discharged.

Cats with a clinical suspicion of chronic pancreatitis are treated in essentially the same manner as cats with chronic enteropathies or diagnoses of idiopathic inflammatory bowel disease. There is no meaningful way to distinguish between chronic pancreatitis as a solitary disease entity and the presence of multiorgan inflammatory disease (so-called feline inflammatory disease or "triaditis"). Initially, dietary modification, typically by use of a novel protein source or hypoallergenic diet, is suggested. In contrast to dogs, where fat restriction is a cornerstone of management for most cases of chronic pancreatitis, fat restriction is not recommended in the cat due to their high constitutive requirement for both fat and arachidonic acid intake. Many cats will respond to dietary manipulation; in those who fail to respond to dietary manipulation, it is rational to consider antiinflammatory or immune modulatory therapies, assuming that no other co-morbidities are present that would contraindicate the use of these medications.

A common additional finding in cats with chronic pancreatitis, particularly in those with significant gastrointestinal disease accompanying their pancreatic disease, is the presence of hypocobalaminemia. Cats with hypocobalaminemia (low vitamin B_{12}) are known to be less responsive to treatment for other diseases, such as chronic inflammatory bowel disease, if this hypocobalaminemia is not addressed via supplementation. Supplementation of cats with cobalamin is straightforward, and can be carried out using injectable or oral supplementation regimes. In some cats, particularly those with diffuse small intestinal disease, serum folate

concentrations are also low. Supplementation of cats with low folate has not been investigated as thoroughly as cobalamin supplementation, but is also readily achieved with oral supplement products. Often, initial supplementation by injection followed by oral supplementation in the home environment provides a good balance between costs, convenience, and ease of owner compliance.

Complications of Pancreatitis in Cats

Given the apparent frequency of chronic pancreatic disease in the feline population, the occurrence of severe complications is actually remarkably low. While objectively severe disease in cats presenting with hemodynamic shock, systemic inflammatory response syndrome and abdominal pain is life-threatening and associated with a substantial risk for mortality if not addressed appropriately, most cats with chronic pancreatitis require life-long management for their disease, but other than waxing and waning clinical signs, most do not develop additional complicating diagnoses.

The two most common and important complications of pancreatic disease in the cat are exocrine pancreatic insufficiency (EPI) and diabetes mellitus.

Chronic pancreatitis is most likely the most common cause of EPI in cats. Loss of exocrine tissue due to ongoing inflammation and fibrosis can eventually lead to the development of clinical signs related to insufficient digestive enzyme synthesis. In comparison to dogs, and a recurring theme in feline medicine, the way in which EPI manifests in cats is different in terms of both history and clinical signs reported. While in the dog the most common cause of EPI is an early-onset pancreatic acinar atrophy (PAA), in the cat the disease is an end-result of a chronic, typically years-long inflammatory disease. Dogs with EPI secondary to PAA are usually young and usually are otherwise healthy, with good to ravenous appetites. In the cat, there is typically a long history of poor appetite and possible weight loss resulting from the underlying pancreatitis. By the time cats reach an end-stage of chronic pancreatitis, they are usually chronically unwell, and they do not develop compensatory polyphagia. Cats also are less likely to produce voluminous stools and frank steatorrhea; this is probably due to the very prolonged course of the disease in this species, which allows other compensatory mechanisms (such as intestinal brush border enzyme upregulation) to be more effective.

Exocrine pancreatic insufficiency should be suspected in any cat with a history of diagnosed chronic pancreatitis that then goes on to show worsening clinical signs, particularly weight loss. In some cases weight loss will be the only additional clinical sign that suggests the onset of EPI.

Diagnosis of EPI in the cat is based on the measurement of serum concentrations of TLI, not Spec-fPL. While Spec-fPL values are almost invariably very low in cats with EPI, this is also seen in some normal cats, resulting in an unacceptably low specificity of the Spec-fPL assay for the diagnosis of EPI in cats. DGGR-lipase activity assays have no diagnostic utility for EPI in cats, as most cats with EPI show DGGR-lipase activities that are indistinguishable from normal cat values.

Diabetes mellitus can develop in cats with chronic pancreatitis due to progressive loss of islet tissue with inflammation and fibrotic change. These cats may spend extended periods as "prediabetic" patients, with reduced glucose tolerance. The actual frequency of chronic pancreatitis as a cause of diabetes mellitus in the cat is unknown, and likely underestimated, due to the low frequency of pancreatic biopsy in these cats. The occurrence of diabetes mellitus in feline patients can significantly complicate their management for chronic pancreatitis, particularly if the cat is being managed with glucocorticoid medications to mitigate inflammation. Equally, the presence of chronic pancreatitis in a diabetic cat is a common cause of difficulty in achieving adequate glycemic regulation, and chronic pancreatitis is one of the most important diseases to screen for in cats with diabetes that is hard to regulate. The difficulty of managing diabetic cats with chronic pancreatitis, and the confounding influence of glucocorticoid therapy on glycemic regulation, makes one of the strongest arguments for early intervention using predominantly dietary changes in the management of chronic pancreatitis in the cat.

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57

Rectoanal Diseases – Medical and Surgical Management

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Rectoanal diseases are frequent reasons for presentation of companion animals for veterinary attention. Clinical signs and symptoms, such as straining, "scooting," fecal incontinence, and paradoxical diarrhea, are very distressing to owners. An effective approach to recognition and management of these diseases relies on a thorough history and clinical examination, including rectal examination wherever possible. In smaller patients, and those that resent digital rectal palpation, effective sedation is needed to allow this examination to proceed. Diseases involving the distal rectum and perineum are often well characterized by local examination and palpation, but the intrapelvic rectum can be difficult to fully assess, as many important structures (pelvic urethra, cranial prostate in larger dogs, intrapelvic lymph nodes) are difficult to reach. Diagnostic imaging of this area is also challenging in many cases. Contrast-enhanced CT examination is the imaging method of choice for many of these cases.

In this section, a variety of rectoanal diseases is briefly discussed. For some diseases, medical management is appropriate, while in others surgical management is the primary management modality.

Anal Sac Adenocarcinoma

Clinical Presentation

Incidental finding or visible perianal mass/swelling, tenesmus, polyuria/polydipsia, anorexia or inappetence, lethargy, weight loss, constipation, or posterior weakness.

Pathophysiology

Anal sac adenocarcinoma arises from malignant transformation of the secretory epithelium of the anal sacs.

Diagnosis and Medical Management

In up to a third of dogs, anal sac adenocarcinoma is discovered as an incidental finding on routine examination. When clinical signs are present, they may be a result of the local mass effect (straining to defecate, constipation due to enlargement of retroperitoneal and intrapelvic lymph nodes with metastatic disease). In some cases the primary presenting complaint is polyuria and polydipsia resulting from loss of concentrating capacity due to hypercalcemia. Routine clinical chemistry panels will often reveal both total and ionized hypercalcemia, with or without concurrent hypophosphatemia. A finding of hypercalcemia in a dog undergoing assessment for polyuria and polydipsia should prompt thorough anal sac and rectal digital examination, using sedation if necessary. With advanced disease and metastasis to the abdominal lymph nodes dorsal displacement of the colon may be visible on plain abdominal radiographs. Abdominal ultrasonography and, if available, computed tomography will usually have a much greater diagnostic yield than plain abdominal radiography. On diagnosis, complete pretreatment staging calls for either three-view thoracic radiographs and/or computed tomography. Conclusive diagnosis can usually be obtained by examination of fine needle aspiration cytology of the mass. In some cases, the cytology may be interpreted as "hepatoid" but a benign cytologic appearance does not rule out anal sac adenocarcinoma.

Surgical Management

Preoperative patient staging for sublumbar lymph node and/or pulmonary metastasis is mandatory as this information influences surgical approach (e.g., determines whether concurrent sublumbar lymph node extirpation is indicated). Surgical removal of the affected anal sac is performed via closed anal sacculectomy. The size and

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adherence of the mass to the surrounding tissues influence the technical difficulty of the surgery. By the time of diagnosis, most tumors have caused enough distortion and adhesion to the perineal tissues (i.e., external anal sphincter, rectal wall, caudal rectal nerve) to be significantly more challenging than anal sacculectomy for nonneoplastic causes. Removal of involved external anal sphincter muscle is tolerated with loss of up to two-thirds of the circumference of the anus, as well as the ipsilateral caudal rectal nerve, with most dogs regaining fecal continence after a variable period of transient incontinence. Some dogs may have bilateral anal sac adenocarcinoma, which requires meticulous surgical technique to preserve fecal continence.

The most common complication after surgical excision of anal sac adenocarcinoma is tumor recurrence, with rates up to 42–45% reported. Other less common complications include surgical site infection, hypocalcemia, tenesmus, perianal fistula, and death.

Prognosis

Postoperative adjuvant therapy in the form of chemotherapy and/or external beam radiation therapy is quickly becoming the standard of care as several reports have documented prolonged survival in patients receiving multimodal treatment. With surgery alone, reported median survival times range from 7.9 to 16.4 months. In dogs receiving postoperative adjuvant melphalan, median survival time was 20 and 29.3 months in dogs with and without sublumbar lymph node metastasis, respectively. Another study combing postoperative radiotherapy with mitoxantrone reported medial overall survival of 956 days with one- and two-year survival rates of 87% and 66%, respectively. A large (over 800 dogs) multicenter retrospective study in preparation at time of writing found prolonged median survival time (approximately five years) for dogs with sublumbar lymph node metastasis that were treated with surgery and chemotherapy, which was similar to the overall survival time for dogs without metastasis treated with surgery alone (J Liptak, personal communication).

Anal Sac Impaction

Clinical Presentation

Anal sac impaction is one of the most common rectoanal diseases in companion animal practice, and a very common cause for presentation of dogs in particular. The clinical signs are of tenesmus, "scooting," excessive licking of the perineum region, and pain on palpation of the anal sacs (which are distended). Overall, smaller breed dogs appear to be predisposed to anal sac impaction.

Pathophysiology

Impaction of the anal sacs can occur secondary to a variety of primary causes or inciting disorders. Inadequate emptying of the anal sacs may occur in obese dogs, dogs consuming "low-residue" diets with reduced fecal bulk, and in dogs with seborrhea (which results in increased secretion of the sebaceous glands within the anal sacs). Complications of anal sac impaction can occur, such as anal gland abscessation.

Diagnosis and Medical Management

In most cases, diagnosis and management of anal sac impaction is fairly straightforward. Diagnosis is based on palpation of the enlarged anal sac on routine physical examination. In many cases, diagnosis and management are concurrent, as the impacted sacs may be able to be gently manually expressed. Heavily impacted and painful glands may require sedation of the patient and irrigation of the sacs with saline. Uncomplicated cases are then managed by addressing diet, providing regular opportunities for the dog to defecate, and client counseling. Sacs that have become abscessed should be cultured and appropriate antibiotic treatment administered. Uninfected impacted anal sacs do not warrant antibiotic therapy.

Surgical Management

The decision to proceed with surgical intervention for anal sac impaction or abscessation is based on failure to respond to appropriate medical management, including lancing, flushing, culture and sensitivity testing, use of appropriate antimicrobials, and prevention of self-trauma (i.e., use of an Elizabethan collar). Surgical intervention generally consists of anal sacculectomy and may be performed unilaterally or bilaterally, depending on the patient's condition. When planning bilateral anal sacculectomy, it may be prudent to separate the two procedures by 2–4 weeks to allow any transient neuropraxia-related fecal incontinence to resolve before performing surgery on the contralateral side.

Anal sacculectomy for nonneoplastic disease can be performed using either an open or closed technique. With either method, the following principles apply: remove the entire gland such that no secretory epithelium remains in the patient; minimize trauma to the external anal sphincter muscle and avoid damage to the caudal rectal nerve (branch of the pudendal n.) to

prevent fecal incontinence; and ligate the anal sac duct near its opening, removing it *en bloc* with the gland itself. These goals are most readily achieved with the patient positioned in sternal recumbency in a perineal stand with the tail in an elevated position and an anal purse-string suture placed cranial to the opening of the anal sac ducts. If a closed technique is chosen, the anal sac itself can be distended with various materials (e.g., yarn, silicone sealant, Foley balloon catheter, plaster of Paris, agar base gel, dental molds, etc.) to facilitate palpation of the gland itself during dissection. Closure is typically performed in two layers; 3-0 or 4-0 monofilament absorbable suture for the subcutaneous tissues and either similarly sized nylon skin sutures or an intradermal skin closure can be used.

Prognosis

The prognosis for patients with anal sac impaction is generally excellent, regardless of whether they require surgical intervention or respond to medical management.

Atresia Ani and Rectoanal Strictures

Clinical Presentation

Atresia ani is the most common congential rectal/anal anomaly in dogs (Figure 57.1). Four types are recognized: type I (stenosis), type II (persistent anal membrane with the rectum ending immediately cranial to the imperforate anus), type III (as with type II but the rectum ends further cranially), and type IV (terminal rectum and anus may be normal but there is a discontinuity in the rectum with a blind pouch within the pelvic canal). These animals appear normal until 2–4 weeks of age at which time they become unthrify, anorexic, and restless with abdominal distension, possibly with perineal bulging.



Figure 57.1 Type II atresia ani in an 8-week-old mixed-breed puppy. Note the imperforate anus and absence of rectal lumen. This particular puppy presented later than is typical for this disorder due to the concurrent presence of a rectovaginal fistula that prevented colonic and rectal obstruction. Note also the abnormalities in vulval anatomy.

Rectoanal strictures appear to be more common in cats than dogs, but can occur in either species, most typically after trauma (iatrogenic or spontaneous). Clinical signs may vary depending on the underlying cause, but include tenesmus, dyschezia, hematochezia, and passing of ribbon-like feces. Megacolon is a possible sequel, especially in cats with chronic partial rectal narrowing (e.g., due to malunion after pelvic fractures).

Pathophysiology

The functional diameter of the distal colon, rectum or anus is reduced, due to either congenital (atresia ani) or acquired anatomic abnormalities.

Diagnosis and Medical Management

Atresia ani may be diagnosed at the time of birth, or in the neonatal period, with failure of the infant to defecate and possibly the development of abdominal distension. Later, adult-onset disorders are usually presented for constipation/obstipation, and can have a history of prior trauma or injury to the pelvis or perianal region.

Surgical Management

Atresia ani type I is treated with gentle bougienage. Type II and III atresia ani are treated surgically via a vertical incision at the anal dimple with caudal advancement of the rectum. The rectum is sutured to the skin at the level of the anus in two layers using 4-0 or 5-0 monofilament absorbable simple interrupted sutures. Dissection must be particularly gentle as the tissues are friable and every effort must be made to preserve the anal sphincter as well as opening to the anal sacs, both of which are typically normal and present. Animals with type IV atresia ani may require an abdominal approach with or without a pelvic osteotomy to access and anastomose the rectum.

Treatment chosen for anorectal strictures is dictated by the severity and location of the stricture. Mild cases may respond to bougienage, but more severe conditions may require surgical resection and anastomosis. However, recurrence of stricture after surgical resection and anastomosis, especially in cats, is relatively common.

Prognosis

Surgical repair of type I or II atresia ani often results in long-term survival and fecal continence. Patients with type III or IV atresia ani have poorer outcomes and the prognosis depends on the possibility of reconstructing the terminal rectum.

Prognosis following treatment for anorectal stricture largely depends on the underlying cause. Benign causes may carry a good prognosis but strictures associated with rectal adenocarcinoma are associated with a more guarded to poor prognosis. Surgical complications following rectal stricture resection and anastomosis may include dehiscence with sepsis and/or recurrence of stricture.

Constipation, Obstipation, and Megacolon

Clinical Presentation

Constipation and obstipation are both manifestations of difficult defecation, and fall within a spectrum of severities. Constipation is defined as difficult or effortful defecation, but feces is passed after some effort. Obstipation is a state of more severe constipation, and may result in intestinal obstruction. Both constipation and obstipation are the result of disorders in large bowel motility that slow fecal transit, but an implication of both diagnoses is that there is some degree of large bowel and rectal motility remaining. Obstipation should be treated aggressively, and the early use of promotility agents is recommended in many cases, as failure to restore functional motility in these patients can result in progression to megacolon, a state in which all large bowel and normal rectal motility is lost. Once established, megacolon is not effectively treated with laxative or prokinetic medications, as both of these families of medications require some degree of intrinsic motility in order to be effective.

Pathophysiology

Constipation and subsequent obstipation can result from any disorder or abnormality that slows fecal transit through the large intestine, decreases large intestinal and rectal motility, or mechanically obstructs passage of the fecal material to the rectum and anus. Slower passage of fecal material results in greater dehydration of the large intestinal content, as water absorption by the large intestinal mucosa continues unabated. Progressive overloading of the large intestine will eventually lead to large intestinal atony and flaccid paralysis, as seen with chronically obstructed urinary bladders. Similarly to the urinary bladder, loss of large bowel intrinsic motility is almost universally irreversible, resulting in megacolon.

Diagnosis and Medical Management

A history of unproductive straining or tenusmus, in concert with a readily palpable, heavily feces-laden large intestinal loop in the mid to distal abdomen, establishes a diagnosis of constipation readily. Differentiation of constipation/obstipation from megacolon can be more challenging, however. On plain abdominal radiographs, measurement of the maximal colon diameter:L5 vertebral body length ratio has been suggested as a method to help differentiate constipation from megacolon. A colon diameter:L5 length ratio of >1.48 has a sensitivity of approximately 77% with a specificity of 85% for establishing a diagnosis of megacolon. Similarly, a ratio of <1.28 is a strong indicator of a normal colon (sensitivity 96%, specificity 87%).

In patients where imaging findings do not suggest the presence of megacolon, medical treatment for constipation and obstipation is indicated. Particularly for patients with obstipation, it is critical to clearly indicate to the animal's owners that failure to treat effectively may lead to life-long, severe consequences.

Most uncomplicated cases of constipation can be treated with warm water, saline or water-lubricant enemas. Laxative medications, such as lactulose or emollient, paraffin-based products, can be trialed. The diet history should be considered, and addition of indigestible fiber as a bulking agent may be necessary. In patients with more severe disease, and definitely if constipation has progressed to obstipation, more aggressive treatment may be required.

Some patients with long-standing constipation/obstipation can present with quite severe dehydration, electrolyte, and acid–base abnormalities; this is particularly common in feline patients. Patients presenting with evidence of significant dehydration and fluid deficits should be stabilized with parenteral fluid therapy, possibly over 24 hours or more, before anesthesia for deobstipation and enema therapy. In these patients, the dehydration is more immediately life threatening than the fecal load, which has typically been present for days to weeks.

Patients with obstipation should be treated with prokinetic medications after obstipation is relieved. Unfortunately, only a small number of medications is available that may assist with large intestinal motility. Two medications with at least some evidence to suggest they are worth trialing are low-dose erythromycin and cisapride.

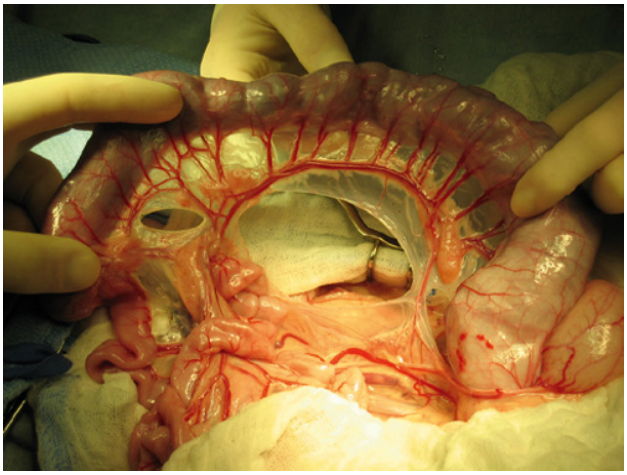


Figure 57.2 Intraoperative view of a severely distended and atonic colon in a feline patient with idiopathic megacolon. Patients in whom constipation and obstipation have progressed to this degree are best managed via subtotal colectomy.

Failure of medical management for obstipation is not uncommon, and likely reflects failure to recognize that the disease has already proceeded to megacolon. In patients that have proceeded to megacolon, surgical intervention is warranted (Figure 57.2).

Surgical Management of Megacolon

Megacolon should be treated via surgical subtotal colectomy once clinical signs progress beyond the ability of medical management to maintain the patient's quality of life. This is typically soon after diagnosis, as the condition is generally progressive and quickly becomes refractory to dietary modification, laxatives, prokinetics, and/or enemas. Although surgical treatment is essentially an intestinal resection and anastomosis, several anatomic factors combine to make this procedure significantly more challenging than a typical midintestinal resection and anastomosis. These include tension at the level of the ileocecocolic junction, lack of physical space to suture the aborad intestinal segment due to the bony pubis, a higher bacterial load within the colon compared to other segments of intestine, potential luminal disparity between the two segments of bowel to be sutured together, proximity to the ureters, and necessity for specific transection locations if preserving the ileocolic valve.

Surgical subtotal colectomy should aim to remove as much of the colon as possible to prevent recurrence. Some surgeons prefer to preserve the ileocolic valve with the idea that it may reduce duration of diarrhea postoperatively, as there is some support for this concept in the published literature. Regardless of whether the valve is removed or not, a transient period of watery to mucoid diarrhea postoperatively can be expected, lasting from several weeks up to three months. Various methods of anastomosis (end-to-end, end-to-side, side-to-side) have been described, including hand-suturing, GIA and TA stapling devices, transanal or transcecal circular end-to-end anastomotic stapling, and biofragmentable anastomotic rings. Excellent outcomes have been reported with all the above methods and the exact technique chosen should depend on the planned resection, surgeon experience, and equipment availability.

In cases of secondary megacolon due to pelvic canal narrowing, typically due to malunion following pelvic fracture, a pelvic osteotomy may be required. Duration of clinical signs has been associated with outcome, with cats that have had clinical signs for less than six months experiencing better resolution of constipation postoperatively. Cases with longer durations of clinical signs may require a combination of subtotal colectomy along with pelvic osteotomy to resolve their condition.

Prognosis

The long-term prognosis after surgical treatment of megacolon via subtotal colectomy in both dogs and cats is generally considered excellent, with four-year survival rates reported of 90–100%. Patients should be monitored for potential postoperative complications such as dehiscence with development of septic peritonitis, stricture, and/or recurrent constipation.

Perianal Fistulae

Clinical Presentation

Perianal fistulation, as the name implies, is the development of ulcerative, fistulated tissue tracts in the perianal skin. Owner history generally includes excessive anal and perianal licking, the presence of foul-smelling discharge, dyschezia, and tenesmus. Affected dogs are often extremely painful, and show a "dropped" tail posture. These patients often resent tail handling during physical examination, and may need to be deeply sedated or anesthetized to allow full examination. The perianal skin shows areas of ulceration and draining tract/fistula formation; these fistulas may extend up to 7 cm deep, and the entire circumference of the anus may be affected (Figure 57.3). Anal gland impaction and abscess formation are common co-morbidities, but they are not a prerequisite for development of this disorder.

Perianal fistulation can be a devastating disease, with some dogs showing altered temperament and increasing difficulty in handling due to ongoing pain.



Figure 57.3 Composite images of the perineum of an 8-year-old spayed female German shepherd dog with perianal fistula formation. The left panel shows the dog at diagnosis, while the right panel shows progress in resolution of the lesions at five weeks following commencing cyclosporin-A treatment. This dog also has an ulcerated perianal adenoma at the 12 o'clock position.

Pathophysiology

Perianal fistulae are most commonly encountered in the German shepherd dog, with over 80% of reported cases being in this breed. Sporadic cases are recognized in other medium- to large-breed dogs. This disease, in common with many of the apparently immune-mediated gastrointestinal diseases, is most commonly recognized in middle-aged to older dogs. In the German shepherd dog a linkage to specific major histocompatibility complex types has been documented. Recent work has suggested that the underlying genetic and immunologic defect in these dogs is similar to that underlying perianal fistula formation in some forms of Crohn disease in humans. The underlying pathology of this disorder is not well characterized in either the dog or humans. The disease is generally thought to revolve around inappropriate inflammatory response to commensal microbes on the skin or in feces, dietary components, or possibly to a combination of both immunogens. Approximately 50% of dogs with perianal fistula formation have concurrent colitis or both small and large intestinal inflammatory disease, suggesting the presence of a systemic dysregulation of gastrointestinal immune function.

Treatment Approaches

Both surgical and medical management approaches may be considered for dogs with perianal fistula formation, with some cases requiring a combined approach. The mainstay of therapy, though, remains immune modulation with ciclosporin or tacrolimus. If necessary and indicated, surgical removal of impacted or abscessed anal glands (see Anal Sac Impaction) and aggressive resection of fistulated tissue are associated with resolution of clinical signs in some dogs, and should be considered in dogs with deep fistulae and extensive disease.

Medical management of perianal fistula revolves around immune modulation therapy. Ciclosporin and tacrolimus, both of which block early T cell activation, are the mainstay drugs for medical management of this disease (Table 57.1). In one study, five of 10 dogs with anal fistulae treated with topical tacrolimus showed complete resolution of clinical signs at 16 weeks, while 9/10 showed at least "noticeable improvement." Interestingly, most of the dogs that failed to show resolution were sexually intact, and neutering/spaying is recommended as part of the treatment regime if not previously performed.

At least some dogs will respond to dietary modification following aggressive surgical resection, with one recent study of 33 dogs reporting 29/33 having complete resolution at one year following surgery when dogs were exclusively fed a fish- and potato-based hypoallergenic diet.

Pseudocoprostasis

Clinical Presentation

Pseudocoprostasis refers to the accumulation of fecal matter in the hair surrounding the anus. This condition is recognized in both dogs and cats, typically in long-haired breeds. Presenting complaints from owners are typical of rectal/anal disease, and include unproductive straining to defecate, tenesmus, dyschezia, excessive anal/perianal grooming, and a foul odor.

Table 57.1 Drugs commonly used in the management of rectoanal disease in the dog and cat

Agent	Indication	Typical dose	Administration notes
Anti-inflammatory, immune modulating			
Predniso(lo)ne	Chronic idiopathic inflammatory diseases	1–2 mg/kg/day, tapering to minimum effective dose	Counsel owner that withdrawal from high doses is risky.
Cyclosporin	Anal fistula	3–5 mg/kg SID	Tacrolimus is more expensive than cyclosporin, but topical use provides greater cost-effectiveness
Tacrolimus	Anal fistula	0.1% Topical ointment, cover affected area SID to BID	
Laxative			
Lactulose	Constipation	0.5 ml/kg TID	
Prokinetic			
Cisapride	Constipation, early megacolon	2.5–5.0 mg/cat TID	Pharmaceutical-grade cisapride is no longer marketed, but reagent-grade material remains accessible via compounding pharmacies
Prucalopride	Megacolon	Limited data available	$5–HT_4$ receptor agonist, potential replacement for cisapride

BID, twice a day (*bis in die*); SID, once a day (*semel in die*); TID, three times a day (*ter in die*).

This condition most commonly accompanies or follows the presence of diarrhea. Poorly formed stool accumulates and dries in the perianal hair, resulting in hair clumping and poor drainage of the underlying skin. Obstruction of the anal opening and pain due to pulling action on the hair result in distress on defecation and often lead to constipation.

Secondary perianal dermatitis is common, and increases the risk of maggot infestation.

Diagnosis is straightforward, and made entirely by physical examination. Clipping of the hair surrounding the anus to remove the dried fecal material is necessary to allow proper examination of the skin and anal glands, and is also fundamental to initial treatment.

Treatment Approaches

Clipping of the impacted hair mats and gentle cleaning of the perianal skin are typically all that is required for the treatment of uncomplicated cases. Attention to the cause of underlying diarrhea, and owner counseling to maintain grooming of the perianal skin and, for more chronic cases of diarrhea, regularly bathing the patient are important for longer term management and prevention of recurrence.

More complicated cases, featuring maggot infestation, deep pyoderma of the perianal skin or anal glad abscesses, may require additional topical medical or surgical management, as appropriate. The prognosis is good for full recovery, assuming that owners remain diligent in maintaining effective grooming.

Rectal Foreign Bodies

Clinical Presentation

Foreign bodies lodged in the rectum typically present with signs of constipation, including straining to defecate, tenesmus, and occasionally paradoxical diarrhea. The owner history may reveal evidence of foreign body consumption and bouts of vomiting or poor appetite in the prior several days. Very rarely, linear or penetrating foreign bodies are found in the rectal area, but most foreign bodies of this type cause signs in the more cranial segments of the gastrointestinal tract.

Pathophysiology

In most cases, the large intestine is obstructed by the foreign body, resulting in excessive fecal loading and constipation signs. Most rectal foreign bodies are objects (either food or toys/other foreign objects) that have been voluntarily consumed and pass through the gastrointestinal tract, before accumulating sufficient adherent firm material to obstruct in the rectum, often just cranial to the anal sphincter.

Diagnosis and Medical Management

Diagnosis is typically made on physical examination and palpation of the object. Once detected, most rectal foreign bodies can be removed readily using manual distraction and adequate lubrication. The patient should be

deeply sedated or anesthetized for these procedures. In some cases, foreign bodies can be broken up using rectally passed heavy forceps, aiding their eventual passage.

Surgical Management

Surgical management of rectal foreign bodies is not typically required as nonsurgical removal is almost always possible. In the event of rectal tears or trauma developing as a consequence of a rectal foreign body, surgical repair of the defects may be indicated (see Rectal Tears and Trauma section).

Prognosis

Most rectal foreign bodies are removed with minimal to no complications and prognosis is excellent.

Rectal Polyps

Clinical Presentation

Adenomatous rectal polyps are the most common benign tumor of the rectum. The most common site for these growths is at the terminal rectum or anorectal junction. Affected animals present with hematochezia, tenesmus, dyschezia, and/or diarrhea.

Pathophysiology

In dogs, most rectal polyps are thought to arise as a consequence of long-standing colonic and rectal wall inflammation. Fibrous proliferation of the submucosa results in the development of polypoid "proud" intrusions into the rectal lumen. The mucosa covering the polyps is usually also dystrophic, raising some concerns that these may be preneoplastic lesions. There is little support for this concern, however, with the great majority of these lesions being benign.

Diagnosis and Medical Management

Often, the primary presenting sign for dogs with rectal polyps is hematochezia, usually accompanied by tenesmus, but usually without other overt evidence of constipation. Many rectal polyps are located in the very distal rectum, 1–3 cm orad to the anal sphincter, and are readily palpable on digital rectal palpation.

Routine diagnostic imaging, including abdominal ultrasonography, usually has a low diagnostic yield for these lesions.

Proctoscopy/colonoscopy is very valuable in assessing these lesions, allowing visualization of the lesion base and extent for adequate surgical planning, and also to assess the remainder of the rectal mucosa and distal colon, as more than one lesion may be present. The rectum and distal colon are adequately assessed using rigid proctoscopes, and these instruments may also allow sufficient room for removal of pedunculated lesions using polyp snares. More complete examination of the entire colon requires the use of flexible colonoscopes and adequate preprocedural preparation, such as administration of oral laxative solutions and preanesthetic enemas (Figure 57.4).

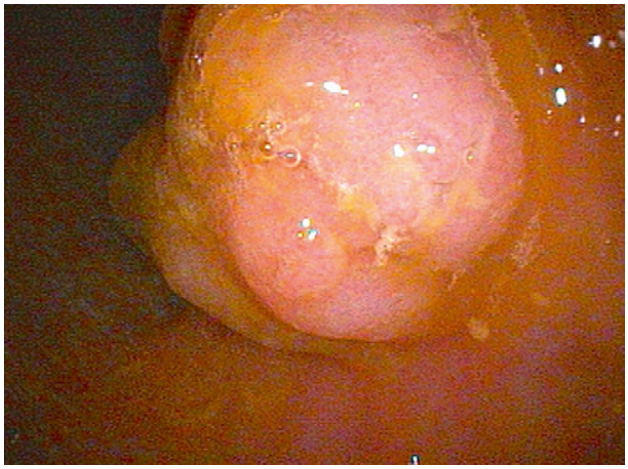


Figure 57.4 Endoscopic view of a benign rectal polyp in a dog. A large, semipedunculated mass is visible, and the mucosal epithelium is mildly disorganized and folded.

Medical management of rectal polyps can be attempted via diet modification (increasing indigestible fiber) and trial treatment with either oral or topical (via foaming enema) glucocorticoid administration. These strategies have variable, and usually poor, efficacy. Large polyps associated with frequent hematochezia and tenesmus are generally best managed via surgical removal.

Surgical Management

Most benign adenomatous polyps can be surgically removed via a transanal rectal eversion procedure (also called a "rectal pull-out"). Stay sutures are placed cranial to the lesion and used to prolapse the rectum around the mass. Metzenbaum scissors or a scalpel blade are used to resect the mucosa around the base of the tumor down to the muscularis, avoiding a full-thickness incision. The mucosal defect is sutured using monofilament absorbable suture in a single, simple continuous or simple interrupted layer. The mass should always be submitted for histopathology to confirm a benign tumor. Postoperative antibiotics are usually not indicated.

Some benign rectal polyps can be more extensive and warrant a more aggressive surgical approach. See the Rectal Tumors section for more details.

Prognosis

The prognosis for dogs with benign rectal polyps is good, but a regular monitoring schedule should be instituted to assess for recurrence and potentially progression of disease towards a malignant state. If caught early in the course of disease, lesions undergoing malignant transformation treated appropriately (e.g., carcinoma *in situ* resected with histologically complete surgical margins) can be successfully treated with good long-term survival.

Rectal Prolapse

Clinical Presentation

Depending on whether only anal mucosa is protruding or all layers of the terminal rectum are protruding as a cylindrical mass, rectal prolapse can be classified as either partial or complete, respectively. Most commonly occurring in younger animals, prolapse is typically a secondary condition, caused by tenesmus from presence of parasites, foreign bodies, or urogenital diseases.

Pathophysiology

Rectal prolapse is generally due to excessive straining, and may be seen in any patient that has an underlying disease that will result in tenesmus. Rectal prolapses are most commonly diagnosed in younger animals, likely reflecting the higher frequency of parasite infestation and other diarrheal diseases in these patients. Prolapse can also occur secondary to straining due to constipation, but this is less common than with the diarrheal diseases.

Following initial prolapse of the rectal mucosa, venous congestion of the prolapsed tissue will result in swelling. This swelling may actually increase straining, leading to a progressive worsening of the prolapse that can proceed to complete prolapse (Figure 57.5).



Figure 57.5 Rectal prolapse in a puppy with a history of diarrhea. Note the prolapsed, swollen mucosa with areas of drying and early devitalization. This dog was successfully treated with lubrication, gentle manual pressure to reduce the prolapsed tissue, and a purse-string suture.

Diagnosis and Medical Management

Although the diagnosis of a rectal prolapse may be straightforward, identification of the underlying cause may be more challenging. A thorough history and physical exam (including a well-lubricated digital rectal examination) are essential, with additional diagnostics to consider including fecal examination, complete blood count, serum biochemical profile, urinalysis ± culture, and abdominal imaging.

Initial treatment attempts are directed at lubrication of the prolapsed segment of rectum with manual replacement via digital pressure. Tissue edema can be reduced to aid with reduction by application of a topical 50% dextrose solution or live yeast cell derivatives (available for treatment of human hemorrhoids). An anal purse-string suture (nonabsorbable monofilament) is placed after reduction, tightened around a syringe case inserted into the anus to prevent overtightening. The suture is maintained for 3–5 days while the underlying condition is treated.

Surgical Management

For patients that have failed more conservative treatment as described earlier, or for those with prolapsed tissues that have undergone necrosis, surgical partial rectal amputation with or without colopexy may be indicated.

Surgical rectal amputation is performed in stages, using Metzenbaum scissors to resect the prolapsed necrotic portion of the rectum and anastomosing the cut section using monofilament absorbable suture in an interrupted or continuous pattern. The author prefers to perform this procedure in thirds, to prevent the cranial

end of the cut rectum from retracting prior to suturing. Three to five stay sutures placed cranial to the proposed site of resection help maintain exposure. Suturing should be performed in a single layer, ensuring each bite engages the submucosa to minimize risk of postoperative dehiscence, leakage, or stricture.

Colopexy may help prevent recurrence of rectal prolapse. In cats failing more conservative management (purse-string placement), because of a high rate of rectal stricture following circumferential rectal amputation, colopexy is preferred as long as the prolapsed tissue is considered viable. Two methods of colopexy have been described: nonincisional and incisional. Nonincisional colopexy uses two rows of five or six simple interrupted sutures between the antimesenteric colonic wall and the left abdominal wall. Incisional colopexy requires the creation of a linear incision in the serosamuscularis of the colon with a matching incision in the peritoneal lining of the left abdominal wall with two simple continuous suture lines joining the two incisions, similar to incisional gastropexy. In either technique, secure purchase of the colonic submucosa is important to ensure a successful colopexy. No differences have been reported in outcomes after either colopexy technique.

Prognosis

The prognosis depends on the underlying cause of the prolapse. Uncomplicated prolapse in young animals, often associated with gastrointestinal parasitism, is frequently responsive to minor therapeutic interventions (e.g., purse-string) and the prognosis can be excellent. More severe cases have necrosis of prolapsed tissue with significant underlying co-morbidities.

Rectal Tears and Trauma

Clinical Presentation

Rectal trauma causing perforation is a relatively rare condition that may result from pelvic fractures, foreign objects, iatrogenic causes (e.g., examination, thermometers, enemas, surgery), or penetrating wounds. Depending on the degree of rectal trauma and duration of injury, animals may present in varying degrees of septic shock and/or rectocutaneous fistulation.

Pathophysiology

Clinical signs develop from contamination of the perineal tissues with feces, leading to abscessation and/or sepsis. If a perforation occurs cranial to the retroperitoneal reflection, septic peritonitis may develop.

Diagnosis and Medical Management

Careful physical examination is the primary method for diagnosis of rectal trauma. Rectal tears are most commonly located in the distal (extraperitoneal) portion of the rectum. A complete blood count and serum biochemistry profile are recommended for patients suspected of sustaining rectal trauma. Diagnostic imaging (ultrasound and/or negative contrast pneumoradiography) can be performed to further characterize the defect.

Small, partial-thickness rectal tears will resolve with medical management. However, larger or full-thickness tears require prompt surgical intervention. Medical treatment with correction of electrolyte abnormalities, hypotension, and administration of appropriately targeted antimicrobials is important prior to surgery.

Surgical Management

The surgical approach used will depend on the location and extent of the tear. Transanal rectal eversion with stay sutures will allow access to distal tears, but larger defects will require a perineal approach (dorsal or lateral), possibly combined with an abdominal approach with or without pelvic osteotomy. Placement of drains is typically indicated to address perineal tissue contamination. Secure closure of the rectal wall, typically with monofilament absorbable suture in one or two layers, is of the utmost importance to resolution of the condition and ensuring a good long-term prognosis. Because a perineal surgical wound is typically heavily contaminated with feces, it may be partially closed or left open to heal by second intention.

Prognosis

Appropriately managed rectal perforations should heal with a good prognosis, but the patient may be threatened by concurrent trauma to other organ systems associated with the inciting cause of rectal perforation. Therefore, the prognosis depends on co-morbidities and aggressive management of polytrauma patients is recommended. If dehiscence of the rectal tear occurs, a rectocutaneous fistula may form which requires reoperation.

Rectal Tumors

Clinical Presentation

For the purposes of this chapter, rectal tumor is taken to refer to any neoplastic or hyperplastic process affecting the rectum or internal anus other than benign inflammatory polyps, which have been described separately.

The clinical signs accompanying rectal tumors are similar to most other rectal diseases, featuring histories of straining to defecate and occasionally the presence of narrow "ribbon-like" stool due to partial restriction of the rectal lumen. Hematochezia is variably present, depending on the involvement of the mucosa. Tumors such as adenocarcinoma and mucosal lymphoma often present with histories of hematochezia, while tumors affecting the muscularis and deeper mural layers, such as leiomyoma or GI stromal tumors, usually do not feature hematochezia.

Pathophysiology

Rectal tumors result from neoplastic or hyperplastic changes in normal tissue of the rectum or anal sphincter. Any of the various tissue types within the rectum can be involved (mucosa, secretory epithelia, smooth muscle, lymphoid tissue, etc.), but tumors affecting other than the epithelia (such as leiomyoma or GIST tumors) are uncommon. Of all the potential rectal tumor types, adenocarcinoma (possibly resulting from malignant transformation of rectal polyps) is the most common.

Diagnosis and Medical Management

Direct digital rectal examination will often reveal the presence of intrarectal masses, and may allow some determination of mucosal vs deeper mural location. Accessibility of mass lesions will depend upon the depth of the lesion within the rectum, the size of the animal and examiner's reach. Effective digital rectal examination often requires sedation of the patient, particularly with smaller animals.

Routine diagnostic imaging, such as abdominal radiography, has a low yield in the assessment of rectal tumors. Abdominal ultrasound examination can also fail to fully appreciate the size and location of rectal tumors within the pelvic canal. In patients where rectal malignancies are suspected, a combination of colonoscopy (allowing biopsy and assessment of the adjacent mucosa) and abdominal/pelvic CT examination (for staging, assessment of bone involvement and invasion into other pelvic organs such as the urethra or prostate) is generally recommended.

Medical management of nonpolypoid masses in the rectum is generally fruitless. Dietary change to "low-residue" diets and use of laxatives such as lactulose will improve clinical signs in some patients and can allow a degree of conservative management, but most patients will require surgical management for the best long-term treatment effect and prognosis.

Surgical Management

In preparation for surgery of the rectum, many surgeons recommend feeding a low-residue diet for 4–5 days preoperatively and avoiding enemas in the three days preceding surgery. Perioperative antibiotic cover typically consists of cephalosporins but some surgeons prefer metronidazole or other agents that may target colorectal anaerobic bacteria. The need for postoperative antibiotics depends on degree of contamination during surgery, but is typically not necessary beyond 24 hours postoperatively.

Rectal surgery can be divided into two general categories: procedures that can be performed from a perineal or transanal approach and procedures that require an intraabdominal approach. The first is the simpler and more commonly performed option. The exact distance accessible depends on the patient's size and should be assessed via digital rectal exam prior to deciding upon the approach. Transanal rectal eversion (i.e., prolapse; also called "rectal pull-out" procedure; Figure 57.6) using stay sutures allows access to tumors of the distal rectum. If not circumferential in nature, such tumors may be removed by scalpel blade and hand-sewing, or by use of a thoracoabdominal stapling device. For circumferential lesions, a transanal rectal pull-through resection and anastomosis may be performed.

The author prefers to transect and suture the circumference of the rectum in thirds, preventing the orad segment from retracting too far cranially. A grossly normal tissue margin of 0.5–1.0 cm is typically feasible with either transanal rectal eversion or transanal rectal pull-through. If larger margins are required based on preoperative diagnostics, a more aggressive surgical approach is required, as described below.



Figure 57.6 Early intraoperative view of a rectal pull-through procedure to remove a large, benign rectal polyp (2 cm diameter) in a Labrador retriever.

Surgical removal of tumors not confined to the distal rectum is performed via a perineal or anal approach, which can be combined with intraabdominal dissection to mobilize the descending colon along with the cranial end of the rectum. Preservation of the external anal sphincter muscle may be possible, depending on the tumor location and extent. Pelvic osteotomy techniques may need to be employed. This is an advanced procedure used for malignant tumors of the rectum (e.g., carcinoma) and can allow for removal of up to 6 cm of grossly normal tissue margins *en bloc* with the primary tumor, as well as extirpation of regional lymph nodes. Morbidity (especially fecal incontinence) and mortality with combined approaches can be significant but dogs surviving the postoperative period can experience long-term disease-free intervals.

Prognosis

Prognosis depends upon the histologic tumor type, margin status, and staging results. Benign tumors (e.g., adenomatous polyps, *in situ* carcinomas, leiomyomas) can be cured with surgical resection. Rectal lymphoma, although rare, carries a good prognosis following surgery and chemotherapy, with a reported overall median survival time of 1697 days. Canine rectal adenocarcinoma carries a worse prognosis, with reports ranging from six to 24 months, depending on staging and completeness of excision.

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58

Dysbiosis and the Use of Pre-, Pro- and Synbiotics

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The Importance of the Gastrointestinal Microbiota

The intestinal microbiota is the collection of all live microorganisms (bacteria, fungi, protozoa, and viruses) that inhabit the gastrointestinal (GI) tract. The word *microflora* is often used in older textbooks, but microbiota (from *bios*, Greek: life) is the technically correct term.

The total microbial load in the intestine is estimated to represent between 10^{12} and 10^{14} organisms, which is about 10 times the number of cells composing the host body. Because the majority of intestinal bacteria cannot be cultured using commonly used plating techniques, molecular tools (mostly targeting the 16S rRNA gene) are now the standard for identification of microbiota, and have improved our understanding of the complex microbial diversity in the intestine. It is estimated that the intestine harbors several hundred bacterial phylotypes. The microbiota differs substantially on the species and strain level in each individual animal yet despite these differences, the metabolic end-products in the intestine are similar between individuals. This new insight into the complexity and individuality of the gastrointestinal microbiota has increased research efforts to better understand the importance of a balanced microbial ecosystem for regulation of host immunity in health and disease.

The interactions between intestinal bacteria and the host immune system are mediated through various mechanisms, either via direct contact between bacteria and the innate immune system (e.g., via Toll-like receptors, NOD2 receptors), or through microbial-derived metabolites. These metabolites can be either directly produced by bacteria (e.g., vitamins, short-chain fatty acids [SCFA]), or may be primary host metabolites that are converted through bacterial enzymes into secondary metabolites (e.g., conversion of primary to secondary bile acids, tryptophan into indole). Consequently, many studies in humans and animals have associated intestinal dysbiosis, defined as alterations in intestinal microbiota composition and/or richness, with various disorders such as inflammatory bowel diseases (IBD), granulomatous colitis, obesity, diabetes mellitus, and allergies. For these reasons, the normalization of dysbiosis appears to be a prudent therapeutic goal.

The Gastrointestinal Microbiota in Healthy Dogs and Cats

We are just beginning to understand the complexity of the microbiota and are only at a very early stage in our abilities to properly assess the entire microbiota and its functions. The microbiota varies along the GI tract, and there are also clear differences between the mucosa-associated and luminal microbiota. Additionally, we are not yet able to fully assess the interactions between the microbiota and the host immune system. Several recent studies have described which bacterial groups reside in the GI tract of dogs and cats, and some initial work has been done to understand the metabolic interactions between microbiota and host.

Studies using traditional bacterial culture estimated that the bacterial load in the small intestine of healthy dogs is typically 10^2–10^5 cfu/g of small intestinal content, but can reach as high as 10^9 cfu/g. In the colon, the number of cultivable bacteria is much higher, with up to 10^{11} cfu/g. Molecular studies using high-throughput sequencing are now the standard for microbiota characterization and have identified many novel and important bacterial genera that were previously not appreciated in the canine and feline GI tract.

The predominant phyla in the feces of healthy dogs are Bacteroidetes, Firmicutes, Fusobacteria, and Proteobacteria. Lower abundance phyla (less than 1% of

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the micriobiota) include Spirochaetes, Tenericutes, and Verrucomicrobia. The Firmicutes can be divided into several subgroups on a family and genus level. It comprises many phylogenetically distinct bacterial groups. These groups (e.g., *Ruminococcus* spp., *Faecalibacterium* spp., *Dorea*), together with Bacteroidetes and Actinobacteria (i.e., *Bifidobacterium*) are producers of metabolites that have direct impacts on host health. For example, bacteria can utilize complex carbohydrates (e.g., starch, cellulose, pectin, and inulin) as nutrient sources, and their fermentation produces SCFA (e.g., acetate, propionate, and butyrate). These act as energy sources for the host, regulate intestinal motility, and are important growth factors for epithelial cells. SCFA are also important antiinflammatory molecules, as they induce immunoregulatory T cells (T_{reg}). Other bacteria-derived metabolites, such as indoles (a byproduct of tryptophan degradation) or secondary bile acids, are also antiinflammatory, thereby maintaining immune homeostasis and strengthening intestinal barrier function.

The microbiota primes the immune system, aids in the defense against potential intestinal pathogens, and provides nutritional benefits to the host. Bacteria communicate with the host's innate immune system through cell-associated receptors such as Toll-like receptors (TLR) and dendritic cells. The resident intestinal microbiota is also a crucial part of the intestinal barrier, due to the phenomenon of "colonization resistance" which protects the host from invading pathogens through competition for oxygen, nutrients, and adhesion sites on the mucosa.

The Gastrointestinal Microbiota in Disease

There is clear evidence that altered microbial communities play a role in the pathophysiology of various disorders. Chronic dysbiosis is likely an important environmental risk factor for development of several chronic diseases in genetically susceptible individuals. For example, recent epidemiologic studies in humans have linked antibiotic administration in early childhood with an increased risk for development of allergies and obesity. Also, antibiotic-induced reductions in gut microbiota diversity were a risk factor for higher mortality outcomes in allogeneic hematopoietic stem cell transplantation. These initial data in humans suggest that dysbiosis is clinically relevant and the correction of dysbiosis would appear to be a prudent therapeutic goal. However, at this time, there are still only limited clinical data available to guide specific treatments for correction of dysbiosis in dogs and cats.

Dysbiosis occurs in various forms; it may be due to overgrowth of specific pathogens, or due to more general changes in bacterial groups, and/or changes in the functional and immunomodulatory properties of the gastrointestinal microbiota. All these forms overlap to some extent.

There are several physiologic mechanisms that regulate microbial colonization in the GI tract. Gastric acid, bile, and pancreatic enzymes all have antibacterial roles and eliminate a proportion of ingested organisms. Intestinal motility is an important regulator of bacterial adhesion to the mucosa in the small intestine. Microbes that are unable to adhere to the epithelium will be pushed to the large intestine, which has a more stagnant motility and therefore higher bacterial numbers. The ileocolic valve is a natural barrier that prevents retrograde migration of bacteria from the large to the small intestine.

Any changes in these mechanisms may lead to dysbiosis, but whether this leads to disease will depend on the susceptibility of the individual, as not every animal exposed to these risk factors will develop disease. For example, acid suppression therapy increases gastric and duodenal bacterial counts in humans, but not all patients show clinical signs. Similarly, dogs with experimentally induced exocrine pancreatic insufficiency (EPI) have increased bacterial numbers in the proximal small intestine. Rapid diet changes, dietary indiscretion, changes in the architecture of the intestine, or changes in intestinal motility (i.e., surgical creation of intestinal loops, short bowel syndrome, and resection of the ileocolic valve) are also associated with dysbiosis. The development of dysbiosis may then lead to changes in gastrointestinal physiology that will negatively impact function of the GI tract. Examples are an altered intestinal barrier with increased intestinal permeability and direct damage to the intestinal brush border and enterocytes leading to nutrient and vitamin malabsorption. An overgrowth in specific bacterial groups may lead to increased competition for nutrients and vitamins and to increased deconjugation of bile acids, resulting in the creation of potentially deleterious metabolites.

The intestinal microbiota also plays a role in the pathogenesis of IBD. Intestinal inflammation leads to a shift towards gram-negative bacteria (i.e., Proteobacteria) that may perpetuate the disease. Existing dysbiosis may trigger alterations in the immune system, which in turn diminish the colonization resistance of the resident microbiota. Several studies in dogs and cats have reported increases in Enterobacteriaceae in the GI tract of dogs and cats, and these are associated with inflammation and altered mucosal architecture. In contrast, a reduction in some major bacterial groups (i.e., Lachnospiraceae, Ruminococcaceae, *Faecalibacterium prausnitzii* and *Clostridium coccoides* subgroups) occurs in GI disease, suggesting a loss of normal and protective microbiota in GI disease (Figure 58.1).

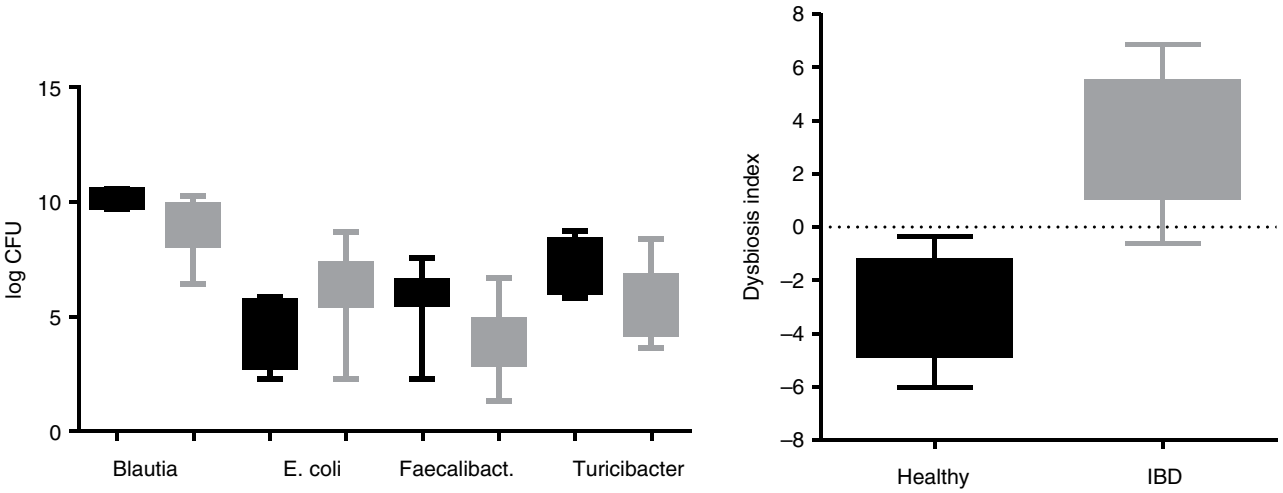


Figure 58.1 Dysbiosis in dogs with IBD. (*Left*) Several major bacterial groups are decreased in healthy dogs (*black*) vs dogs with IBD. In contrast, *E. coli* is typically increased in IBD. These data illustrate that IBD is associated with loss of normal and protective microbiota. (*Right*) The same data are displayed as an dysbiosis index (DI) that summarizes the abundances of these major bacterial taxa as one single numerical value (a positive number indicates dysbiosis).

These groups are mainly producers of SCFAs and other immunomodulatory metabolites. Consequently, decreased fecal propionate, reductions in secondary bile acids, and a reduction in indole concentrations are reported in dogs with acute and chronic diarrhea. This depletion of commensal groups and their respective immunoregulatory metabolites may impair the ability of the host to downregulate the intestinal immune response, and dysbiosis becomes a part of the pathophysiology of the chronic disease process.

Therapeutic Approach to Dysbiosis

As outlined earlier, the intestinal microbiota will affect the health status of the host, and shifts in bacterial groups have been associated with GI diseases such as antibiotic-responsive diarrhea and IBD. Dysbiosis is defined as an altered composition of the microbiota, yet some disorders may be associated with changes in microbiota function (e.g., reduced SCFA, altered bacterial enzymes) rather than shifts in microbial communities. These functional changes are difficult to detect, as there is no comprehensive method to assess the entire microbiota, including its metabolism and its interactions with the host immune system. The microbiota varies along the GI tract, and between mucosal and luminal sites. Because all these factors potentially play roles in the development of clinical signs, assessment of bacterial changes in intestinal (fecal) samples most often does not reveal the entire disease process. Nevertheless, it is now better understood which bacterial groups and which metabolites are commonly altered in GI disease.

The best therapy for dysbiosis is currently unknown. At this time, therapy is based on empirical approaches with improvement of clinical signs being the most useful outcome measure. Due to vast interindividual differences in the intestinal microbiota, it is difficult to define what constitutes a normal and balanced intestinal ecosystem. Dietary manipulation, the administration of antibiotics or pre- and/or probiotics are common strategies. It is important to note that while such interventions may cause shifts in the composition of the intestinal microbiota, these changes are largely individual to each animal. Clinical experience shows that dietary changes or antibiotic administration often lead to an improvement in GI signs, although the exact mechanism remains unclear. Antibiotics can eliminate specific pathogens or can lead to more general modulations of the intestinal microbiota. This may result in a lesser burden of stimulating antigens. While in some animals, the use of antimicrobials is useful (e.g., animals with ARD), their use may exacerbate dysbiosis in other GI diseases that do not respond to antibiotics. Recent epidemiologic studies in humans have suggested that the chronic use of antimicrobials is a strong risk factor for the development of asthma, obesity, and diabetes mellitus. Therefore, alternative approaches to antibiotic therapy to treat dysbiosis are desirable.

Probiotics, Prebiotics, and Synbiotics

Probiotics are currently defined as live microorganisms, which when administered in adequate amounts confer a health benefit on the host. Synbiotics are a combination of probiotics and prebiotics. They are often administered

together to add a growth substrate for the administered probiotic. Prebiotics are nondigestible food ingredients (e.g., fructooligosaccharides [FOS] and galactooligosaccharides [GOS]) that are added to diets to stimulate the growth of native probiotic bacteria. Prebiotics are typically added to diets to enhance the growth of endogenous microorganisms or stimulate their metabolism. The target groups for prebiotic administration, for example *Bifidobacterium* spp., were believed to be major bacterial groups in the canine and feline GI tract before the advent of molecular studies. However, only minor changes in microbiota are typically induced through prebiotics, as the administered compounds fulfill only some of the nutrient requirements for their target bacteria, and other essential nutrients remain at growth-limiting amounts. In addition, because of the individuality of the microbiota, not every animal will have the same bacterial strains and enzymes that are needed to utilize the administered prebiotics. Therefore, only a portion of animals will respond with increases in the targeted bacterial groups. It is also unclear whether the bacterial groups necessary for prebiotic utilization are present in animals with dysbiosis. Consequently, there are no published clinical studies that have evaluated prebiotics in animals with GI disease.

Prebiotics may be useful in stimulating the microbiota and immune system in healthy animals, but their benefit in animals with GI disease has not been widely explored. In contrast, more clinical data are available about probiotics (or synbiotics), and this will be discussed in more detail below.

Selection of Probiotics

The intestinal microbiota is an important modulator of the immune system. Administration of specific bacterial strains as probiotics can potentially mimic the effects of the normal microbiome. It is important that the clinician and client understand that every bacterial strain may differ substantially in its functional and immunologic properties. Therefore, not every strain will elicit the same response, and ideally strains are selected for the right disease and the right patient based on clinical studies. Information regarding strain designations is critically important in clinical studies, to be able to select the proper product containing the clinically tested strain. However, in veterinary practice there are few clinical data available. There are many commercial products available containing various strains that have not been tested in clinical studies.

In the US, probiotics are considered to be nutritional supplements and, therefore undergo little regulatory scrutiny. Unfortunately, many commercial products lack acceptable quality. For example, in one study almost 50% of products did not list any information about the organisms (i.e., did not provide the strain designation) and their numbers. Also most products did not contain the stated numbers of bacteria. Therefore, at this point it is recommended to only select probiotic products that have clinical and published data behind them.

There are only a few probiotic strains with extensive *in vitro* as well as clinical data (mostly in humans) published in primary literature (e.g. VSL#3 strains, *Lactobacillus* GG, *E. coli* Nissle, *Saccharomyces boulardii*). There are data available based on clinical studies in veterinary patients for the following products: *Enterococcus faecium* SF68 (Fortiflora®), Visbiome®, SIVOY®, and Proviable®.

Currently, selection of bacterial strains for most commercial probiotic products is mostly based on their ability to survive the passage through the stomach and small intestine, their ability to adhere to mucus, and *in vitro* immunomodulation. Furthermore, strains are selected that are on the safety list of the FDA, as these are approved for human and animal use, and no additional safety data are necessary. These strains are typically lactic acid bacteria (*Lactobacillus*, *Bifidobacterium*, *Enterococcus*, *Streptococcus*), as these bacterial genera were traditionally believed to confer health benefits. However, due to the complexity of the microbiota, there is no clear correlation between changes in these bacterial groups and health and disease. While lactic acid bacteria are still the most commonly used probiotic strains, in the future novel products may become available containing bacterial groups that are more abundant and depleted in GI disease (e.g., *Faecalibacterium*, *Blautia*, etc.).

The actual mechanisms through which probiotic strains can elucidate beneficial effects are numerous. Some probiotic strains have been shown to modulate the immune system, such as enhancing IgA production and pathogen phagocytosis and stimulating release of antiinflammatory cytokines. Other probiotic strains help to restore mucosal barrier function. Probiotics can also help protect the host from pathogenic bacteria through the production of antimicrobial substances, and through competitive exclusion of pathogens by preventing adhesion, occupying binding sites, or consuming vital nutrients.

While often probiotics are believed to modulate the intestinal microbiota, recent studies suggest that they have no appreciable effect on the overall composition of the intestinal microbiota, as only minor changes were observed in fecal samples in healthy as well as diseased dogs. Rather than changing the entire microbiota, some strains may adhere to the mucosa and directly communicate with the immune system; this has been shown for Visbiome strains in dogs with IBD. In order to impart a health benefit to the host, a probiotic must be able to

survive passage into the gut, adhere to epithelial cells, and proliferate within the GI tract. Even those probiotic strains that fulfill these criteria appear to colonize the GI tract for only relatively brief periods of time, and are usually eliminated within a few days after the end of administration. Therefore, if the goal of therapy is to have a long-term impact on the patient, long-term daily administration of probiotics in high doses is required.

Clinical Data on Probiotics in Veterinary Medicine

In veterinary medicine, we are currently lacking well-designed, properly powered studies that have been reproduced by independent research groups. There are, however, some promising data on a variety of probiotic preparations. These include the prevention and treatment of antibiotic-associated or stress-related diarrhea (boarding, traveling, working dogs), and the prevention and treatment of gastrointestinal signs during periods of dietary change (weaning in puppies and kittens, new diets). Recent studies have also shown antiinflammatory properties of some probiotics in dogs with IBD.

The greatest amount of data is available for amelioration and/or shortening of acute diarrhea. In a large double-blind, placebo-controlled study of shelter cats, significantly fewer animals (7% vs 20% in the placebo group) that received *Enterococcus faecium* SF68 (Fortiflora, Purina; 2 billion cfu/day) developed diarrhea for greater than a two-day duration. Similarly, administration of *Bifidobacterium animalis* strain AHC7 (Prostora®, IAMS; 100 billion cfu/day) to dogs with acute idiopathic diarrhea reduced the time to resolution by 2.5 days and decreased the percentage of dogs that required adjunctive use of metronidazole (38% vs 50% in the placebo group). Probiotic strains (450 billion cfu/day; Visbiome, Exegi Pharma) led to lower mortality when given to puppies with confirmed parvoviral enteritis (90% vs 70% in the placebo group).

Fewer published studies are available regarding dogs with chronic enteropathies (CE). A probiotic cocktail (200–400 billion cfu per dog per day; Visbiome, Exegi Pharma) has been trialed in dogs with idiopathic IBD. Clinical activity and histology scores were reduced similarly to dogs treated with standard therapy (prednisone and antibiotics). Furthermore, the probiotic induced regulatory T-helper lymphocytes (FoxP3) and protein expression that were associated with enhanced mucosal barrier function. In cats, one published open-label trial assessed the use of a multistrain synbiotic product containing lactic acid bacteria and a blend of fructo- and galactooligosaccharides (5 billion per day; Proviable-DC, Nutramax Laboratories) and reported that 72% of owners perceived an improvement in their cat's diarrhea following a 21-day course of supplementation.

Generally, it is believed that prophylactic administration of probiotics may be a more successful strategy for prevention of GI disease. Experimental studies in animal models have consistently shown that probiotic administration before induction of inflammation has a higher success rate compared to therapeutic administration. However, this approach is often not practical in clinical medicine. Also, it is not clear whether long-term administration of probiotics to healthy animals is useful. But if trigger episodes for diarrhea are anticipated, prophylactic administration of probiotics may be prudent. Also, antibiotics induce dysbiosis and may lead to diarrhea, and this is an area where probiotics may be especially useful. For example, administration of *Saccharomyces boulardii* to dogs with experimental lincomycin-induced diarrhea prevented the development of diarrhea, but was not successful in treating diarrhea once it developed.

Safety of Probiotics

Theoretically, probiotics have the potential to cause systemic infections; they can produce deleterious metabolites and can transfer antibiotic resistance genes. However, side-effects are very rarely reported. A limited number of case reports in humans have shown that probiotics (i.e., *Lactobacillus* spp.) can potentially translocate and cause septicemia in hospitalized patients. A study in humans with severe pancreatitis found increased mortality with probiotic therapy. It is currently recommended that probiotics should be used with caution in immunocompromised patients.

Concurrent Antibiotic Use

Probiotics, like any other bacteria, can be either susceptible or resistant to concurrently administered antibiotics. For the prevention of antibiotic-associated diarrhea, antibiotics and probiotics are prescribed concurrently. Many of the prescribed bacterial groups such as *Lactobacillus*, *Enterococcus*, and *Bifidobacterium* spp. are generally resistant to commonly used antibiotics such as metronidazole and tylosin. Therefore, concurrent administration should be acceptable. For other antibiotics, it may be useful to separate antibiotic and probiotic administration by a few hours if feasible.

Species Specificity of Probiotics

There is some thought that a probiotic should be species specific (i.e., the probiotic strain has been isolated from

the same animal species that it will be used in). This theory is based on the fact that the intestinal microbiota differs between different animal species. Furthermore, a host-specific probiotic may be better adapted to its target organism (e.g., stomach pH, bile acid composition, adherence to epithelial cells). However, while it is known that the resident microbiota differs between different animal species, it has never been demonstrated that probiotic effects are species specific. The microbiota differs dramatically even within animals of the same species, so the concept of a species-specific probiotic may not be entirely accurate. Several *in vivo* (based on animal models) and *in vitro* (based on the adherence to epithelial cells) studies have shown that human and canine probiotics are capable of conferring a health benefit to other animal species.

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59

Diagnosis and Management of Chronic Enteropathies

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Definition

Chronic enteropathies (CE) are a group of idiopathic intestinal disorders characterized by chronic persistent or recurrent gastrointestinal (GI) signs, with histologic evidence of inflammation in the lamina propria of the small intestine, large intestine, or both. The diagnosis of CE is one of exclusion and a full diagnostic work-up needs to be done to rule out all known causes of GI inflammation. Currently, endoscopic evaluation and histopathology of intestinal biopsies is the only way to definitively diagnose CE. Although the exact etiology of CE is unknown, it is widely accepted that the pathogenesis involves a complex interplay among host genetics, the intestinal mucosal immune system, the environment, and the intestinal microbiota.

Classification of Chronic Enteropathies

Chronic enteropathies are classified according to the inflammatory cell present and the area of intestine affected, the most commonly encountered CE being lympho-plasmacytic enteritis in both dogs and cats. Eosinophilic enteritis is thought to be the second most common CE, while granulomatous enteritis is rare. Neutrophilic infiltration is also rare in both canine and feline inflammatory gastrointestinal disease.

Clinically, CE patients can be classified retrospectively depending on their response to treatment. The most common recommendation for these patients is to apply a sequential approach to treatment, with the goal of identifying groups of dogs that respond to a certain treatment. Those responding entirely to an elimination diet or a hydrolyzed diet are diagnosed as food-responsive diarrhea (FRD). Those responding to antibiotics are classified as antibiotic-responsive diarrhea (ARD), and CE patients that do not fall into either of these two categories and require immunosuppressive medication to control their clinical signs are commonly classified as having steroid-responsive diarrhea (SRD). As patients with SRD have, ideally, undergone a thorough work-up to exclude other known causes for intestinal inflammation, these patients can also reasonably be diagnosed as having idiopathic inflammatory bowel disease, or IBD.

Certain breeds are highly susceptible to the development of specific unique forms of inflammatory enteropathies; examples include the immunoproliferative enteropathy of basenjis, the protein-losing enteropathy (PLE) and protein-losing nephropathy (PLN) complex in soft-coated wheaten terriers, IBD with PLE in Norwegian lundehunds and granulomatous colitis in boxer dogs.

Etiopathogenesis

In the last few decades, the study of human IBD and animal models of this disease has led to significant advances in our understanding of the pathogenesis of CE in companion animals. These studies have shown that the pathogenesis is complex, involving an overly aggressive cell-mediated response due to the loss of tolerance to antigens of the commensal microbiome and food antigens in genetically susceptible hosts (Figure 59.1).

Genetics

The heritability of human IBD is not fully understood. Genome-wide association studies have revealed over 200 loci that are variably associated with the development of the disease. It is therefore believed to be an autoimmune disease with polygenetic inheritance. Most loci that have been found to play a role in the pathogenesis of human IBD can be traced to proteins in the innate immunity pathways, as well as some involved in autophagy and

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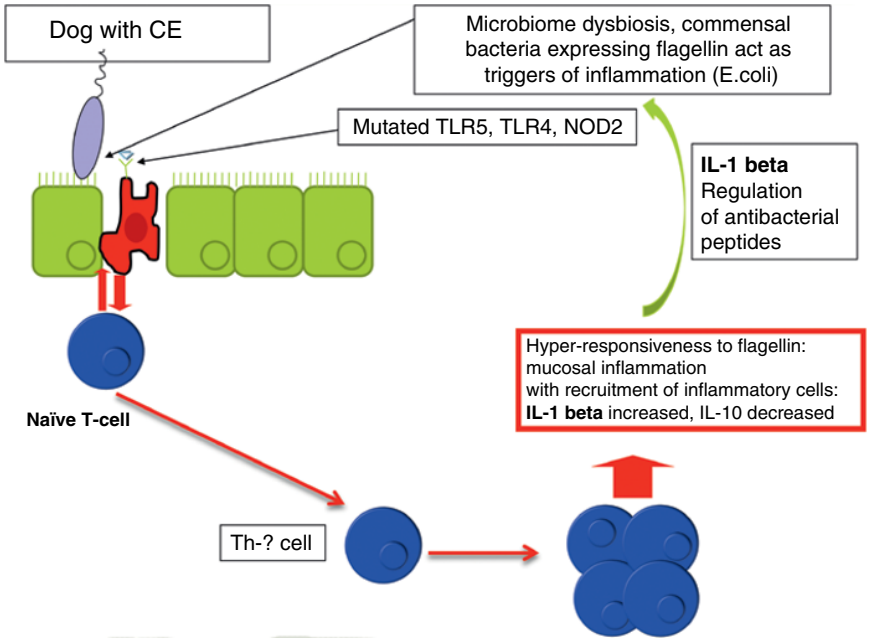


Figure 59.1 Current hypothesis of pathogenesis of CE in dogs. Genetic mutations in pattern recognition receptors of the innate immune system, such as Toll-like receptors, render the intestinal immune system hyperresponsive to commensal bacteria. This leads to danger signals being transferred to T cells in the lamina propria, resulting in increased production of proinflammatory cytokines such as IL-1-beta and decreased production of anti-inflammatory cytokines, such as Il-10. This in turn leads to microbial dysbiosis, which intensifies the trigger for further inflammation.

Th17 cell pathways. These pathways are at the center of gut mucosal immunology, and have led to the discovery of novel biologic treatment options in people with IBD.

The mode of inheritance of CE in companion animals is also incompletely understood, and may differ between dogs and cats and across breeds. A number of breed predispositions have been described in canine CE, thus strongly supporting a role for host genetics. However, few causal genetic defects have been identified to date.

Using candidate gene analysis, polymorphisms in certain pattern recognition receptors of the innate immune system (such as Toll-like receptor [TLR] 4 and TLR5) were shown to be significantly associated with CE in German shepherd dogs (GSDs). In addition, the same polymorphisms in TLR5 were associated with IBD in a heterogeneous population of dogs consisting of 38 different breeds. However, as in human IBD, it is likely that defects in multiple genes involving several regulatory pathways are needed to bring about disease. Therefore, further genetic studies such as genome-wide association are needed in both canine and feline IBD to highlight the complex pathogenesis of this disease.

The Intestinal Mucosal Immune System

The concept that immunoregulation is impaired in patients with CE is supported by observations of increased numbers of immunoglobulin-producing plasma cells and T cell subsets in canine and feline IBD. Inflammation seen in CE is thought to result from the inappropriate cytokine production by these different T cell subsets. In people, Crohn disease (CD) is associated with a Th1 and Th17 cytokine profile and ulcerative colitis (UC) with a Th2 profile, whereas in dogs there is a mixed Th1 and Th2 profile, with no specific bias towards one or the other. Th17 cells seem to play an important role in human IBD, with interleukin (IL)-17 and IL-22 being highly expressed in the intestinal mucosa. However, in dogs, Th17 cell cytokines were not found to be elevated and therefore are believed to be of minor importance. One newer study identified that an innate cytokine, IL-1-beta, was expressed at higher levels in canine FRD cases, and decreased after successful treatment with dietary measures. More studies are needed to investigate this important pathway in canine CE. In cats, the inflammatory infiltrate has been shown to be associated with increased IL-1, Il-8, and IL-12 expression, and correlated with clinical severity of disease and mucosal adherence of bacteria, especially Enterobacteriaceae, *E. coli*, and *Clostridium* spp.

Other immunologic components may also play a role in the inappropriate inflammation seen in a subset of dogs with CE. Indeed, one study demonstrated that CD11c-positive dendritic cells (DCs) were significantly decreased in the intestinal mucosa of dogs with IBD. DCs are important in regulating the immunologic balance and are responsible for eliciting either an inflammatory or a tolerant immune response to an antigen. Thus, a decrease in the number of DCs in the inflamed mucosa of dogs with CE may explain the exaggerated inflammation seen in this disease.

The Intestinal Microbiota

The importance of commensal bacteria in the pathogenesis of human IBD has been well documented in animal

models. Chronic intestinal inflammation does not develop in mice reared in germ-free environments. In addition, the role of luminal bacteria in the pathogenesis of human IBD is strongly supported by the fact that clinical symptoms improve following intestinal washes and antibacterial treatment. Similarly, a subset of canine IBD patients (ARD patients) respond solely to antibiotics with subsequent relapse of clinical signs on withdrawal. This notion, in addition to recent discoveries of genetic mutations rendering pattern recognition receptors hyperresponsive to bacteria in the intestinal lumen, makes it likely that the microbiome plays an important role in canine and feline CE as well.

In recent years, investigation into the microbiome of the intestine has moved away from bacterial culture, but has used molecular methods such as polymerase chain reaction (PCR) to determine the variety and species present in the sample. Using such molecular methods, the microbiome of people with IBD was found to be of decreased complexity compared to samples from healthy controls. Similarly, the species richness in the duodenal lumen of dogs with IBD is reduced. Some species are also found to be significantly over- or underrepresented compared to healthy controls, such as a reduction in members of the phyla Bacteroidetes and Firmicutes, whilst there is an abundance of *E. coli*. Dogs with CE also exhibit a dysbiosis, with an abundance of members belonging to the Enterobacteriaceae family. In addition, dogs with CE have significantly higher number of clones belonging to Proteobacteria and a significantly lower abundance of Clostridia. Therefore, the compositional changes of the microbiota seen in CE emphasize the role of bacteria in this complex disease and may well contribute to ongoing inflammation.

Epidemiology

Few larger studies of CE in dogs are available which can be used to predict treatment responses in clinical cases. One larger study, with over 70 cases, has shown that about 60% of cases seen in a referral population are FRD, and that these dogs go into remission very quickly, within about 10–14 days of starting dietary intervention. FRD dogs also seemed to be more commonly younger, large-breed dogs with colitis signs. The other groups in this study consisted of about 30% of dogs that responded to steroids, and about 10% that were steroid resistant and needed rescue treatment with cyclosporin. A newer study comprising over 200 dogs at another referral center confirmed these findings, with about 65% of dogs in the FRD group, 16% in the ARD group, and 19% in the SRD group. Outcome was significantly better in FRD groups at various time points over a year after diagnosis, and the worst outcome was seen in the ARD group. The latter was probably due to relapses being very common in ARD dogs, as their clinical signs invariably flare up when antibiotics are discontinued. Furthermore, clinical severity indices were lowest in the FRD groups and serum albumin concentrations were lowest in the SRD groups, which are known predictors for outcome.

History, Clinical Signs, and Diagnostic Work-Up

Faced with a small animal patient exhibiting signs of possible intestinal disease, the first differentiation should be to establish whether it is an acute or chronic disease. Diarrhea, vomiting, dehydration, weight loss, lethargy, and melena can all be signs of small intestinal disease. The disease is acute if the signs have been present only for a few days, but if disease persists for more than three weeks and/or is intermittently present for more than three weeks, it is defined as chronic.

The next step in taking a thorough history is to determine whether the animal shows signs of small intestinal, large intestinal or mixed diarrhea (Table 59.1).

Diagnostic Work-Up of Chronic Small Intestinal, Large Intestinal or Mixed Diarrhea

Once the clinical signs have persisted for more than three weeks, more work-up is required in order to investigate the correct diagnosis. In chronic cases, it is more common for systemic, nongastrointestinal problems to cause the signs, and therefore the first diagnostic steps must be directed at excluding these extragastrointestinal causes (Box 59.1).

The use of clinical severity indices such as the Canine Chronic Enteropathy Clinical Activity Index (CCECAI)

Table 59.1 Differentiation of small intestinal and large intestinal diarrhea according to clinical signs

	Small intestinal	Large intestinal
Volume	xxx	x
Mucus	–	xxx
Frequency	x	xxx
Tenesmus	–	xxx
Dyschezia	–	xxx
Weight loss	–	xxx
Vomiting	x	x
General condition	xxx	–

Box 59.1 Causes of intestinal disease

Causes of chronic small intestinal disease

Extragastrointestinal (metabolic) causes
- Hepatic disease (portosystemic shunt!)
- Hyperthyroidism (cats)
- Addison disease (dogs)
- Renal insufficiency
- Pancreatic
- Exocrine pancreatic insufficiency (EPI)
- Chronic pancreatitis

Gastrointestinal causes
- *Giardia* infection, *Tritrichomonas* infection (cats)
- Chronic partial obstruction
- Lymphangiectasia
- Neoplasia: lymphosarcoma
- Food intolerance/food allergy
- Chronic enteropathies/inflammatory bowel disease
  - Eosinophilic
  - Lympho-plasmacellular

Causes of chronic large intestinal disease

Gastrointestinal causes
- *Giardia* infection, *Tritrichomonas* infection (cats)
- Chronic partial obstruction
- Neoplasia: adenocarcinoma, lymphoma
- Polyps
- Food-responsive diarrhea
- Chronic enteropathies/inflammatory bowel disease:
  - Eosinophilic
  - Lympho-plasmacellular
  - Granulomatous

is recommended for all patients at the time of work-up (Box 59.2).

These indices are easily calculated by adding up severity of clinical signs and can give valuable prognostic information. A CCECAI of >12 has been shown to be associated with a much worse clinical prognosis. In these cases, an abbreviated clinical work-up with endoscopy being scheduled earlier, as well as early aggressive treatment, may be indicated.

The diagnostic assessment of chronic gastrointestinal inflammation involves exclusion of other potential causes of the gastrointestinal signs, and thus a full diagnostic work-up needs to be done to rule out all known causes of extragastrointestinal inflammation first. Commonly, this involves complete blood cell count, serum biochemical analysis, urinalysis, and fecal analysis for helminth and protozoal parasites (such as *Giardia*; in addition *Tritrichomonas* in cats should be considered). Further blood tests are indicated if none of the following tests shows any abnormalities: trypsin-like immunoreactivity to exclude exocrine pancreatic insufficiency, pancreatic lipase immunoreactivity (Spec-cPL, Spec-fPL for dogs and cats respectively) to assess the possibility of pancreatic disease, ACTH test or basal cortisol concentration to exclude hypoadrenocorticism and cobalamin concentrations to assess the absorptive function of the distal small intestine. Total T4 and FeLV/FIV should also be assessed in cats. Abdominal ultrasound will be most helpful to determine whether the small and/or large intestine is affected and if there are any mass lesions that need surgical intervention rather than endoscopic evaluation. In the case of PLE, specific findings on ultrasound, such as speckles in the mucosa, can also be useful additional information.

If the results of these tests do not point to an obvious cause for the clinical signs and the patient is stable (i.e., has a normal appetite, good attitude, not lethargic, no to minimal weight loss, normal serum protein concentration with no intestinal thickening on diagnostic imaging) then a well-conducted therapeutic trial with an elimination diet or hydrolyzed diet for at least two weeks can be performed. If there is no response to a trial within two weeks after starting the diet, it is unlikely that the patient is suffering from food-responsive disease (food allergy or food intolerance). Intestinal biopsies for histopathology are collected from those patients that fail to respond to empirical therapy or that are showing worsening of their clinical signs. Most patients with chronic enteropathies can be diagnosed by obtaining endoscopic biopsies, as long as at least 12–15 biopsies from the duodenum, ileum, and/or colon are taken. It is important to realize that good-quality biopsies are critical in order for histopathology to be useful, so more than 10 biopsies per site are usually recommended to make a diagnosis. In some rare cases, a diagnosis of lymphoma can be missed if no full-thickness biopsies are obtained, especially in cats and if the ileum has not been sampled.

Serum and Fecal Markers of Disease

Serum Albumin Concentrations in Dogs

Decreased serum albumin concentrations have been identified as a negative prognostic indicator in both retrospective and prospective studies of canine IBD. PLE accounts for the loss of albumin through the gut mucosa in severely affected dogs with IBD. PLE in dogs can be associated with severe lympho-plasmacytic IBD, intestinal lymphoma, or, rarely, primary lymphangiectasia. One study described 12/80 (16%) dogs with hypoalbuminemia and 4/80 (5%) dogs with panhypoproteinemia.

Box 59.2 Canine Chronic Enteropathy Clinical Activity Index (CCECAI)

Attitude/activity
0 = normal
1 = slightly decreased
2 = moderately decreased
3 = severely decreased

Appetite
0 = normal
1 = slightly decreased
2 = moderately decreased
3 = severely decreased

Vomiting
0 = normal
1 = mild (1× per week)
2 = moderate (2–3× per week)
3 = severe (>3× per week)

Stool consistency
0 = normal
1 = slightly soft feces or fecal blood, mucus or both
2 = very soft feces
3 = watery diarrhea

Stool frequency
0 = normal
1 = slightly increased (2–3× per day)
2 = moderately increased (4–5× per day)
3 = severely increased (>5× per day)

Weight loss
0 = none
1 = mild (<5%)
2 = moderate (5–10%)
3 = severe (>10%)

Albumin levels
0 = albumin >20 g/L
1 = albumin 15–19.9 g/L
2 = albumin 12–14.9 g/L
3 = albumin <12 g/L

Ascites and peripheral edema
0 = none
1 = mild ascites or peripheral edema
2 = moderate amount of ascites/ peripheral edema
3 = severe ascites, with pleural effusion and peripheral edema

Pruritus
0 = no pruritus
1 = occasional episodes of itching
2 = regular episodes of itching, but stops when dog is asleep
3 = dog regularly wakes up because of itching

Score:

Total score 0–3 Clinically insignificant	Total score 4–5 Mild disease	Total score 6–8 Moderate disease	Total score 9–11 Severe disease	Total score ≥12 Very severe disease

Seven of these 12 dogs were eventually euthanized due to intractable IBD, identifying decreased serum albumin concentrations as one of the major risk factors associated with a poor outcome. In another recent prospective study, 12/58 (21%) cases initially presented with hypoalbuminemia. Of these 12 dogs, seven were panhypoproteinemic with severe hypoalbuminemia (mean albumin level 1.1 g/dL) and three of those were eventually euthanized. However, it is important to note that relatively mild reductions in serum albumin (>2.0 g/dL) were already associated with an increased risk of refractoriness to treatment. At this level, most patients will not yet show any clinical signs of hypoalbuminemia, such as ascites, peripheral edema, or pleural effusion, but are already at risk of euthanasia because of intractable disease.

Another study found that severely hypoalbuminemic dogs that had failed to improve on immunosuppressive doses of steroids were successfully treated with cyclosporin. This suggests that early aggressive treatment in hypoalbuminemic dogs may potentially decrease mortality rates in severely ill animals. Serum albumin concentrations can also be a good measure of monitoring such patients, as improvement of serum albumin concentrations above 2.0 g/dL usually indicates treatment success, even if clinical improvement has been seen earlier in some of these cases. It is therefore recommended to serially evaluate serum albumin concentrations every 2–3 weeks in order to assess when treatment can be tapered off or discontinued.

Serum Albumin Concentrations in Cats

There is not much published information available regarding serum albumin concentrations in cats with chronic intestinal disease. PLE as a clinical syndrome likely does not exist in cats, as clinical signs such as ascites and peripheral edema do not usually occur in cats with hypoalbuminemia due to intestinal disease. In addition, the hypoalbuminemia seen in such cases is usually mild. However, there is accumulating evidence that cats with chronic intestinal disease and decreased albumin serum concentrations may have concurrent pancreatic disease.

In one recent retrospective study, cats diagnosed with IBD and serum feline pancreatic lipase (Spec-fPL) concentrations ≥12.0 µg/L had a lower median serum albumin concentration than cats with IBD and a normal Spec-fPL concentration. Further analysis in this study did not identify hypoalbuminemia as a predictor of negative outcome on survival.

Therefore, hypoalbuminemia in cats with chronic intestinal disease should prompt the clinician to measure Spec-fPL concentrations and/or to perform abdominal ultrasound examination in order to evaluate any concurrent pancreatic disorders. Depending on the severity of the hypoalbuminaemia, the clinician's approach to treatment might be altered.

Serum Cobalamin Concentrations in Dogs and Cats

Serum cobalamin concentrations should be measured in any small animal patient with chronic intestinal disease. As cobalamin is absorbed in the ileum, decreased serum cobalamin concentrations are most commonly seen when this part of the small intestine is affected. However, absorption of cobalamin also involves intrinsic factor, which in dogs and cats is mainly produced in the pancreas. This is the reason why most small animals with exocrine pancreatic insufficiency will have low serum cobalamin concentrations. Furthermore, serum cobalamin concentrations have been shown to be a negative prognostic factors in dogs with CE. If cobalamin serum concentration is below the reference range, the risk for later euthanasia increases to a factor of 10. It is therefore important to supplement dogs with hypocobalaminemia while they undergo treatment for IBD, as this risk of euthanasia can be reversed by supplementation.

Serum cobalamin concentration has long been known to be an important negative prognostic factor in cats with chronic enteropathies. The prevalence of decreased serum cobalamin concentrations in cats with chronic gastrointestinal signs has been reported to be 16–60%. In cats, it has also been reported that cobalamin supplementation can improve clinical signs regardless of the underlying diagnosis and even if given as the sole treatment for their disease. It is therefore recommended that cats with chronic intestinal disease be supplemented with cobalamin regardless of whether a specific cause for the disease can be identified. Recent studies have also shown preliminary data indicating that cobalamin can be given orally to supplement deficiencies. However, large amounts have to be given by this route of administration and concentrations decreased much more rapidly after discontinuation of oral treatment, compared to injectable forms.

Supplementation Recommendations for Cobalamin

Supplementation of cobalamin should be given parenterally (SC) as a weekly injection for at least six weeks. Exact dosages are not reported, as it is a water-soluble vitamin and cannot be overdosed. For tested recommendations, please visit the website of the Texas GI lab (http://vetmed.tamu.edu/gilab).

Canine Pancreatic Lipase

Canine pancreatic lipase (now measured with the Spec-cPL assay) has recently become available as a commercial test and is useful in the assessment of possible pancreatitis in dogs. However, it can also be elevated in dogs with a primary diagnosis of CE. In a retrospective study of 50 dogs with IBD, clinical signs, age, serum lipase and amylase activities, albumin and cobalamin concentrations, abdominal ultrasound examination, histopathologic review of intestinal biopsies, management of IBD, and follow-up in dogs with CE were evaluated. Sixteen dogs with increased cPL and 32 dogs with normal cPL values were compared. No significant differences were found in clinical activity score, serum amylase activity, serum lipase activity, serum cobalamin concentration, serum albumin concentration, abdominal ultrasound scores, and histopathology scores for IBD. There was also no difference in the frequency of steroid treatment between the groups. Interestingly, dogs with elevated Spec-cPL had a higher risk of a poor follow-up score and were significantly more likely to be euthanized at follow-up.

These data suggest that elevated Spec-cPL in canine IBD identifies a subset of these patients that could also have chronic subclinical pancreatitis. In patients which have been diagnosed with CE and also have elevated Spec-cPL without overt imaging evidence of acute pancreatitis, it is recommended to discuss treatment options for IBD that will also treat possible autoimmune pancreatitis. The author has had anecdotal success with cyclosporin at 5 mg/kg SID for eight weeks in such cases.

C-Reactive Protein

C-reactive protein (CRP) is a serum acute phase protein that can be elevated in many different diseases. In people with IBD, several indices of clinical disease activity incorporate measurements of CRP. In dogs, a similar correlation between the Canine IBD Activity Index (CIBDAI) and CRP serum concentrations has been found in one large study incorporating 58 dogs. CRP was elevated when compared to normal in 28 of the 58 dogs in this study, which had CIBDAI scores above 5 (which represents mild to moderate disease activity). In these dogs CRP decreased significantly after successful treatment.

In another study, CRP did not seem to be very helpful, as it was only elevated in 6/21 dogs with CE. Based on available published data, it is possible that CRP is useful as an additional assessment tool in severely ill patients, even though a large percentage of dogs with IBD do not show any elevations in CRP. Interpretation of elevated levels may also be hampered by increases of CRP related to diseases other than IBD.

Fecal Alpha-1-Proteinase Inhibitor

Fecal alpha-1-proteinase inhibitor (alpha-1-PI) can be used as a test for dogs in which the clinician suspects PLE but clinical signs are not overt. Alpha-1-proteinase inhibitor is a plasma protein of similar size to albumin. If the intestinal mucosal barrier is compromised and loss of protein into the intestinal lumen occurs, alpha-1-PI is lost at approximately the same rate as albumin. Unlike albumin, however, its proteinase inhibitor properties protect alpha-1-PI from being degraded by intestinal proteases. Therefore, it is able to persist throughout the intestinal transit and is passed undamaged in the feces, in which it can then be measured.

Prompt diagnosis of PLE in a patient with IBD is important, as hypoalbuminemia is a risk factor for a negative outcome and the cause should be treated aggressively in order to improve survival. The alpha-1-PI assay is especially valuable in a patient with intestinal disease that also suffers from concurrent renal or hepatic disease. In these patients, measurement of fecal alpha-1-PI can help assess which portion, if any, of the protein loss can be attributed to the intestine. This test is so far only available at the Texas GI lab and ideally, three consecutive freshly collected, frozen fecal samples should be submitted in order to improve the accuracy of the test. This means that fecal alpha-1-PI is to date not a useful test for practitioners outside North America.

Polymerase Chain Reaction for Antigen Receptor Rearrangement from Intestinal Biopsies

Polymerase chain reaction for antigen receptor rearrangement (PARR) amplifies the highly variable T or B cell antigen receptor genes, and is used to detect the presence of a clonally expanded population of lymphocytes. This test has been advocated to be useful when applied on endoscopic biopsies if a diagnosis of intestinal lymphoma is suspected but not confirmed by conventional histopathology. It is, however, important to note that dogs with CE can in up to 20% of cases have biopsies which test positive for clonality. The test therefore needs to be evaluated as an additional measure to help with the differentiation of intestinal lymphoma versus CE, but should not be used as the sole differentiating factor or even the gold standard. Other tests that can help with this question are immunohistochemistry for B and T cells, abdominal ultrasound and possibly fine needle aspirates of enlarged mesenteric lymph nodes, if they are present.

Perinuclear Antineutrophilic Cytoplasmic Antibodies

Perinuclear antineutrophilic cytoplasmic antibodies (pANCA) have been useful in the diagnosis of human IBD for decades. These antibodies are serum autoantibodies similar to antinuclear antibodies (ANA), which seem to be more specific for intestinal disease than ANA in dogs. They are detected by indirect immunofluorescence assays where a typical pattern of perinuclear staining of canine granulocytes can be seen.

In the first study which assessed the possible clinical usefulness of pANCA in dogs with IBD, sensitivity for pANCA was 0.51 and specificity ranged between 0.56 and 0.95. pANCA proved to be a highly specific marker for CE in dogs when the group of dogs with chronic diarrhea of other causes were tested against the group of dogs with CE (specificity 0.95). This is in agreement with reports from human medicine that show a specificity of up to 94% for pANCA when distinguishing between IBD and healthy controls as well as patients with non-IBD diarrhea. Furthermore, when pANCA were tested in a group of dogs with FRD versus SRD, a positive pANCA titer was significantly associated with FRD.

The pANCA assay could therefore provide valuable help to the veterinarian presented with the clinical picture of a dog with chronic diarrhea and possible IBD. If the result is positive, a food-responsive chronic enteropathy is highly likely, but if the result is negative, CE cannot be excluded.

pANCA also seem to be associated with the syndrome of familial protein-losing enteropathy in soft-coated wheaten terriers (SCWTs). pANCA were detectable in the serum of dogs on average 1–2 years before the onset of clinical disease and were highly correlated with hypoalbuminemia. This test could serve as a useful adjunct for this specific disease in SCWTs as an early screening test.

Care must be taken in interpreting a positive pANCA test result if other inflammatory or immune-mediated diseases are present in the dog. A recent study showed that many dogs with various vector-borne diseases or immune-mediated hemolytic anemia (IMHA) were positive for pANCA. Unfortunately, this test is not commercially available yet, but could become one of the standard tests for work-up of CE in the future.

Calprotectin and S100A12

Calprotectin and S100A12 are calcium-binding proteins that are abundant in the granules of neutrophils and macrophages. In people with IBD, serum and fecal concentrations of these proteins have been found to be increased compared to healthy people. In addition, fecal concentrations of calprotectin correlate very well with clinical disease activity in children with IBD.

An immunoassay for measurement of canine calprotectin in serum and fecal samples is now available, and it was shown that a serum calprotectin concentration of ≥296.0 µg/L as a cut-off had a sensitivity of 82.4% and specificity of 68.4% for distinguishing dogs with idiopathic IBD from healthy dogs. However, calprotectin concentrations were not significantly correlated with the clinical severity, serum C-reactive protein concentration, or severity of histopathologic changes. The clinical usefulness of this test when used in serum or fecal samples still needs to be confirmed in prospective studies.

Immunohistochemistry for P-Glycoprotein on Intestinal Biopsies

P-glycoprotein (p-gp) is a transmembrane protein functioning as a drug-efflux pump in the intestinal epithelium. Human patients with IBD who fail to respond to treatment with glucocorticosteroids express high levels of p-gp in lamina propria lymphocytes.

So far, two research groups have evaluated p-gp expression in biopsies of dogs with CE. In one study, duodenal biopsies from 48 dogs were evaluated by immunohistochemistry. The dogs treated with prednisolone showed a significantly higher p-gp expression in lamina propria lymphocytes after treatment compared with expression before treatment. In contrast, the group treated solely with an elimination diet showed no difference in p-gp scores before and after treatment. Moreover, a statistically significant association between refractoriness to steroid treatment and high p-gp expression was found in the steroid treatment group. In another recent study, p-gp expression was compared between dogs with CE and healthy controls, and was found to be higher in duodenal epithelial cells of dogs with CE compared to control dogs. These results indicate that epithelial and lamina propria lymphocyte expression of p-gp is upregulated in dogs with CE, and they are even higher after prednisolone treatment. In addition, high p-gp expression could indicate possible multidrug resistance and should be taken into account when dealing with dogs who have failed steroid treatment before.

Genetic Testing

Over the last decade, numerous genes have been found to be associated with an increased risk of development of IBD in human beings, many of them implicated in the innate immune response in the intestine. In dogs, it has always been obvious to clinicians that IBD could have a genetic component. This is particularly evident in breeds like the boxer, which is predisposed to granulomatous

colitis, and the German shepherd dog (GSD), which is predisposed to CE. Several mutations in TLR4 and TLR5 were found to be significantly associated with an increased risk of development of CE. In a follow-up study, we were also able to show that peripheral blood cells of dogs carrying the mutation are hyperresponsive to flagellin, which is the natural ligand for TLR5. This proves for the first time that a genetic mutation implicated in the pathogenesis of dogs with IBD has functional consequences on the protein level. Taken together, these findings make it very likely that TLR5 mutations are causally associated with canine IBD. Genetic testing for these polymorphisms could become important for breeders and practitioners in the future. However, it is likely that in multifactorial disease like IBD in dogs, other factors such as other genetic mutations and environmental factors will also play a major role in the pathogenesis of the disease.

Work-up and Diagnostic Tests: Abdominal Ultrasound, Endoscopy, and Histopathology

Diagnostic Imaging

Ultrasonographic study is the preferred imaging tool for the investigation of animals with GI disease. The whole of the intestinal tract can be examined and the wall thickness measured. Although CE may cause focal or segmental changes, it does not always induce changes that can be detected ultrasonographically, so intestinal biopsy is required to confirm the diagnosis. Neoplastic infiltration is more often focal, shows more severe thickening, and causes loss of wall layering when compared to inflammatory disease. In addition, lymph nodes tend to be larger and more involved in neoplastic disease. However, the overlap in the sonographic appearances of inflammatory and neoplastic infiltration makes definitive diagnosis difficult, requiring histopathology for differentiation.

Histology and World Small Animal Veterinary Association (WSAVA) Scoring of Intestinal Biopsies

Sampling of intestinal biopsies is considered to be an essential step to exclude neoplastic causes and confirm the presence of intestinal inflammation. However, the interpretation of intestinal biopsies is difficult and subject to controversy. In several recent studies looking at conventional histologic interpretation of intestinal biopsy samples, no correlation of clinical activity with histologic grading either before or after therapy was found. In addition, total lymphocyte counts as well as the number of infiltrating CD3 cells in the lamina propria cannot be used as markers for clinical activity of disease, as there is no difference in cell counts before and after treatment.

These findings suggest that the type and degree of histologic infiltrates in canine IBD may not be as helpful as in human medicine, where the clinical scores correlate very well with the histologic grading. Therefore, a new grading scheme for the histologic interpretation of endoscopically obtained biopsies from dogs and cats with IBD has recently been published by the WSAVA working group. The findings in this study suggest that microarchitectural changes seem to be much more important than cellular infiltrates when assessing histologic severity of disease. However, so far, there is limited information on how well this new grading system correlates with clinical disease. This notion was recently confirmed in a prospective study including 20 dogs with FRD. A second endoscopy was performed in these dogs after six weeks of dietary treatment, and WSAVA scoring was the same as before treatment. However, when looking at electron microscopic changes, mitochondrial and brush border changes indicated mucosa healing which was not obvious on light microscopy. In one retrospective study, the interpathologist variability was still very high even when using the picture guide from the original publication. In addition, it is of concern that the only parameter that correlated with clinical disease was the presence of lymphangiectasia and hypoalbuminemia.

Currently, there is lack of consensus between pathologists when using the WSAVA histopathologic guidelines for intestinal biopsies, and studies have demonstrated that these scores correlate poorly with clinical severity. Therefore, it is likely that additional criteria need to be assessed when scoring intestinal biopsies and further studies are needed to determine other immunologic components that are dysregulated in animals with CE.

Treatment and Prognosis

Inflammatory bowel disease patients that have mild to moderate clinical disease activity and normal serum albumin concentration are first treated sequentially with a dietary and antibiotic trial. If they fail to respond to either of these trials, immunosuppressive therapy is initiated (see following paragraphs).

FRD: Diet

A positive response to a dietary trial allows the patient's CE to be classified as FRD, a term which includes both dietary allergy and intolerance. The main options for a dietary trial include switching to a diet which leads to

antigenic modification (e.g., novel protein source or protein hydrolysate). Whichever type of diet is chosen, it must be palatable and introduced in gradually increasing amounts over 4–7 days. In dogs with FRD, a clinical response is usually observed within 1–2 weeks of changing the diet. One study demonstrated that dogs that respond to diet tended to be younger and had higher serum albumin concentrations and predominantly signs of large bowel diarrhea than dogs that did not respond to diet. FRD is highly prevalent among dogs with IBD (at least 60–70%) and a favorable response to elimination or hydrolyzed diets within two weeks has been shown to be associated with a very good prognosis over one year after diagnosis. It is important to note that in the studies that show these good outcome measures, the dogs were kept on the diet for at least 12 weeks after diagnosis before they were switched back to their original diet.

ARD: Antibiotics

An antibiotic trial typically involves oral administration of tylosin, 10–15 mg/kg q8h, oxytetracycline 20 mg/kg q8h, or metronidazole 10 mg/kg q12h. A positive response suggests ARD. The dog is typically maintained on antibiotics for 28 days; if signs recur after stopping then long-term antibiotic therapy with tylosin 5 mg/kg is used orally every 24 hours. In a recent large retrospective study where all dogs were sequentially treated, only 16% of dogs were ARD. All ARD dogs relapsed shortly after discontinuation of the antibiotics was attempted, making long-term management of these patients difficult. An additional decision-making factor may be the increasing problems with antibiotic resistance in our dog populations, making justifications of long-term treatment with antibiotics difficult. There is also accumulating evidence that antibiotic treatment has long-lasting effects on the intestinal microbiome, which may lead to lasting dysbiosis and in itself could amplify inflammation in the intestine. Many of these patients will therefore need steroids or other immunosuppressives to control their clinical signs long term.

Anti-inflammatory and Immunosuppressive Therapy

Patients that do not respond to a diet or antibiotic trial are usually administered oral prednisolone 2 mg/kg every 24 hours that is tapered over an eight-week period. However, as the side-effects of glucocorticoids are usually more marked in large- than small-breed dogs, azathioprine may be combined with glucocorticoid treatment at a faster taper in dogs weighing more than 30 kg. If there is poor response to immunosuppression or a relapse is seen after tapering, then consider oral cyclosporin at 5 mg/kg every 24 hours for 10 weeks. A response to prednisolone has been shown in up to only 50% of dogs with CE, so if more severe disease is present or severe side-effects of steroids are anticipated, other immunosuppressives can be an option. Many steroid-refractory canine CE cases can be rescued by cyclosporin single therapy. In cats, use chlorambucil 2–6 mg/m^2 q24h with prednisolone if there is inadequate response to glucocorticoid treatment alone. Hematologic parameters should be monitored regularly if chlorambucil is used. If the patient responds then the medication can be tapered gradually, starting with the steroid, to an q48h dosing regimen.

Budesonide is a glucocorticoid medication that has been preliminarily shown to be successful in the treatment of canine IBD. However, hypothalamic-pituitary-adrenal suppression and development of a steroid hepatopathy have been demonstrated in dogs, so the hepatic fist-pass effect of this drug in dogs may not be as great as in human beings. An optimal dose has not yet been determined, although anecdotally a dose of 1 mg/m^2 every 24 hours orally has been recommended. The response rate to budesonide was shown to be similar to the use of prednisolone (about up to 60%), and it should therefore be reserved for dogs that are known to respond to steroids but suffer severe side-effects. Some dogs will, however, still develop side-effects of steroid administration while on budesonide, so owners should be warned about this. Sulfasalazine (20–50 mg/kg q8h for 3–6 weeks) and related drugs are often used in dogs when IBD is limited to the large intestine. However, as side-effects include keratoconjunctivits sicca, tear production should be monitored regularly.

Treatment of Patients with Severe Protein-Losing Enteropathy

Protein-losing enteropathy is a recognized complication in a subset of CE cases and a low serum albumin concentration has been shown to be a poor prognostic indicator for CE. Patients with albumin concentrations below 1.5 g/dL are at risk of developing ascites, pleural effusion, and subcutaneous edema. Many of these patients will succumb to the disease within the first 1–2 months of starting prednisolone treatment. As some studies have shown better outcome with single-therapy cyclosporin at 5–10 mg/kg PO SID, this latter regime may be a better option for many of these patients. One recent study has also shown that the combination of prednisolone and chlorambucil was superior to prednisolone and azathioprine for survival. Evaluation of hemostatic function in these patients is recommended to ascertain if hypercoagulability has developed as a consequence of enteric protein loss. Concurrent therapy with ultra-low-dose

aspirin (0.5 mg/kg) or other platelet inhibitors is recommended in these patients in order to prevent thromboembolism. In addition, the use of elemental diets and partial parenteral nutrition may be indicated in some dogs with severe PLE.

It is worth mentioning that some PLE patients can fare relatively well with dietary treatment alone, and there are some studies that show that Yorkshire terriers may be a subgroup of dogs developing PLE which can be solely diet responsive. In such cases, it is indicated to try a low-fat diet first, and wait before adding in immunosuppressive treatment for 1–2 weeks.

Finally, these patients may also be at risk of complications associated with intestinal biopsy by laparotomy, so plasma transfusion, human albumin infusion or synthetic colloid may be indicated during anesthesia for endoscopy.

Adjunctive Therapy

The use of probiotics in people with IBD has led to some promising results, although there is still an insufficient number of large, multicenter, randomized, double-blind, placebo-controlled trials that investigate the efficacy of probiotics in human IBD. Similarly, only one randomized, placebo-controlled trial investigating the use of *E. faecium* probiotics in canine FRD as an adjunctive treatment has been performed so far. No additional effect could be demonstrated in the group of dogs receiving probiotics. More studies are needed to be able to make recommendations for the use of probiotics in cats and dogs with CE (see also Chapter 58).

Prognosis

One retrospective study demonstrated that only 26% of canine CE cases progress to complete remission, with intermittent clinical signs remaining in approximately half of cases, and 4% were completely uncontrolled, with 13% being euthanized because of poor response to treatment. This suggests that the prognosis of CE patients can be poor. The main negative prognostic indicator for CE was identified to be hypoalbuminemia in dogs. Clearly, more prospective treatment trials are necessary, especially in the severely affected and hypoproteinemic animals, in order to improve long-term survival in these cases.

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Section 7

Diseases of the Liver, Gallbladder, and Bile Ducts

60

Approach to the Patient with Liver Disease

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The liver plays a central homeostatic role within the body, involved in the orchestration of a vast array of metabolic pathways. The metabolic functions performed include carbohydrate, protein and lipid metabolism, drug metabolism, vitamin storage and activation, endocrine hormone metabolism, removal of endogenous and exogenous toxins (e.g., ammonia) along with excretory, digestive, and storage functions (e.g., iron, copper, glycogen, triglyceride). The liver is also the site of synthesis of albumin and the majority of clotting factors and plays a key role in immune surveillance.

The liver's position, between the gastrointestinal tract and the systemic circulation, aids its roles in digestion, detoxification, and immune surveillance. However, it also leaves the liver vulnerable to injury from drug or toxin exposure and prone to the secondary effects of dysfunction at other sites in the body. The normal liver is typically functioning with significant reserve capacity (approximately 70–80%), providing an important buffer should an animal sustain liver injury. In addition, the liver has a huge regenerative capacity, affording the animal significant ability to recover from injury.

All of these features of liver function have an important impact on the clinical presentation of animals with liver disease. Symptoms of liver disease typically only become apparent once the reserve capacity of the liver has been exceeded, hence diseases may remain subclinical for long periods of time, with animals presenting later in the disease process. The vast array of liver functions is reflected in the wide variety of possible clinical symptoms. The early clinical signs typically observed include intermittent anorexia, polyuria/polydipsia, vomiting, and lethargy, all nonspecific signs that could be referable to other body systems. More specific clinical signs, such as jaundice or ascites, tend to occur later in the disease process. For example, jaundice occurs in only approximately 20% of dogs and 30–40% of cats with hepatobiliary disease and hence, although more specific, it is an insensitive indicator of hepatobiliary disease. The aim when approaching patients is to maintain a clinical suspicion of liver disease, particularly in patients with vague, waxing and waning signs, from a breed with known predispositions to hepatobiliary disease. The important challenge when approaching these patients is to diagnose the disease early in its course in order to provide a chance to intervene before the disease becomes too advanced and irreversible.

Hepatobiliary diseases rarely present with clinical features pathognomonic for a particular disease. However, there are distinct groups of clinical signs that can be appreciated to occur, reflecting important pathophysiologic mechanisms involved in liver disease. In view of this, a basic understanding of these mechanisms is helpful in order to understand both the clinical presentation of patients and the choice of tests to used diagnose them.

Pathophysiology of Important Clinical Presentations of Liver Disease

Cholestasis

Cholestasis is the term used for impaired bile flow, which can result from a wide variety of intra- and extrahepatic causes. Normal bile production starts with canalicular bile formation. The active secretion of bile salts by hepatocytes into the bile canaliculi results in a large osmotic gradient and secondary movement of water, which in turn drives bile flow. The bile flows sequentially along the biliary tree through bile ductules, various ducts and then finally into the common bile duct. Throughout this passage, it is modified by secretion and reabsorption of

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fluid and inorganic solutes. The bile ducts contribute substantially to this bile formation and flow, with secretion of bicarbonate, chloride, and water. Approximately 50% of bile is released immediately into the gastrointestinal tract, while the remainder is stored and concentrated in the gallbladder. Intrahepatic cholestasis disrupts this bile flow mainly at the level of the hepatocytes, their canaliculi or the bile ductules, in the periportal zone (zone 1) of the liver lobule, whereas extrahepatic cholestasis results from obstruction of the common bile duct. In both of these situations, significant hepatic reserve and compensatory changes have the net result that, typically, overt clinical signs of cholestasis, such as icterus (jaundice), only result from diffuse liver pathology or severe impairment of the common bile duct flow.

Intrahepatic cholestasis occurs commonly to varying degrees in most clinical cases, with various proposed mechanisms involved. Damage to tight junctions separating the bile canaliculi from blood sinusoids can result from endotoxemia, sepsis, some *Leptospira* infections or following an adverse drug reaction. At the cellular level, swollen hepatocytes may directly obstruct bile flow through canaliculi or bile ductules. In addition, necrosis of hepatocytes may disrupt hepatic architecture, allowing communication between canaliculi and sinusoidal lymph or blood, aided by the inherent biliary pressure. Physical obstruction to bile flow from lobules can occur with any processes causing accumulation of tissue (inflammatory, neoplastic or collagen) in portal or periportal regions. This obstruction can occur at any level in the biliary tree with any process disrupting the normal architecture, for example in cirrhosis or with metastatic tumors. Extrahepatic cholestasis is far less common, with important causes including biliary or pancreatic adenocarcinoma, duodenal disease or pancreatitis causing blockage of the duodenal papilla.

Cholestasis can be recognized clinically in several ways which can be helpful to consider when approaching a clinical case. Severe cholestasis results in icterus. Less severe cholestasis can be recognized in varying degrees on the biochemistry panel. This is discussed further in the section on biochemical evaluation, but it is important to be aware of the frequency with which some degree of cholestasis occurs in a wide variety of liver disease.

Icterus

Icterus (or jaundice) is the yellow discoloration of tissues resulting from hyperbilirubinemia and the build-up of bile pigments (Figure 60.1).

Bilirubin is the major bile pigment and is the normal end-product of the catabolism of hemoproteins, a broad group of molecules including hemoglobin, myoglobin, and many enzymes located within the liver, (e.g., cytochromes). Senescent or damaged erythrocytes are removed from the circulation by cells of the mononuclear phagocyte system located within the spleen, liver, and bone marrow. These cells break down hemoglobin and release unconjugated, hydrophobic bilirubin into the circulation where it is carried, reversibly bound to albumin, to the liver for clearance. The hepatocytes take up the bilirubin and conjugate it, predominantly with glucuronide, to aid solubility for biliary excretion. This conjugated bilirubin is released into the intestine where it is not reabsorbed but is either excreted unchanged or degraded by intestinal bacteria to urobilinogen and then the stercobilins (brown fecal pigments).



Figure 60.1 Canine eye showing jaundiced sclera.
Source: Photograph courtesy of Sheila Brennan.

Hyperbilirubinemia results from disruption of this normal production and/or processing of bilirubin and can be considered to result from three broad mechanisms.

- Prehepatic causes where there is increased production of bilirubin in excess of the hepatic capacity for excretion, for example severe hemolytic anemia.
- Hepatic causes where there is impaired uptake, conjugation, and excretion of bilirubin as a result of marked cholestasis. As described in the section on cholestasis, extrahepatic causes such as sepsis can also result in intrahepatic cholestasis due to cytokines directly inhibiting bilirubin transport.
- Posthepatic causes reflect reduced excretion of bilirubin due to disruption of bile flow within the extrahepatic bile ducts.

Portal Hypertension

Portal hypertension is abnormally high pressure within the portal circulation, the result of increased blood flow or resistance within the portal circulation or a combination of the two. It is an important consequence of a variety of clinical conditions, including liver disease, and is associated with significant morbidity and mortality. The development of multiple acquired portosystemic shunts (MAPSS) and ascites with or without hepatic encephalopathy (HE) are important sequelae of the condition and are essential to recognize clinically from a diagnostic, prognostic, and treatment perspective.

In health, the portal blood flow to the liver supplies 75–80% of liver blood supply through a low-pressure system. The portal pressure is kept low and relatively constant, despite variations in portal blood flow, by a large sinusoidal reserve capacity and the ability to adapt the blood flow as necessary to maintain compliance. In disease, changes in this compliance alter the inherent resistance to blood flow and hence the portal pressure. These changes may be static, in the form of structural changes such as fibrosis, or dynamic, such as increased production of inflammatory mediators and vasoconstrictor agents along with reduced production of vasodilator agents. In most cases, there will be a combination of these processes occurring progressively with activation of hepatic stellate cells and progressive injury. In addition, splanchnic vasculature tends to undergo progressive vasodilation, as a result of many of the vasoactive agents released, further aggravating portal hypertension due to increased portal blood flow.

Ascites

An important consequence of significant portal hypertension is ascites. Starling's law describes that the net movement of fluid between compartments is proportional to the balance between the relative hydrostatic and oncotic pressures in each region. Hence, the forces keeping fluid within the vascular space become imbalanced, with portal hypertension tending to favor fluid movement into the interstitium. Ascites develops once this fluid movement exceeds the capacity of the local lymphatic system. This situation is exacerbated by splanchnic vasodilation, which lowers the effective circulating blood volume due to pooling of blood. Over time, compensatory cascades, including the renin-angiotensin-aldosterone system, sympathetic nervous system and antidiuretic hormone release, produce blood volume expansion, further favoring the formation of ascites. Hypoalbuminemia and reduced oncotic pressure also tend to favor net fluid movement and the development of ascites, although typically this does not occur until albumin concentrations are below about 1.5 g/dL. These levels would be unusual for patients with liver dysfunction, occurring only with severe disease. A situation that happens more frequently in patients with liver disease is that a moderately reduced serum albumin (1.8–2.2 g/dL) occurs in combination with portal hypertension, resulting in exacerbation of the ascites.

Acquired Portosystemic Shunts

As portal hypertension reaches a threshold level, small embryonic vessels open up within the omentum and mesentery, allowing blood flow between the portal circulation and the vena cava. These acquired portosystemic shunts (APSS) may initially lower the portal venous pressure, but this effect is quickly mitigated by increased portal blood flow. The clinical importance of these APSS is that they result in a collateral circuit that effectively short-circuits the liver. The net result is the delivery of toxins from the gastrointestinal tract directly into the systemic circulation. These toxins can trigger the vomiting center, causing nausea, vomiting, and inappetence. Clinical signs of HE may also develop.

Hepatic Encephalopathy

Hepatic encephalopathy is a clinical syndrome of brain dysfunction occurring secondary to liver dysfunction. It is a fairly common cause of morbidity and potentially mortality in dogs with liver disease, occurring less frequently in cats. The clinical signs of HE can be quite variable, with early signs being quite nonspecific, for example, apathy or reduced alertness. In more advanced cases, circling, head pressing, altered mentation, salivation, seizures, stupor, and coma may occur (Figure 60.2).

The reserve capacity of liver function is such that, typically, HE only develops when there is concurrent significant impairment of parenchymal liver function and portosystemic shunting, a situation that can occur in patients with congenital or acquired portosystemic shunts (PSS). More rarely, HE can result from fulminant hepatic failure or inborn errors of ammonia metabolism. In cats, an obligatory requirement for arginine to allow normal function of the urea cycle means that arginine deficiency in this species (e.g., the result of anorexia) can also result in HE.

The pathogenesis of HE is complex and likely multifactorial. Normally, the liver removes neurotoxic substances from the portal circulation, preventing their delivery to the brain in the systemic circulation. HE develops with failure of this mechanism, the resultant delivery of toxins triggering neurotransmitter dysfunction and a



Figure 60.2 Dalmatian showing head pressing as a manifestation of hepatic encephalopathy.

constellation of potential clinical signs ranging in severity from apathy and reduced awareness to coma and unresponsiveness. The most commonly implicated toxin in HE is ammonia, although there are some cases where the plasma ammonia concentration is normal or only slightly raised despite signs of HE. Other potential triggers that have been studied include mercaptans, manganese, systemic inflammation, altered gamma-aminobutyric acid (GABA, an inhibitory neurotransmitter), benzodiazepine receptor signaling and altered catecholaminergic signaling due to changes in branched chain aromatic amino acid profiles. Whatever the underlying cause, the overall result is a disruption of brain function, typically leading to waxing and waning clinical signs.

Gastroduodenal Ulceration

Patients with hepatobiliary disease are predisposed to gastric and duodenal ulceration for a number of reasons. Portal venous hypertension is an important risk factor resulting in vascular stasis and venous congestion, which together increase the risk of mucosal ulceration due to reduced mucosal blood flow and secondarily reduced bicarbonate and mucus secretion. This risk is further increased in anorexic animals or those exposed to non-steroidal antiinflammatory drugs or potentially corticosteroids. Gastrointestinal ulceration and bleeding is an important consideration in any patient with HE that suddenly deteriorates or in any patient with liver disease that becomes more subdued or develops a reduced appetite.

Coagulopathy

The liver is involved in the manufacture of the majority of the coagulation factors, including fibrinogen (factor I), prothrombin (factor II) and factors V, VII, IX, X, XI, and XIII. The site of factor VIII production is controversial, but it is likely that the liver plays an important role in its production. It is also the site of the vitamin K-dependent activation of factors II, VII, IX, and X and protein C. In addition to this, the liver is involved in the clearance of activated clotting factors and the production of clotting factor inhibitors (e.g., antithrombin and alpha-1-antitrypsin) and fibrinolytic proteins such as plasminogen. Hence, in liver disease there is the potential for disrupted production of coagulation factors and their inhibitors along with impaired clearance of both activated coagulation factors and the products of the fibrinolytic system. The extent of the resulting abnormalities reflect the severity of the underlying liver disease, ranging from individual factor deficiencies to disseminated intravascular coagulation (DIC).

A study of 42 dogs with histologically confirmed liver disease demonstrated that one or more coagulation abnormalities was present in 57% of the dogs. These abnormalities ranged from single factor deficiencies in four of the dogs to DIC in three dogs. An older study suggested a figure of 93% of dogs with liver disease having abnormal coagulation parameters, although this study involved more severely affected cases. A study of 45 cats with liver disease showed that 98% of the cats had one or more abnormality detected. What is important to recognize clinically is that, whilst spontaneous hemorrhage may be rare in animals with hepatic disease, hemostatic abnormalities occur commonly. Hence, the clinician needs to exercise caution when considering interventional diagnostic procedures and a coagulation profile should be performed in all such cases.

Signalment

Patient signalment is very important when approaching the patient with hepatobiliary disease. There are a variety of known or suspected breed predispositions to hepatic disease which can be helpful to consider, particularly in view of the occult nature of many cases of early liver disease. Congenital portosystemic shunts (CPSS) have worldwide breed predispositions including Irish wolfhounds, cairn terriers, Labrador retrievers, dachshunds, Yorkshire terriers, Australian cattle dogs, Maltese terriers, and miniature schnauzers. In cats, the condition is seen most frequently in mixed-breed cats, although Persian and Himalayan breeds are also overrepresented. Additionally, copper-associated hepatitis has been

described in several breeds, including the Bedlington terrier, Dalmatian, Doberman pinscher, Labrador retriever, West Highland white, and Skye terriers. A recent study documented breeds at risk of developing chronic hepatitis in the UK (see Chapter 64). These included three breeds in agreement with a previous, older study from Sweden: the American and English cocker spaniel, Doberman pinscher and Labrador retriever, and additionally highlighted an increased risk in the cairn terrier, English springer spaniel, Great Dane, and Samoyed. However, it should be recognized that the gene pools in different countries can vary, such that certain breed characteristics and predispositions may be more regional.

In addition to the breed, the age at onset of clinical signs can be very helpful in aiding diagnosis of some hepatobiliary conditions. For example, animals with CPSS typically present at a younger age. This has classically been described to be less than 1 year of age, although increasingly older dogs seem to be recognized, presumably as clinicians are looking more widely for the condition. There have been reports of increasing numbers of miniature schnauzers not being diagnosed until they are over 7 years, presenting with only mild signs. Reports looking at the age and gender distribution of dogs presenting with chronic hepatitis have shown the mean age at diagnosis to be approximately 8 years when all breeds were considered together, although some breeds tended to present at a younger age (e.g., English springer spaniel). In general, females are overrepresented, although again there are occasional breeds where this does not appear to be the case.

History and Clinical Signs

A thorough history with good attention to detail is key to approaching any clinical case. This is particularly pertinent with potential hepatobiliary cases for a variety of reasons. As outlined in the introduction, the large hepatic functional reserve means that in order to diagnose diseases before there is significant, irreversible loss of healthy liver tissue, the clinician needs to identify cases with subtle and often vague clinical signs. Symptoms such as anorexia, vomiting, lethargy or mild polyuria/polydipsia, which are often waxing and waning, should alert the clinician that liver disease is a potential differential diagnosis. The onset of clinical signs may initially appear acute in nature but careful discussion with the owner might elucidate a more chronic background than initially described. Box 60.1 summarizes clinical signs that may be observed in animals with liver disease.

The potential for toxin exposure should always be considered so a detailed description of the animal's potential access to toxins and a history of any recent drug administration are extremely relevant. The clinician should maintain a high index of suspicion whenever a patient develops new clinical signs within four weeks of starting a new drug. There are many known potentially hepatotoxic drugs, common examples being phenobarbital and itraconazole, but most drugs have the potential for an idiosyncratic reaction in an individual patient. Consumption of a hepatotoxin is also possible, such as certain mushrooms, xylitol (contained in sugar-free sweets) or even herbal/dietary supplements that the owner might be administering.

Hepatobiliary disease can result in a very broad range of clinical signs reflecting both the sheer variety of functions the liver performs and the central role it plays in many metabolic and detoxifaction pathways. This central role means that hepatic disease can result in the secondary dysfunction of other organs, as in HE. It also places the liver in a position where it can itself become secondarily affected, for example with hyperadrenocorticism or hepatic lipidosis. The net result is that the clinician needs to be alert to this when approaching a case, aiming to first decide if hepatobiliary disease could be present in an animal but then, importantly, whether this represents a primary or secondary phenomenon. These key questions sound very straightforward, but they can be challenging to address in many patients and will be reconsidered as different aspects of the investigation of liver disease are explored.

Diagnosis

Biochemical Evaluation

The employment of clinical pathologic testing is central to the approach to animals with hepatobiliary disease. In many cases, recognition of abnormal test results often provides the first indication that liver disease may be present. It is not uncommon to detect high liver enzyme activities as the only abnormality on preanesthetic or health screens, prompting further investigation. In addition, as outlined above, in view of the typical presentation of hepatobiliary cases, it is important to use clinical pathology to aid in the diagnosis is liver disease early on in the disease process. Often at this stage the clinical signs may be vague and nonspecific with clinical pathology aiding greatly in the decision making and further defining of such cases.

The laboratory evaluation of hepatobiliary patients has several broad aims: to determine/confirm the presence of hepatobiliary disease and assess hepatic function, to aid in distinguishing primary or secondary hepatic disease and to contribute to diagnostic planning or

Box 60.1 Clinical signs and clinical examination findings that may occur in animals with liver disease

- Vague signs
  - Vaguely "off form"
  - Lethargy
- Signs related to gastrointestinal tract
  - Vomiting
  - Diarrhea
  - Anorexia
  - Weight loss
  - GI bleeding - melena
- Signs related to cholestasis
  - Jaundice
  - Acholic feces - with complete extrahepatic biliary obstruction
- Signs related to hepatic encephalopathy
  - Vague signs of dullness
  - Alterations in behavior
  - Ptyalism – particularly in cats
  - Head pressing
  - Disorientation
  - Stupor
  - Seizures
  - Vague neurologic signs, seizures or syncope may occur with hypoglycemia
- Signs relating to CPSS
  - Hepatic encephalopathy signs (see above)
  - Stunting
  - Microhepatica
  - Dysuria – relating to ammonium biurate urolithiasis
  - Hematuria – relating to ammonium biurate urolithiasis
  - Copper-colored iris (some cats)
- Signs relating to disorders of hemostasis
  - Gastrointestinal bleeding - melena
  - Increased bleeding from invasive procedures
- Signs relating to the urinary tract
  - Polyuria/polydipsia
  - Discolored urine – jaundice/hematuria
  - Dysuria (see above)
  - May have prolonged recovery from sedation/general anesthesia
- Clinical findings
  - Poor body condition score
  - Mucous membrane pallor
  - Abdominal discomfort – organomegaly, abdominal distension, inflammation (hepatic/peritonitis/cholecystitis)
  - Pyrexia – with some inflammatory, infectious or neoplastic causes
  - Ascites - relating to portal hypertension, hypoalbuminemia, biliary peritonitis or neoplastic effusion
  - Hepatomegaly +/- irregularity of liver margins – with infiltration, some inflammatory conditions
  - Skin lesions may be seen with hepatocutaneous syndrome (superficial, necrolytic dermatitis)

monitoring response to treatment. Occasionally, diagnostic testing may allow definitive diagnosis of hepatobiliary disease although more typically, it acts as a piece within the overall jigsaw. The biochemical tests directly utilized in the evaluation of liver disease comprise the liver enzymes and liver function tests, which appraise impaired metabolic function or synthetic capacity. However, evaluation of the full hematology and biochemistry panel is important to gain insight into the animal's general health. This aids clarification of the likelihood of another disease process that may either be the cause of a secondary hepatopathy or represent an additional consideration in patient management.

Enzyme Markers of Liver Disease

The liver enzymes evaluated can be divided into two main groups dependent on their cellular location and clinical utility. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are the two most commonly measured markers of hepatocellular injury and are found primarily within the hepatic cytosol. Alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) are the most commonly measured biliary enzymes. They are located mainly on hepatobiliary membranes and are markers of cholestasis or drug induction (see later). In general, the liver enzymes are sensitive indicators of liver disease or injury but are not specific. There are far more animals in which elevated liver enzyme activities are detected than actually have clinically significant liver disease. This lack of specificity arises from a combination of the susceptibility of the liver to secondary or "reactive" disorders, the ability of certain hormones or drugs, such as corticosteroids, to induce production of particular liver enzymes and the presence of isoenzymes within tissues other than liver. The clinical interpretation of the significance of liver enzyme elevations is challenging and must always be considered in the context of the patent, its history, and the full clinical pathology results.

It is important to realize that the liver enzymes do not offer any indication of liver function. In an animal with a primary hepatopathy, the magnitude of hepatocellular enzyme release may broadly relate to the number of hepatocytes affected, particularly in the acute setting. However, in view of the regenerative capacity of the liver, the magnitude offers no prognostic information. It is also

important to appreciate that in severe chronic disease, such as cirrhosis, the liver enzyme release may be minimal due to reduced hepatic synthetic capacity. In addition, the serial evaluation of serum enzyme activities can be more useful than a single time point in determining the importance of liver enzyme elevation and the likely prognosis in a patient. It is generally considered a favorable sign if values continue to fall gradually after a single liver insult whereas ongoing persistent elevation may indicate a chronic hepatopathy and the requirement for further investigation.

The serum enzyme activity at any point in time is dependent on the overall hepatic activity of the enzyme or the capacity for *de novo* synthesis (in response to cholestasis or drug induction), the serum half-life of the enzyme, and the cellular location of the enzyme (determining the ease of release of the enzyme, e.g., "leakage" of cytosolic enzymes). These factors vary not only between different enzymes but also between species, as will be discussed below. Hence, it is important to ensure species-specific criteria are being used when interpreting the values in a given patient. When evaluating the liver enzymes, it is important to consider the pattern of enzyme increase (hepatocellular or cholestatic), the magnitude of this change and the temporal pattern of the enzyme changes over time. For example, are they decreasing gradually, fluctuating or progressively increasing? The reference intervals for liver enzymes vary considerably between laboratories due to different assay methods. In view of this, it is more appropriate to consider the magnitude of increase in relation to the upper limit of the reference interval when comparing values between labs.

Hepatocellular/Leakage Enzymes

Alanine aminotransferase is a cytosolic enzyme that is released into the serum from hepatocytes with increased hepatocyte membrane permeability or following hepatocellular necrosis. This enzyme is considered to be a sensitive indicator of hepatocellular injury in dogs and cats and is also considered to be the most liver-specific enzyme in these species. Although ALT is also found in cardiac and skeletal muscle and the kidneys, this is not generally of clinical significance as the isoenzymes found in these other locations either have short half-lives or are present at low concentrations. However, occasionally severe muscle injury can result in ALT elevation.

The half-life of ALT in the dog is controversial, with reports ranging from about six hours to 2.5 days. What is clear is that the half-life is considerably shorter in the cat, with the result that smaller elevations are far more clinically significant in this species. The highest increases in ALT activity, in either species, are seen during acute hepatic inflammation or necrosis, the magnitude of elevation, in this setting, being roughly proportional to the number of hepatocytes affected but providing no insight into the severity of injury or its reversibility.

Rapid elevations in enzyme activity occur following changes in hepatocyte membrane permeability. Following experimental toxin administration, values rise sharply within 24–48 hours, peaking at values up to 100 times normal within approximately five days and then falling back to normal within 2–3 weeks. In general, with hepatic injury, a reduction in the enzyme activity of approximately 50% every 2–3 days would be viewed as a good prognostic sign. Elevated ALT activity can also occur with cholestasis due to the damaging effect of accumulated bile acids on hepatocyte membranes. The elevations that occur in this setting are typically more gradual in onset and are not as dramatic overall. Certain drugs can also result in ALT enzyme increases, for example anticonvulsant drugs or corticosteroids. These elevations tend to be dose dependent but also show considerable inter individual variation. The elevations seen with phenobarbital administration would typically be within the 4–5-fold range compared to a 10-fold or higher elevation occurring in animals with hepatotoxicity. However, the results need to be interpreted in light of the overall clinical picture and in combination with liver function evaluation where there is any concern.

The interpretation of ALT elevation in the clinical setting frequently poses a diagnostic challenge. Persistent elevations of ALT are characteristic of canine chronic hepatitis and can be the only abnormality noted on a blood panel in animals in the early stages of the disease. Hence, elevations in excess of twice the upper limit of the reference range occurring over 1–2 months are potentially significant and should not be disregarded. However, frequently up to five-fold elevations in ALT are observed in dogs with primary gastrointestinal diseases such as inflammatory bowel disease or pancreatitis. In addition, hemolytic anemia or cardiovascular disease can cause significant elevations in ALT secondary to hypoxia. Endotoxemia or sepsis can cause secondary hepatic changes, as can many endocrinopathies. These examples demonstrate the limitations of ALT; while it is very sensitive for the detection of hepatocellular insult and hence cases with potential primary hepatopathies, it is equally sensitive for the detection of secondary hepatopathies and "reactive" liver changes occurring in response to other systemic illness or drug exposure. In view of this, the clinician should interpret ALT activity in combination with the remainder of the clinical biochemistry, knowledge of the animal's breed and history along with maintaining an awareness of the potential interference of extrahepatic disease.

Aspartate aminotransferase is also a marker of hepatocellular damage within the group of "leakage" enzymes,

having a predominantly cytosolic location within hepatocytes. However, there is in addition a mitochondrial fraction, comprising about 30% of the total hepatic enzyme activity, which is only released during hepatocellular necrosis. The half-life of AST is about 4–20 hours in the dog and one hour in the cat. In general, in acute liver injury, elevations of AST mirror those of ALT although the overall values tend not to be as high (10–30-fold increases in the dog and up to 50-fold in the cat). Following the insult, the AST values should return to normal more quickly than ALT reflecting its shorter half-life. Hence, it has been suggested that persistent AST elevation in this setting is a poor prognostic sign. In cats, AST has been shown to be more sensitive than ALT for the detection of hepatobiliary diseases, with sensitivities reported to be approximately 83% and 76% sensitivity respectively in one report. Elevations in AST also occur with skeletal muscle disease so any elevation occurring in the absence of ALT elevation should be cross-referenced with creatinine kinase measurement to exclude this possibility. In general, most biochemical profiles offer only one hepatocellular enzyme measurement, typically ALT, and the measurement of AST in addition to this is unlikely to offer a marked clinical advantage.

Biliary Enzymes

Alkaline phosphatase is a membrane-bound enzyme that has been shown to have a high sensitivity (85%) but low specificity (51%) for the detection of hepatobiliary disease in dogs. The converse is true for cats, with reported values of 48% sensitivity and 93% specificity. These performances reflect differences in the half-lives and overall enzyme activity in the two species along with differences in the isoenzymes and their potential for induction (discussed further later).

In dogs and cats, there are a variety of tissues known to exhibit ALP activity, including intestinal mucosa, renal cortex, placenta, liver, and bone. There are two genes encoding ALP in the dog with post-translation modifications resulting in different isoforms of the enzyme. The tissue nonspecific ALP gene is responsible for the transcription of liver ALP (L-ALP), bone ALP (B-ALP), and kidney ALP (K-ALP), whereas the second gene encodes intestinal ALP (I-ALP). An additional isoenzyme, glucocorticoid-induced ALP (G-ALP), is important in the dog and is thought to represent a post-translational modification of I-ALP. In the dog, the total serum ALP (T-ALP) measured on clinical biochemistry profiles reflects the combination of L-ALP, B-ALP, and G-ALP; other isoenzymes fail to contribute to this measurement due to a combination of their short half-life and/or low overall tissue activities. In the cat, T-ALP comprises L-ALP and B-ALP due to a lack of G-ALP in this species, although placental isoenzyme has also been detected late-term in this species.

An appreciation of the contributions of these isoenzymes is important when interpreting biochemistry results. For example, B-ALP increases with osteoblastic activity and hence its contribution to T-ALP varies with age. In view of this, in young growing animals T-ALP is approximately twice the normal adult reference range purely as a result of increased B-ALP. In addition, elevations may occur in adult dogs with active bone lesions, such as osteomyelitis or osteosarcoma, but these are rarely more than five-fold increases. Where there is concern in interpretation, it may occasionally be helpful to look at an additional enzyme, such as GGT, with no bone isoenzyme, to clarify the situation. The isoenzyme that causes far more problems for interpretation is G-ALP, as discussed later.

Liver ALP is found predominantly within the periportal zone of the liver, bound to hepatocyte canalicular and sinusoidal membranes. The serum activity of this enzyme is increased in response to cholestasis (intra- and extrahepatic) and induction of *de novo* synthesis. ALP is released into the circulation by enzyme-induced solubilization from the hepatocyte membranes, a process that is enhanced by bile salts and hence increases with cholestasis. In the latter situation, accumulated bile salts also induce production of L-ALP, significantly enhancing the resultant increase in serum ALP activity. The half-life of L-ALP is approximately 70 hours in the dog and six hours in the cat. This short half-life in the cat, combined with a lower ALP activity in feline liver, is important practically. Clinically significant elevations of ALP activity in the cat are considerably smaller than those seen in the dog. Cats with hepatic disease may have ALP elevations two- or three-fold higher than normal as opposed to dogs where values are often more than four- or five-fold normal. This situation, in combination with the lack of G-ALP enzyme in the cat, results in the far lower sensitivity of ALP for liver disease in the cat (48%) but enhanced specificity (93%). In view of this, the interpretation of ALP elevation in dogs and cats differs considerably.

In dogs, ALP induction occurs in response to endogenous and exogenous corticosteroids and phenobarbital. The response to corticosteroids is rapid (increased ALP mRNA within 24–48 hours) and may occur following oral, topical (including ear/eye preparations) and parenteral exposure, with elevations in serum enzyme activity persisting for up to six weeks after exposure has ceased. In addition, a vacuolar hepatopathy, with glycogen accumulation within hepatocytes, occurs with exposure to excessive corticosteroid levels. This too may contribute to ALP elevation by generating intrahepatic cholestasis. The overall ALP elevations can be dramatic and complicate the interpretation of ALP activity in the dog. G-ALP,

as outlined earlier, is the product of the I-ALP gene. As with L-ALP, the hepatocyte is the site of *de novo* synthesis of G-ALP, with membrane accumulation and elution occurring in the same way. Exposure to endogenous or exogenous corticosteroids results in G-ALP induction and hence increased serum activity. It was hoped that measurement of the distinct isotypes of ALP within a serum sample would aid the interpretation of serum T-ALP, but this has not been found to be the case clinically. While normal dogs have low G-ALP (<15% T-ALP) and dogs exposed to corticosteroids have much higher G-ALP, the specificity of G-ALP for corticosteroid exposure is low. Elevations in G-ALP are observed in dogs with primary liver disease, diabetes mellitus, and other chronic illnesses. G-ALP synthesis is also induced in addition to L-ALP by phenobarbital.

In a published series of 270 dogs with histopathologically confirmed hepatobiliary disease, the most marked elevations of T-ALP were documented in dogs with cholestasis (median 10-fold increase) followed, in order of magnitude, by steroid-induced hepatopathy, chronic hepatitis, and hepatic necrosis (all medians approximately six-fold increase or slightly less). Periportal injury tends to result in more marked increases in T-ALP activity than centrilobular pathology. Hepatocellular and biliary carcinomas have also been documented to show increases in serum ALP activity, as have some nonhepatic tumors. Metabolic diseases with fatty infiltration of the liver, such as diabetes mellitus and hepatic lipidosis, are also associated with significant elevations in ALP. In general, extrahepatic causes of ALP elevation are less important in the cat and corticosteroid-induced ALP elevations do not occur in this species. As with ALT, the level of ALP elevation observed does not correlate with the underlying disease process and persistent elevation is a source of more concern than a single abnormal value. Elevations of ALP, like any clinical pathology test, must be interpreted in the context of other laboratory findings and in light of the patient's signalment and history. For example, Scottish terriers are known to have higher ALP activities than other breeds with an, as yet, poorly characterised underlying cause.

Gamma-glutamyltransferase is also a membrane-bound biliary enzyme. The serum GGT activity is largely derived from liver sources of the enzyme, with increased activity resulting from, as with ALP, *de novo* synthesis or increased elution from biliary membranes in response to cholestasis. In general, GGT elevations parallel rises in ALP. GGT also shows corticosteroid induction but, unlike ALP, has no bone isoenzyme and shows less induction with phenobarbital administration.

The relative diagnostic performances of GGT and ALP were compared in a study of 270 dogs with confirmed hepatobiliary disease. GGT was found to be more specific for liver disease than ALP (87% compared to 51%), but it showed considerably less sensitivity (46% compared to 85%). In this study, it was suggested that the diagnostic value of the enzymes could be increased by considering the two enzymes in series, first looking at ALP and then GGT. In this setting, the positive predictive value and specificity were improved without a major decrease in the negative predictive value. The specificity of increased ALP and GGT activity used in this series was 91%. When comparing the relative performance of the two enzymes in cats, the converse is true: GGT is more sensitive but less specific than ALP. In a study of 54 cats with hepatic disease, the sensitivity and specificity of GGT were found to be 83% and 67% respectively, compared to 48% and 93% for ALP. There was, however, one notable exception to this situation. In cats with hepatic lipidosis, ALP is more sensitive than GGT, with the latter within the reference interval or only mildly elevated in a number of cases.

In summary, the measurement of ALP is probably preferable to GGT in the dog but the converse is true for the cat. However, there are likely to be some additional benefits from the measurement of both enzymes.

Markers of Liver Function

Plasma Proteins

The liver is the exclusive site of albumin production and hence liver disease is an important differential diagnosis to consider in an animal with hypoalbuminemia. The liver's reserve capacity for albumin production is large and the half-life of albumin in the circulation is in excess of a week. In view of this, hypoalbuminemia tends to occur in animals with chronic hepatic disorders, such as cirrhosis, or with , where liver synthetic capacity is severely compromised. Hence, serum albumin measurement is a relatively insensitive measure of hepatic insufficiency. In addition to this, hypoalbuminemia is not specific for hepatic disease. It can occur with protein-losing enteropathies and nephropathies, exudative skin conditions, vasculitis, third space loss, acute blood loss, and secondary to inflammation, reflecting albumin being a negative acute-phase protein.

The liver produces alpha- and beta-globulins, whereas lymphoid cells produce gamma-globulins, meaning that the liver is not the exclusive source of the globulins measured on a biochemistry profile. Whilst hepatic synthetic failure may result in hypoglobulinemia, reflecting the liver's role in production, more commonly hyperglobulinemia occurs with acquired liver disease. This can result from a variety of causes including an underlying inflammatory disorder with enhanced gamma-globulin production, the generation of increased quantities of acute phase reactants (within the alpha- and beta-globulin fractions) or as a result of systemic immune

stimulation following decreased antigen clearance by Kupffer cells. It is important to note that in some cases, the globulin elevation may be sufficient to mask hypoalbuminemia if only the total protein concentration is measured on a blood panel.

Coagulation Factors

The role of the liver in the production of coagulation factors and the frequency with which coagulation parameter abnormalities occur were discussed earlier. As with albumin, whilst reduced coagulation factor production can result from hepatic synthetic failure, it is an insensitive indicator of dysfunction. In addition, the overlap between the liver's role in factor production, activation and clearance, along with fibrinolysis, make interpretation of the results of hemostatic testing challenging. From a clinical perspective, the evaluation of a coagulation profile is important in any patient suspected to have liver disease that is scheduled to have further invasive diagnostic procedures, such as a liver biopsy.

Protein Catabolism

The liver produces urea from ammonia, releasing it into the systemic circulation for renal excretion. The serum urea concentration may be close to or below the reference interval in patients with hepatic insufficiency, PSS, and urea cycle abnormalities. Reports have suggested that approximately 65% of dogs and cats with PSS have low blood urea levels, reflecting reduced synthetic capacity. However, as with other tests, this finding is not specific to liver disease. Serum urea concentrations may also be decreased by diuresis and medullary wash-out, malnutrition or a protein-restricted diet. Conversely, gastrointestinal bleeding can result in a disproportionately high serum urea concentration relative to serum creatinine and should alert the clinician to this possibility if observed on biochemistry results.

The catabolism of dietary amino acids and urea by bacteria within the gastrointestinal tract produces ammonia, which is normally cleared from the portal circulation by the liver. The bulk of this ammonia is then converted within the liver to urea during the urea cycle. In view of this, hyperammonemia can result from hepatic insufficiency, portosystemic shunting or dysfunction of the urea cycle. The latter group includes rare genetic cycle abnormalities, cobalamin deficiency or arginine deficiency (cats). The large reserve capacity of the urea cycle makes hyperammonemia a relatively insensitive test of liver function. The measurement of blood ammonia concentration is far more sensitive for the detection of acquired and CPSS, which effectively short-circuit the liver, with reported sensitivities ranging between 80–100% in dogs and just over 80% in cats. These values are increased further by the measurement of postprandial blood ammonia levels, with one paper showing sensitivities of 81% and 91% in pre- and postprandial samples. The reported sensitivity of ammonia for the detection of hepatocellular dysfunction in this paper was 36%, highlighting its limitation.

Another paper compared the diagnostic utility of plasma ammonia and fasting serum bile acids in the diagnosis of PSS in dogs. They found bile acids to be a little less sensitive, but considerably less specific than ammonia measurement, although the use of postprandial samples would have been likely to improve the sensitivity (see later). With adjustment of the cut-off value for the ammonia level to 75 µmol/L, the sensitivity and specificity for the detection of congenital or acquired PSS were optimized at 92% and 98% respectively. Hence, it can be very useful for the diagnosis of these conditions.

One of the limiting factors for ammonia measurement is the sample handling requirements. Samples should be collected immediately onto ice, the plasma separated from erythrocytes rapidly and the assay performed within 30 minutes, rendering measurement in a practice setting challenging. This problem is further compounded by the fact that the results of dry chemistry tests have frequently been shown to be unreliable. More recently, however, point-of-care analyzers have become increasingly available, offering a viable, more reliable option.

Carbohydrate Metabolism

The liver plays a central role in variety of pathways involved in carbohydrate metabolism, but from a diagnostic standpoint, the main assay relating to these functions is blood glucose. Hypoglycemia can occur with liver disease, although again this is a very insensitive test reflecting the significant reserve capacity for glucose production. Some cases of CPSS can present with hypoglycemia, as can animals with severe hepatic compromise such as massive hepatic necrosis or severe cirrhosis. Hepatic neoplasms can occasionally result in hypoglycemia due to either the release of insulin-like factors (e.g., IGF-2) or excessive glucose consumption. Glycogen storage diseases and rare congenital hepatic enzyme deficiencies can also result in hypoglycemia, as can a variety of extrahepatic diseases. Hence hypoglycemia is neither sensitive nor specific for the identification of hepatic disease.

Lipid Metabolism

The liver is involved in a variety of metabolic pathways, with the synthesis of cholesterol and lipoproteins most relevant from the point of view of laboratory results. The serum cholesterol and triglyceride concentrations observed in animals with liver disease vary considerably from normal to increased or decreased. Since these

analytes are also affected by a variety of other extrahepatic causes, neither test offers utility as a specific marker for liver disease. They are, however, useful in contributing to the overall clinical picture and may aid in the identification of relevant extrahepatic illnesses.

Hypercholesterolemia occurs with severe hepatic insufficiency or in animals with congenital or acquired PSS, but can occur with a variety of conditions, including gastrointestinal disease and hypoadrenocorticism. Hypercholesterolemia may occur with cholestasis, but again is not specific for liver disease as it can occur with endocrinopathies, protein-losing nephropathies, pancreatitis, and primary hyperlipidemias. A mild hypertriglyceridemia may occur with cholestasis. In addition, hypertriglyceridemia has been associated with a proportion of dogs with biliary mucoceles.

Others

Bilirubin metabolism was discussed in an earlier section. From a diagnostic standpoint, it is helpful to consider the potential causes of hyperbilirubinemia by dividing the causes into prehepatic, hepatic, and posthepatic. The former can be quickly identified by significant anemia and enhanced erythrocyte breakdown and once excluded, the presence of hyperbilirubinemia becomes far more specific for liver disease than many of the other clinical pathology analytes. Despite this, bilirubin measurement still has important limitations. As with other parameters, it is still a relatively insensitive measure of hepatic insufficiency, becoming elevated only once significant hepatic reserve is exhausted, for example with end-stage cirrhosis patients. In addition, hyperbilirubinemia does not distinguish between primary and secondary hepatopathies. Sepsis can cause significant cholestasis and hyperbilirubinemia, and many of the causes of posthepatic jaundice are extrahepatic, such as pancreatitis and pancreatic or duodenal neoplasia. In cats, hyperbilirubinemia is a more sensitive indicator of hepatobiliary disease than it is in dogs, reflecting the increased proportion of liver diseases in the cat that involve biliary disease.

When approaching a patient with hyperbilirubinemia, having excluded prehepatic jaundice, the next stage is to try to establish whether hepatic or posthepatic pathology is most likely. Evaluation of the remainder of the biochemistry panel is important to establish if there are other features suggestive of hepatic insufficiency, for example hypoalbuminemia, and to examine the hepatic enzyme activities. Typically, with posthepatic jaundice there is dramatic elevation of the cholestatic liver enzymes, more so than the hepatocellular leakage enzymes, hypercholesterolemia and no evidence of hepatic insufficiency. However, the picture is often not clear-cut, with hepatocellular enzyme activities increasing in patients with posthepatic cholestasis over time due to the toxic effects of accumulated bile salts, and markers of hepatic insufficiency unchanged due to their lack of sensitivity. Abdominal ultrasound is the next step in examining such a patient, and is typically the most useful method to distinguish between hepatic and posthepatic jaundice (see later). In some patients, the distinction between hepatic and posthepatic disease is blurred with their presentation involving components of each, for example cholangitis.

Bile Acids

Bile acids are steroid acids that are a normal constituent of bile and function in fat digestion within the intestine. The two primary bile acids, cholic and chenodeoxycholic, are synthesized in the liver from cholesterol and are then conjugated, mainly with taurine, before being excreted in bile for release into the gut or storage in the gallbladder. These conjugated bile acids are ionized at intestinal pH and function in fat digestion by aiding the formation of micelles. Intestinal bacteria metabolize some of the primary bile acids to the secondary bile acids, deoxycholic and lithocholic acid, within the gut lumen. Once in the ileum, primary and secondary bile acids bind to specific receptors, allowing their reabsorption and enterohepatic circulation. This system sees a maximum of approximately 5% fecal loss per day of bile acids, with the remainder returned to the liver in the portal circulation for removal and reexcretion. The daily losses are replaced by liver manufacture of new bile acids, maintaining a constant bile acid pool in the normal animal. This low-level replacement is not affected by reduced liver function.

This enterohepatic circulation of bile acids forms the basis of the serum bile acid assay, a dynamic liver function test. The rationale for this test is that reduced liver function or impairment of the enterohepatic circulation, due to either reduced biliary excretion or disruption of the portal circulation, results in elevation of the serum bile acid concentration measured in peripheral blood. The indications for its use are in the diagnosis of PSS and the assessment of liver function in cases where liver disease is suspected but hyperbilirubinemia is not present. The latter is a less sensitive indicator of hepatic dysfunction; once hyperbilirubinemia is present in a patient, the measurement of serum bile acids offers no further information.

A fasted serum bile acid is obtained after a 12-hour fast and assesses enterohepatic circulation in the fasted state. A postprandial sample taken two hours after feeding provides an endogenous challenge. The rationale for the latter is that feeding stimulates gallbladder contraction with release of stored bile and hence increased quantities of bile acids for enterohepatic circulation, thus providing an additional challenge for the assessment of liver function.

It has been shown that a proportion of PSS cases have results within the reference interval for fasting bile acids

but abnormal results on a postprandial sample. However, rather than the postprandial sample specifically providing additional information over the fasting sample, use of the paired pre- and postprandial samples together increases the overall sensitivity of the test. The postprandial bile acid value may be the lower of the two values in some cases, potentially reflecting factors such as gallbladder contraction during the fasting period, incomplete gallbladder contraction, delayed gastric emptying, altered intestinal motility, and decreased bile acid absorption. When interpreting these paired samples, the higher value should be interpreted. Most veterinary laboratories utilize enzymatic fluorimetric or spectrophotometric methodologies for the assay, which means that lipemia and hemolysis can affect the results. The reference intervals provided by individual labs vary based on their individual methodology but are generally very approximately <5 µmol/L and <10 µmol/L for pre- and postprandial values, respectively. However, some normal animals have values within these intervals, necessitating adjustment of the cut-off values used for interpretation.

Serum bile acid assays (SBA) represent one of the more sensitive measures of liver function available at this time. Their utility relies on the fact that they give an indication of liver function whereas liver enzymes offer markers of liver insult or drug induction. In general, the lower sensitivity of bile acids for the detection of hepatobiliary disease makes them poor screening tests. They are more appropriately employed as a function test to evaluate patients prescreened by routine biochemistry, with the aim of identifying those patients in whom a liver biopsy should be considered. One exception to this situation is their performance in patients with PSS. Sensitivity of 100% for the detection of PSS in cats and dogs has been quoted using cut-off values of 20 µmol/L and 25 µmol/L respectively, for postprandial samples. The sensitivities noted in these papers for the identification of other causes of hepatic dysfunction were considerably lower than these values, as has been noted elsewhere.

The values gained for SBA provide no indication of the underlying cause of hepatic dysfunction, do not differentiate between primary and secondary hepatopathies, and provide no information about disease severity or overall prognosis. An early paper identified 100% specificity for the presence of histopathologic abnormalities on hepatic biopsies using cut-off values of 20 µM/L for preprandial and 25 µM/L postprandial samples. These results were gained in a highly prescreened population, suspected by experts to have liver disease based on clinical findings and routine clinical pathologic testing. Hence, the prevalence of hepatobiliary disease in this population was high. This fact affects the test performance considerably and should be remembered when tests are being utilized in very different clinical situations. When SBA have been present on biochemistry panels and used more as screening tests, some spurious high values have been observed in animals with no other evidence of liver disease. Research suggests that these values may relate to bacterial overgrowth and the measurement of increased concentrations of deconjugated bile acids in some patients. In other animals, extrahepatic disease is likely to be resulting in high values and secondary hepatopathies.

The point is that care must be taken to consider the context in which test results are gained; the specificity of the test will be lower in a population with a lower prevalence of hepatobiliary disease. Using increased cut-off values for the assay will increase the specificity of the test, but this is usually at the expense of sensitivity.

Values above 40 µmol/L are more likely to indicate primary hepatic dysfunction unless underlying causes such as hyperadrenocorticism are identified. In view of this, the author typically takes this value as more indicative of the need for further evaluation, such as a liver biopsy. However, values between 20 and 40 µmol/L represent an important "gray-zone" and warrant critical evaluation in relation to the patient, its clinical signs, and the potential for extrahepatic causes. The evaluation of pre- and postprandial samples may aid clarification, if not already performed, and the test should be repeated after a period of time where there is any uncertainty. It should always be remembered that the test, while helpful and better than most measures of liver function, still has limitations. Where there is persistent liver enzyme elevation over time, even without elevation of SBA, a liver biopsy may well be indicated on a case-by-case basis (see later). Patients with values in the "gray-zone" with clinical signs suggestive of liver disease or those without clinical signs in which elevations persist with no other explanation are also likely to warrant a liver biopsy. The measurement of urine bile acids has been investigated but does not appear to offer particular advantage over the SBA.

Hematology

Mild to moderate anemia is common in patients with liver disease. The more common causes include anemia of chronic disease and gastrointestinal bleeding. Acute bleeding following liver biopsy, rupture of neoplasm or hepatic rupture, resulting from trauma or pathologic processes such as peliosis or hepatic amyloidosis, can also occur, as can hemostatic disorders. Morphologic changes in erythroctes (poikilocytes) are seen in some dogs with chronic liver disease. These include irregularly speculated cells, or acanthocytes and target cells, both of which are thought to result from altered phospholipid metabolism. In addition, microangiopathy with neoplasia

or DIC may result in the generation of schistocytes. A frequent finding in dogs with CPSS is microcytosis, thought to reflect altered iron metabolism.

There are no specific leukocyte changes seen with liver disease. An inflammatory leukogram may occur with any inflammatory, infectious (e.g., leptospirosis) or neoplastic process. In one report, 16 out of 36 dogs (44%) with chronic hepatitis were found to have an inflammatory leukogram. Thrombocyte changes may also be seen in dogs with liver disease, although again the changes are nonspecific. Thrombocyte counts may be reduced in animals with DIC and significantly lower thrombocyte counts were reported in dogs with chronic hepatitis and cirrhosis.

Urinalysis

Ammonium biurate crystals have been reported to occur in 40–70% of dogs with CPSS and may provide an early clue to diagnosis in such patients, although they are not a specific finding. Bilirubinuria can also be an important finding. Since cats have a high renal threshold for bilirubin and their renal tubules do not make bilirubin, its presence is always significant in this species. In dogs, lower levels of bilirubin are a normal finding, particularly in male dogs. High levels suggest hemolytic or hepatobiliary disease and discolored urine may be one of the first reasons an owner seeks veterinary attention for a jaundiced pet. Urine specific gravity may be reduced in animals with CPSS and hepatic insufficiency in line with the observed polyuria/polydipsia in these cases.

Serology

Dependent on the geographic location, serologic testing for a variety of infectious agents may be appropriate, for example *Leptospira*, *Neospora*, **Toxoplasma**, Rocky Mountain spotted fever, *Dirofilaria*, *Ehrlichia*, and systemic mycoses.

Genetic Tests

The deletion mutation that causes copper hepatotoxicosis in the majority of Bedlington terriers has been identified and is now available as a genetic test for the disease in this breed (www.vetgen.com). This test is run alongside a previously identified linkage marker to identify any dogs in the breed that are affected by copper toxicosis but do not have this specific deletion mutation. The occurrence of many chronic hepatopathies in specific breeds and the recognition of inheritance patterns in some of the breeds make it likely that more genetic tests will become available as the genetic bases of these diseases are identified.

Newer Tests

There are a variety of newer assays being investigated, for example, ^{13}C-labeled galactose breath test for assessment of liver function and serum protein C for the differentiation of portal vein hypoplasia without portal hypertension (formerly known as microvascular dysplasia) from PSS.

Summary of the Interpretation of Clinical Pathology

As discussed, there is no one clinical pathology finding that defines a specific diagnosis of hepatobiliary disease in dogs and cats. The clinician needs to interpret all the tests together in the context of the patient and its clinical presentation. Consideration of patterns of abnormalities in the clinical pathology tests rather than individual tests in isolation can be helpful in increasing or decreasing the index of suspicion of different conditions, as outlined in Table 60.1. Once this type of interpretation has been considered, the use of diagnostic imaging allows further refinement and direction towards either the pursuit of potential extrahepatic causes of the animal's signs and laboratory findings or more specific hepatic testing such as cytology or biopsy.

Diagnostic Imaging

Diagnostic imaging is a very important component of the investigation of a patient with suspected hepatobiliary disease, typically performed in combination with clinical pathology evaluation. Imaging can aid directly in the identification of hepatobiliary disease and the presence of any extrahepatic conditions that may be of relevance or directly contributing to the generation of secondary hepatopathies. In some situations, imaging may allow direct identification of the specific cause of the hepatobiliary disease, for example congenital PSS, although more typically it adds pieces to the overall clinical picture being built up for a given case. In some situations, prognostic information may be contributed, for example the finding of a very nodular and irregular liver in a dog suspected to have cirrhosis.

Abdominal ultrasound is particularly useful in guiding the approach to jaundiced patients, as outlined earlier, and the identification of biliary tract abnormalities such as biliary mucoceles or cholecystitis. It can also be helpful to establish if hepatic lesions are localized or generalized within the parenchyma and to provide guidance in gaining targeted biopsies or bile samples as indicated. Further detail on imaging in the investigation of hepatobiliary disease is covered in Chapter 61.

Table 60.1 Typical examples of use of pattern recognition in clinical pathology for canine liver disease

	ALT	ALP	Bilirubin	Serum bile acids	Ammonia	Albumin	Glucose	Other
Acute hepatitis/ hepatic necrosis	Rapid ++ to +++	Slower, + to ++	N to +++ with the latter in severe cases	N to +++ depending on overall severity	N to ++ depending on overall severity	N	May be low with fulminant disease	
Chronic hepatitis	Persistent + to ++ possible. May fluctuate over time	Persistent + to ++ May fluctuate over time	N to ++ possible but the latter only occurs with late-stage disease	N to ++	N to ++ but insensitive	N early in disease. More likely to decrease with later disease and often poor prognostic indicator	Usually N	May see poikilocytes. One report 44% inflammatory leukogram
Cirrhosis	N to ++	N to ++	N to +++ increased with disease progression	+ to +++ More sensitive than bilirubin	N to ++ Latter occurs late in disease process	Reduced	Hypoglycemia with end-stage disease. Poor prognostic indicator	May have low serum urea. May see poikilocytes
Congenital portosystemic shunts	N or +	N or +	N	Fasting samples may be N to ++ Postprandial samples typically ++ to +++	+ to +++ Postprandial sampling increases sensitivity	Frequently reduced	May be low	Microcytosis frequent finding in dogs. Ammonium biurate crystaluria common
Biliary tract obstruction	N to ++ The latter occurring with chronicity	+++	++ to +++	Increased but measurement not indicated with jaundice	N	N	N	Hypercholesterolemia
Nonobstructed biliary tract disease	N to ++ The latter occurring with chronicity	+ to ++	N	N May see mild increase if significant cholestasis	N	N	N	
Hepatic neoplasia	N to ++	N to ++	May see jaundice if biliary carcinoma. Other tumor types infrequently cause jaundice	N most commonly but may be +	Most commonly N	Most commonly N	Occasionally hypoglycemia with large hepatomas	May see hypercalcemia with lymphoma
Glucocorticoids	+ to ++ typically. Marked interindividual variation	+ to ++ Marked interindividual variation. Typically disproportionate increase in ALP compared to ALT	N	Usually N but + to ++ possible with vacuolar hepatopathy	Usually N	N	May also have mild hyperglycemia	May also be hypercholesterolemia
Benign nodular hyperplasia	Usually N or minimal increase	+ to +++	N	N	N	N	N	

N Within the reference interval.
+ Mildly increased.
++ Moderately increased.
+++ Markedly increased.
Scottish terriers and Siberian huskies are noted to have elevated ALP activities compared to the general reference interval for all breeds.
ALP, alkaline phosphatase; ALT, alanine aminotransferase.

Cytologic and Histopathologic Evaluation in Liver Disease

The results gained from diagnostic imaging and clinical pathology testing do not typically provide a definitive diagnosis in patients with liver disease, except in cases such as CPSS. The gold standard for diagnosis in these patients is usually histopathologic evaluation of a liver biopsy. The liver biopsy can provide a definitive diagnosis in some situations, for example neoplasia. In other cases, while a specific diagnosis may not be made, the biopsy provides important information about the pathologic reaction pattern observed, including the location of lesions, cell types involved, and the chronicity of the changes. This information is invaluable in guiding therapeutic intervention and providing prognostic information. In addition, follow-up biopsies offer an important guide to the clinician when assessing the response to therapy. Cytologic evaluation of samples may be considered in some situations and is discussed below. In general, liver histopathology offers significant diagnostic advantages over cytologic samples.

Cytologic Evaluation

It is possible to gain cytologic samples from liver patients by performing percutaneous ultrasound-guided fine needle aspiration of liver parenchyma or bile by cholecystocentesis. Percutaneous aspiration of ascitic fluid can also provide useful information. These techniques are minimally invasive and are associated with a low risk of complications. The clinician should exercise caution when approaching patients with hemostatic disorders, although the risk is far less with a fine needle aspiration compared to liver biopsy.

In general, the indications for fine needle aspirates of hepatic parenchyma are the same as those outlined later for liver biopsy. However, the main disadvantage of fine needle aspirates and cytologic evaluation is the limited diagnostic accuracy of this approach. The sample size gained provides a limited number of cells to evaluate, hemodilution may cloud interpretation and in addition, no morphologic information about the lesion is provided, as it is with histopathology.

Studies that have compared results gained with fine needle aspiration and histopathology have generally shown poor concordance rates. One study evaluated 56 dogs and 41 cats and showed agreement between fine needle aspirates and histopathology in approximately 30% of dogs and 50% of cats. The greatest agreement was seen with vacuolar hepatopathies, largely accounting for the higher accuracy in cats. However, this category also had a high rate of misdiagnosis as the primary underlying lesion was missed on cytologic examination in many cases. Since hepatic lipidosis in cats is frequently a sequel to an underlying disease rather than a primary diagnosis, this would place important limitations on cytology as a sole means of diagnosis. With diffuse or focal neoplastic disease, aspirates can prove useful; for example, a diagnosis of lymphoma may alleviate the need for a biopsy. However, this is not the case in all situations; the differentiation of nodular hyperplasia and hepatoma is not possible cytologically. In addition, the performance for canine inflammatory liver diseases is generally poor. This relates to both the importance of liver architecture in the categorization of the diagnosis (e.g., chronic hepatitis versus cirrhosis) and the chances of missing inflammatory cells where there are areas of fibrosis. Occasionally, infectious agents such as histoplasmosis can be diagnosed by fine needle aspiration.

Overall, the clinician must be aware of the limitations of fine needle aspirates of liver parenchyma and regard them more as a contributor of information rather than providing a definitive diagnosis in most situations. The main advantages are the safety aspects in high-risk patients and the general requirement for only limited sedation. They can also be performed quickly, contributing to patient planning and even a final diagnosis in some cases.

Cytologic evaluation of ascitic fluid in combination with analysis of the total protein content and cell count allows determination of the nature of the ascites, for example whether it is a transudate, modified transudate or exudate. In general, accurate categorization of the ascites aids in diagnostic planning by narrowing down the potential differentials considered in a case. For example, demonstration of an exudate with a bilirubin concentration greater than twice that of the serum would suggest bile peritonitis and should prompt surgical intervention. More frequently with liver disease, a modified transudate is obtained, resulting from portal hypertension and increased hepatic lymph leakage.

Bile cytology can also provide important information where clinical signs are suggestive of cholestasis or gallbladder abnormalities are detected ultrasonographically. These samples can be gained by cholecystocentesis either percutaneously by ultrasound guidance or directly during laparoscopy or laparotomy. The finding of bacterbilia and/or neutrophils within the bile supports a diagnosis of bacterial cholecystitis, or cholangitis if there is histopathologic evidence to support hepatic changes. In addition to cytologic evaluation, anaerobic and aerobic bacteriologic culture of bile should be performed. In the author's experience, bacteria are evident within bile far more frequently than inflammatory cells and occasionally provide evidence of a bacterial etiology in patients where bile culture proves negative due to antibiotic administration. In other patients, bacterial culture may be positive in the absence of any cytologic abnormalities.

In general, bacteriologic culture of bile yields far more positive results than culture of liver parenchyma.

Histopathologic Evaluation

Indications

As discussed earlier, the laboratory tests for liver disease rarely identify a specific etiology. Having employed clinical pathology and ultrasonography as diagnostic tests to identify potential liver disease, evaluation of a liver biopsy aids the provision of a diagnosis and prognosis and in guidance of therapeutic intervention. In general, a liver biopsy is indicated in the following circumstances.

- Asymptomatic patients with persistent, serial elevations in liver enzyme activities.
- Asymptomatic patients with abnormal hepatic function tests (e.g., fasting serum bile acid or postprandial serum bile acid).
- Where hepatic parenchymal abnormalities are identified ultrasonographically.
- Where there is unexplained hepatomegaly.
- To assess response to therapeutic intervention.
- Evaluation of animals with potential breed-specific hepatopathies.
- Any animal with progressive signs of liver disease.

It is important to recognise the potential for the occurrence of liver enzyme elevation and secondary "reactive" hepatopathies as a result of extrahepatic causes. Consideration of and, if appropriate, evaluation for the presence of potential extrahepatic causes, such as hyperadrenocorticism in dogs, hyperthyroidism in cats and gastrointestinal or pancreatic disease, is important before pursuing a liver biopsy, particularly where only liver enzyme elevation is noted on a biochemistry panel. The consideration of more than one liver enzyme activity, evaluation of results on more than one occasion and performing a liver function test, such as pre- and postprandial bile acids, can be helpful to clarify the situation where there is any doubt.

Prebiopsy Considerations

When planning liver biopsy, there are several important factors to consider, including risk to the patient and the type of biopsy procedure to be used. The main types of biopsy approaches available are ultrasound-guided needle biopsy, laparoscopic biopsy, and surgical biopsy. The most important potential complications of liver biopsy are hemorrhage, trauma to adjacent organs, and infection, the relative risks of which vary with the technique used and are discussed further later.

It is important to evaluate the overall clinical stability of a patient and hemostatic function prior to obtaining a liver biopsy. The circulatory status and potential for hemorrhage should be considered in addition to how well the animal will tolerate sedation or general anesthesia. The latter is particularly a consideration in patients with signs of HE where medical management to stabilize the patient prior to more invasive procedures is often necessary. A minimum database to screen hemostatic function should include a platelet count, prothrombin time (PT), and partial thromboplastin time (PTT). The measurement of buccal mucosal bleeding time (after establishing a normal platelet count on a blood smear) is also recommended due to some reports of increased complications due to primary hemostatic abnormalities (platelet dysfunction) rather than secondary hemostatic (coagulation factor) abnormalities. Measurement of fibrinogen along with fibrin degradation products (FDPs) and D-dimers to assess for increased fibrinolysis might also be considered. However, it should be noted that there is often poor correlation between coagulation parameters and major complications at liver biopsy. Although there is little veterinary literature published in the area, one study suggested that a platelet count below 80×10^9/L, a PTT more than 1.5 times the reference interval in cats and a PT above the reference interval in dogs were all associated with an increased risk of minor complications in animals undergoing ultrasound-guided needle biopsies.

Some clinicians suggest administration of vitamin K 24 hours prior to biopsy in all cases. It is certainly appropriate to treat any patients with prolonged coagulation screens, as administration has been shown to improve clotting times in many patients. The administration of vitamin K to all hyperbilirubinemic patients, particularly cats, is probably prudent in view of the role of bile in the adsorption of fat-soluble vitamins and the insensitivity of PT and PTT in detecting bleeding diatheses. The use of fresh-frozen plasma to deliver coagulation factors to patients with mildly increased PT and PTT is also an option. Following a liver biopsy, it is essential that patients are closely monitored over at least 12 hours for clinical signs of postbiopsy hemorrhage. Evaluation of heart rate, mucous membrane color, abdominal size, and mentation is important. Measurement of total protein and packed cell volume does not provide useful information when monitoring for acute hemorrhage.

Ultrasound-Guided Biopsy

Ultrasound-guided biopsies involve the use of a cutting-type needle which is ideally automated or semiautomated. These are spring-loaded needles similar to the manual Tru-cut style and help when coordinating operation of the ultrasound probe with one hand and the biopsy gun with the other. The fully automated devices initially fire the inner part of the needle containing the biopsy channel and then the outer cutting device rapidly afterwards. The semiautomated ones allow the operator

to position the inner part of the needle and then fire the outer section. There are advantages to each type but the semi-automated ones probably offer greater accuracy in positioning the needle for more precise sampling. There are reports of increased risk of fatal complications when using the fully automated Tru-cut biopsy needle in cats so its use in this species is not recommended.

The advantages of ultrasound-guided biopsy are the less invasive nature of the procedure compared to laparotomy and the need for sedation rather than general anesthesia in most patients. Multiple sites may be sampled along with the additional advantage of targeting potentially abnormal areas identified ultrasonographically. The relatively low cost to the owner and reduced recovery times are also beneficial. However, there are significant limitations to the technique. The risk of hemorrhage is important and is greater with this technique than with laparotomy or laparoscopy where there is more scope for both the detection of hemorrhage and intervention where necessary. Large-volume ascites is a contraindication for this type of biopsy technique as it may increase the risk of significant hemorrhage. Microhepatica is also a contraindication due to the risk of inadvertent damage to other tissues.

Another important limitation of Tru-cut style biopsies is the small sample size and hence the diagnostic accuracy of samples gained. A study looking at biopsy samples from 98 dogs and 26 cats compared the results gained by three different pathologists evaluating two needle biopsies (18 gauge automated string-triggered needle) and a wedge biopsy from the same animal. All three pathologists agreed on the morphologic diagnosis for a given patient 44% of the time using needle biopsies and 65% of the time when relying on evaluation of the wedge biopsies. Overall, the results gained from the needle biopsies concurred with those gained from the wedge biopsies in only 47% of dogs and 50% of cats. The discordance rate increased still further when patients with inflammatory or vascular disease or those with significant fibrosis were considered separately. The use of a 14 or 16 gauge needle rather than an 18 gauge needle is likely to increase the accuracy of diagnosis by increasing the average number of portal triads sampled. However, the risk of hemorrhage is increased with increased needle size. The use of a 16 gauge needle for dogs and 18 gauge for cats is often most practical, taking a larger number of needle biopsies (3–5) from multiple sites so that the risk of missing a lesion due to patchy distribution or small sample size is further reduced. Despite this approach, with the ultrasound-guided approach there is often a tendency to biopsy a more limited number of liver lobes than with surgical approaches due to the limitations of access and ease of imaging.

Surgical Biopsy

A wedge biopsy gained at laparotomy is another method for obtaining a liver biopsy. This may be performed by performing a random biopsy from the edge of a liver lobe using a guillotining suture or in a more directed way in an abnormal area using transfixing ligatures or a biopsy punch (see surgical texts for more detailed information about biopsy method). This approach offers the advantage of the clinician being able to grossly examine the liver and extrahepatic biliary tract along with other intraabdominal organs that may impact the liver, for example the pancreas and duodenum. There is also the option to biopsy other organs and gain bile samples for cytology and culture. Multiple, large biopsies may then be taken from areas the clinician identifies to be abnormal, potentially finding smaller lesions that may not have been apparent at ultrasound. This significantly reduces the problems of sampling error and allows samples to be gained from multiple liver lobes. This approach is not affected by liver size and allows attention to hemostasis with use of direct manual pressure and/or topical hemostatic agents (e.g., Gelfoam®). The main disadvantages of surgical biopsies are the more invasive nature of the procedure, the increased recovery time, and requirement for general anesthesia. The cost to the owner is also significant.

Laparoscopic Biopsy

Laparoscopic biopsy of the liver affords many of the advantages of surgical liver biopsies but is far less invasive and allows faster patient recovery. The clinician is able to grossly inspect the entire liver and extrahepatic biliary system, again taking bile samples as indicated. Surrounding structures can also be examined and in some cases biopsied, although the latter is more straightforward with laparotomy. The biopsy samples are taken using specially designed forceps and can be taken easily from multiple regions with clear visualization allowing attention to hemostasis. As with laparotomy, local pressure, hemostatic agents or electrocautery may be employed to limit any hemorrhage. The sample size gained is good, again reducing problems with sampling error. The main disadvantages of laparoscopy are the cost of equipment and the need for significant training. As with surgery, there is a need for general anesthesia and the cost is higher than ultrasound-guided sampling. A recent retrospective paper showed low complication rates, although potential complications, other than hemorrhage, include air embolism, damage to viscera with trocar placement and the potential for seeding of neoplastic cells through port sites. The latter would also be a potential complication with needle biopsies. Approximately 4% of cases in this study required conversion to a laparotomy.

Overall, there are significant advantages provided by surgical or laparoscopic biopsies and these are the

preferred choice of the author if the pet owner is willing to take this approach. When approaching cases with jaundice, it is important to utilize clinical pathology findings in combination with ultrasound to try to establish if jaundice is hepatic or posthepatic in origin (having excluded prehepatic – see earlier). If extrahepatic bile duct obstruction is suspected, laparotomy and laparoscopy allow direct visualization of the extrahepatic biliary system and local organs, evaluation of patency of the bile duct, bile sampling and, if necessary, cholecystectomy. Surgical intervention, such as biliary diversion or resection of a mass, is also possible with a laparotomy. Ultrasound-guided liver biopsy should be avoided in this situation due to risks of rupture to the biliary tree. The author still prefers the surgical or laparoscopic approach even in cases of suspected intrahepatic jaundice due to the advantages offered in examining and sampling the gallbladder and local organs. Ultrasound has been shown to be insensitive in diagnosing gallbladder rupture in dogs with both gallbladder mucoceles and cholecystitis. In addition, the sensitivity of ultrasound for detection of cholecystitis is not 100%. In view of this, direct evaluation can be useful.

In acute cases where ultrasound is suggestive of pancreatitis, surgical intervention should be avoided while initial symptomatic management is evaluated. Many such cases will improve without further intervention and the attendant risks of anesthesia and reduced pancreatic perfusion. Only if the jaundice persists despite this management is surgery indicated.

Liver Histopathology

There are a variety of additional stains that can be used along with the standard hematoxylin and eosin for further evaluation of liver histopathology. When a clinician performs a liver biopsy, they should be ready to work with the pathologist reading the biopsy. Providing a clear clinical history is imperative. Understanding that the biopsy represents only a small fraction of the overall liver is key. The clinician should always relate the information gained to the patient's clinical picture and bloodwork, remembering that there is the possibility of significant sampling error, as discussed in the sections above. The biopsy results should be used to guide the treatment by defining the disease processes noted within the sample (e.g., inflammation, vacuolation) rather than necessarily providing a definitive diagnosis.

In breeds in which copper-associated hepatopathies are known to occur, the measurement of hepatic copper is important. Ideally semiquantitative copper staining of biopsy samples and quantitative copper analysis of tissue should both be performed. The latter requires adequate sample size, which typically entails a wedge biopsy. Information for individual cases is probably best discussed with the pathologist involved.

Conclusion

Patients with hepatobiliary disease pose many diagnostic challenges to the clinician. The vast array of liver functions and its tremendous functional reserve mean that patients with significant disease can present in very diverse guises and often very late in the overall disease process. The challenge for the clinician is to become adept at identifying patients with liver disease early on, when they may have vague or minimal clinical signs, as these patients are the ones more likely to benefit from treatment. Diagnostic tests, such as clinical pathology, rarely offer a definitive diagnosis in patients with liver disease. Instead, they should be used to build up an overall picture guiding a rational approach to the patient. A liver biopsy is often necessary, providing the most accurate indication of the underlying disease process, severity, and prognosis.

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61

Imaging in Hepatobiliary Disease

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The aim of diagnostic imaging in hepatobiliary disease is to provide information about the structure and, to a certain extent, the function of the hepatobiliary system. In common with the diagnostic imaging of all other organ systems, the imaging findings are rarely specific for a single disease process and it is not possible to exclude disease on the basis of apparently normal imaging findings. Hepatobiliary imaging should therefore be considered not as an isolated process but as an important part of the overall diagnostic work-up, with the imaging findings always interpreted in the light of all the other available information (patient history, findings on physical examination, results of laboratory investigations, etc.).

Radiography and ultrasonography are the techniques most commonly used in the diagnostic imaging of the hepatobiliary system. Although much less widely available, scintigraphy (nuclear medicine) is also a well-established hepatobiliary imaging technique, useful in providing functional as well as anatomic information. More recently, the advanced cross-sectional imaging techniques of computed tomography (CT) and magnetic resonance imaging (MRI) have become increasingly useful, especially in the anatomic mapping of complicated vascular anomalies and in the evaluation of, and potential surgical planning for, patients with liver masses.

Classification of Hepatobiliary Disease

In 2006, the WSAVA published the outcome of its hepatic standardization project, an initiative started in July 2000 with the aim of describing universally accepted standards and criteria for the diagnosis of all known liver diseases of dogs and cats. In establishing the recommended classification of different hepatobiliary diseases, ultrasonographic findings were considered an important feature, alongside clinical pathologic and histologic findings. As a result of this work, four main groups of liver disease have been established: parenchymal disorders, neoplastic disease, biliary tract disorders, and vascular disorders. In this chapter, the WSAVA classification system is used as a basis for describing the imaging features of commonly encountered hepatobiliary diseases.

Normal Hepatobiliary Anatomy

The canine and feline liver is the largest soft tissue organ in the abdomen and is divided by deep fissures into left and right, quadrate and caudate lobes. The left and right hepatic lobes are further divided into lateral and medial sublobes. The liver is located almost completely within the costal arch, with a convex cranial surface lying immediately adjacent to the diaphragm and an irregularly concave caudal surface lying in contact with the stomach, pancreas, duodenum, and right kidney. On the ventral aspect of the liver, the proximal aspect of the fetal falciform ligament usually remains as an irregular fat-filled fold (falciform fat).

The Biliary System

The canine gallbladder is typically pear shaped and lies between the quadrate and right medial lobes. The feline gallbladder, which is sometimes folded or bilobed, usually lies between two parts of the right medial lobe. The common bile duct is formed by the confluence of the cystic duct (from the gallbladder) with the hepatic duct/s (directly from the liver). The common bile duct leaves the liver at the porta hepatis, where it lies ventral to the hepatic arteries and the hepatic portal vein, and enters the proximal duodenum at the major duodenal papilla. In cats, the pancreatic duct usually joins the common bile duct before emptying via the major duodenal papilla into the proximal duodenum. In dogs, although both the

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pancreatic duct and common bile ducts empty at the major duodenal papilla, they usually remain separate; an additional accessory pancreatic duct empties further distally, via the minor duodenal papilla.

Hepatic Vasculature

The liver is unique in having a dual blood supply. The proper hepatic arteries, which arise from the abdominal aorta via the celiac artery and enter the liver at the porta hepatis, supply approximately one-fifth of the blood supply. The remaining four-fifths of the blood supply is provided by the hepatic portal vein. The portal vein arises in the midabdomen, where it is formed by the confluence of the larger cranial mesenteric and smaller caudal mesenteric veins. It is joined by the splenic vein and gastroduodenal vein, before entering the porta hepatis, where it lies ventral to the hepatic arteries and dorsal to the common bile duct. On entering the liver, the portal vein divides into a smaller right portal branch, which arborizes into the right medial and lateral lobes, and a larger left portal branch, which arborizes throughout the remaining liver. Venous drainage from the liver is through several (usually three) short hepatic veins and multiple tiny tributaries, which empty into the caudal vena cava as it crosses the liver on the right dorsal aspect of the midline.

Lymphatic Drainage

Lymphatic vessels from the hepatic parenchyma and the gallbladder anastomose and drain together into the hepatic and splenic lymph nodes. Variable numbers (typically between one and five) of hepatic lymph nodes lie to the right and left of the hepatic portal vein, just caudal to the porta hepatis, and receive lymphatic drainage from the liver, stomach, duodenum, and pancreas. The splenic nodes are located along the course of the splenic artery and vein and receive lymphatic drainage from the esophagus, stomach, pancreas, spleen, omentum, and diaphragm, as well as the liver. Together with the gastric lymph nodes, which drain the liver mesentery, and the pancreaticoduodenal lymph nodes, the hepatic and splenic lymph nodes form the celiac lymph center.

Hepatobiliary Radiography

Radiographic Technique

A minimum of two orthogonal views, a ventrodorsal and either a right or left lateral recumbent view, is recommended for evaluation of the liver. Good radiographic technique is essential in order to obtain images of high diagnostic quality.

Radiologic Evaluation

The radiologic assessment of the hepatobiliary system relies on the logical evaluation of liver position, size, shape, opacity, and margination.

Normal Findings

The normal liver is of homogenous soft tissue opacity, merging with the soft tissue opacities of the diaphragm and gallbladder to form the "hepatic silhouette." On a lateral view (Figure 61.1a), the hepatic silhouette is approximately triangular in shape, with a sharply pointed caudoventral angle.

The liver lies within the cranial abdomen, immediately caudal to the diaphragm, with the right kidney and stomach lying against its caudal border. The "stomach axis" is an imaginary line running from the fundus to the pyloric antrum of the stomach. This axis, which is most easily recognized when a small amount of gas is present in the stomach lumen, provides a useful reference point for evaluating liver size. In most dogs and cats, the liver is almost entirely contained within the costal arch, and the gastric axis lies approximately parallel to the ribs; however, normal variations, both in the position of the caudoventral hepatic angle with respect to the costal arch and in the orientation of the gastric axis, may be seen between different dog breeds and ages. Deep-chested dogs typically have a relatively cranially located liver, with a more upright gastric axis, while the liver of barrel-chested dogs and puppies tends to extend further caudally and may protrude beyond the costal arch, resulting in caudal displacement and anticlockwise rotation of the gastric axis.

The caudoventral angle and ventral border of the liver are often highlighted against the relative radiolucency of the adjacent falciform fat on a lateral abdominal radiograph; this provides a clearly defined ventral margin, especially in cats, where the gallbladder is occasionally identified as a soft tissue bulge along the ventral hepatic border. The position of the cranial and caudal hepatic margins is inferred from the location of the diaphragm and stomach respectively. Dorsally, the caudate lobe of the liver lies adjacent to the right kidney; in most dogs, these two soft tissue structures merge into a single soft tissue opacity, and the caudodorsal margin of the liver cannot be seen. Cats typically have a larger amount of retroperitoneal fat, usually separating the caudodorsal liver from the right kidney and allowing the two structures to be identified separately.

The hepatic silhouette is less easily appreciated on a ventrodorsal radiograph (Figure 61.1a); while the position of the cranial margin is demarcated by the location of the diaphragm, the caudal margins are poorly defined and can only be inferred from the location of the stomach.

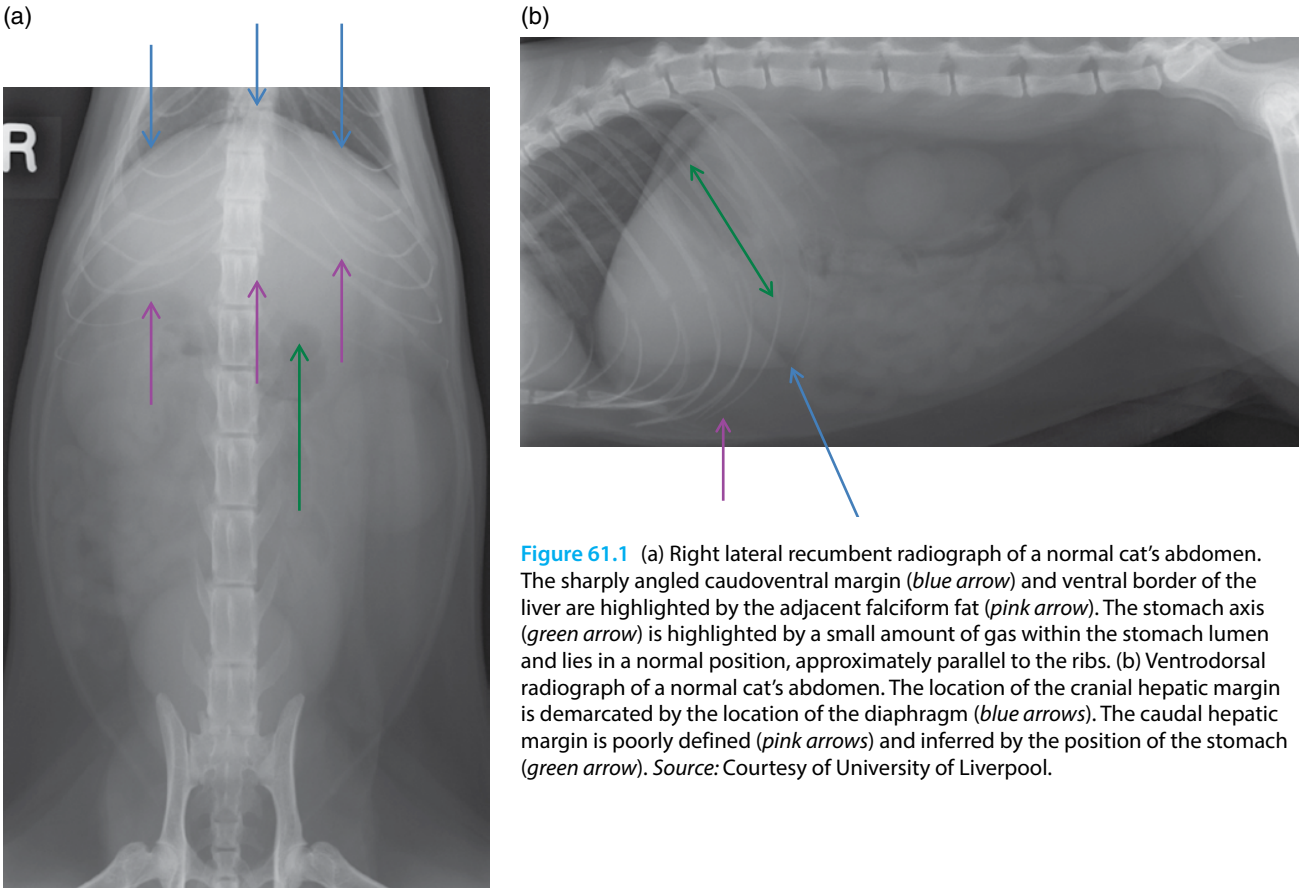


Figure 61.1 (a) Right lateral recumbent radiograph of a normal cat's abdomen. The sharply angled caudoventral margin (*blue arrow*) and ventral border of the liver are highlighted by the adjacent falciform fat (*pink arrow*). The stomach axis (*green arrow*) is highlighted by a small amount of gas within the stomach lumen and lies in a normal position, approximately parallel to the ribs. (b) Ventrodorsal radiograph of a normal cat's abdomen. The location of the cranial hepatic margin is demarcated by the location of the diaphragm (*blue arrows*). The caudal hepatic margin is poorly defined (*pink arrows*) and inferred by the position of the stomach (*green arrow*). *Source:* Courtesy of University of Liverpool.

In the dog, the caudal extent of the liver on the ventrodorsal view is similar on right and left sides; caudal to the liver, the stomach lies approximately perpendicular to the spine, with the fundus located on the left, the lesser curvature centrally and the pylorus and cranial duodenal flexure on the right. In the cat, the liver extends further caudally on the right, with the empty feline stomach located entirely on the left and the pylorus located approximately on the midline.

Changes in Position

Displacement of the liver from its normal subcostal position in the cranial abdomen is almost always due to abnormalities of the adjacent organs and structures rather than primary hepatobiliary pathology. Examples include the cranial displacement of the liver through a ruptured diaphragm and the caudal displacement of the liver due to increased thoracic volume.

Changes in Liver Size and Shape

Generalized hepatomegaly (Figure 61.2) is an increase in overall liver size, recognized on a lateral radiograph as caudal extension, and usually rounding, of the caudoventral hepatic margin beyond the costal arch, together with caudal displacement and anticlockwise rotation of the gastric axis.

Localized hepatomegaly (Figure 61.3) is usually more challenging to identify and in some cases may be difficult to differentiate from diffuse hepatic enlargement.

Lesions bulging from the surface of the liver will cause distortion of the normally smooth hepatic margins and are most easily recognized where they bulge from the ventral or caudal hepatic surfaces. Asymmetric displacement of organs caudal to the liver may be seen in patients with large unilateral lesions: a left-sided liver mass may cause caudal displacement of the stomach and spleen, while a right-sided mass may cause caudal displacement of the right kidney, pylorus and proximal duodenum, together with displacement of the stomach across to the left.

A small liver (*microhepatica*) (Figure 61.4) is usually completely contained within the costal arch and is recognized by cranial displacement of the stomach and clockwise rotation of the gastric axis.

An apparently small liver is often a normal finding in deep-chested dogs and may be difficult to differentiate from genuine microhepatica.

Changes in Opacity

Hepatobiliary mineralization is uncommon. Focal or multifocal mineralized areas are occasionally seen due to dystrophic mineralization of chronic parenchymal disease (see Figure 61.3). Dystrophic mineralization of

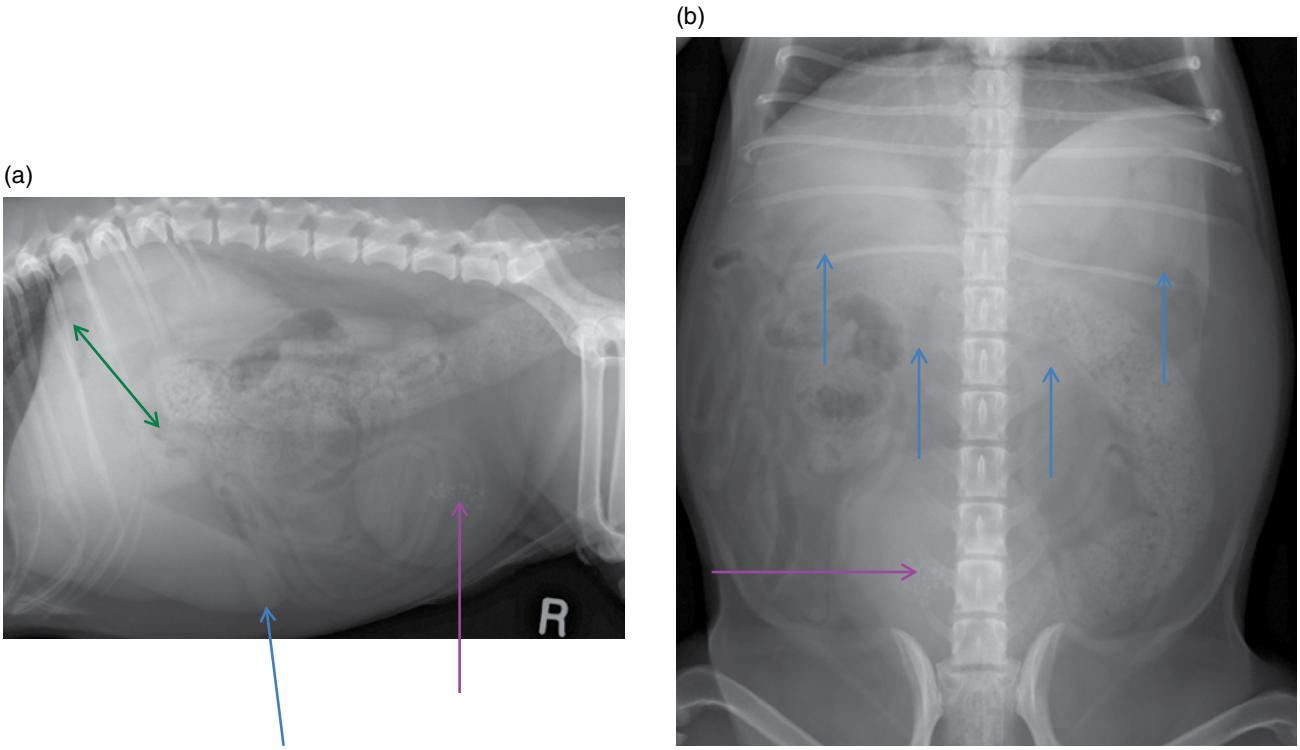


Figure 61.2 (a) Right lateral radiograph showing the abdomen of a dog with hyperadrenocorticism. An enlarged liver is identified extending well beyond the costal arch, with marked rounding of the caudoventral margin (*blue arrow*) and caudal displacement of the gastric axis (*green arrow*). Multiple radiopaque calculi are identified within this dog's urinary bladder (*pink arrow*). (b) Ventrodorsal radiograph showing the abdomen of the same dog with hyperadrenocorticism. The liver can be identified as a large soft tissue opacity occupying the cranial abdomen but the caudal hepatic margin (*blue arrows*) is poorly defined. The radiopaque calculi remain evident within the urinary bladder (*pink arrow*). *Source:* Courtesy of University of Liverpool.

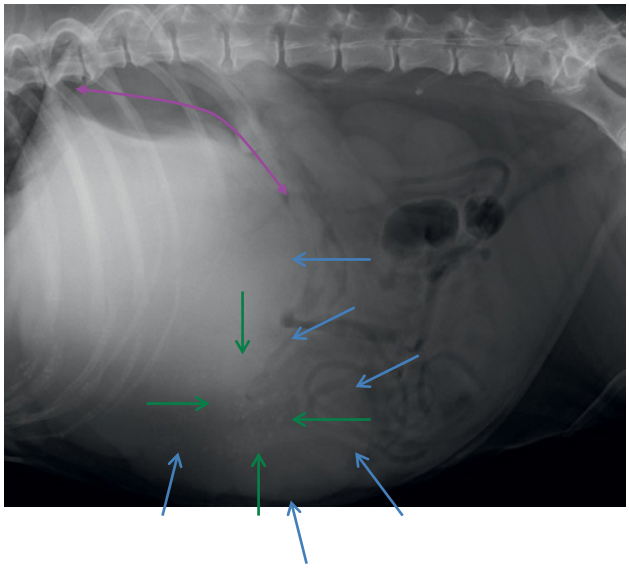


Figure 61.3 Right lateral recumbent radiography of a dog with large mass causing localized hepatomegaly. The mass bulges from the caudal aspect of the liver (*blue arrows*), displacing and compressing the stomach caudodorsally (*pink arrows*). Small mineralized foci scattered throughout the caudoventral aspect of the liver are consistent with dystrophic mineralization (*green arrows*). *Source:* Courtesy of University of Liverpool.

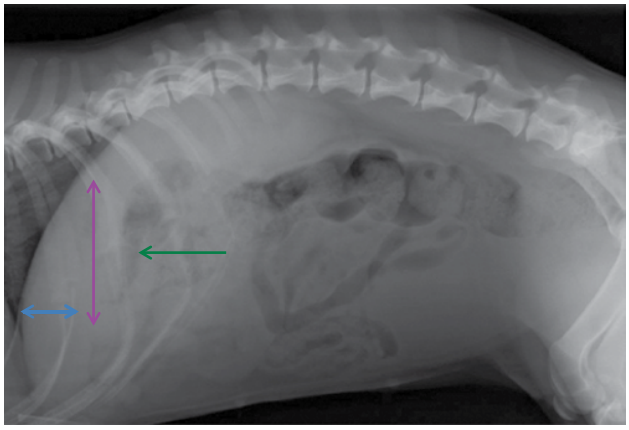


Figure 61.4 Right lateral recumbent radiograph of a female chondrodystrophic dog with microhepatica. A small liver (*blue arrow*) is identified with a very upright stomach axis (*pink arrow*) and a very cranially located transverse colon (*green arrow*). This patient is in poor body condition, with reduced serosal detail due to a lack of mesenteric fat. *Source:* Courtesy of University of Bristol.

the gallbladder wall may be recognized as fine curvilinear mineralization and choleliths are typically seen as multiple small mineralized opacities superimposed on the right cranioventral liver. Branching mineralization is occasionally recognized as an apparently incidental finding in older terrier dogs. The identification of gas opacity within the liver is even less common but may be seen as streaks or patches of gas opacity (e.g., in patients with emphysematous cholecystitis or abscessation) or as branching lucencies due to gas migrating throughout the biliary tree (e.g., due to emphysematous cholecystitis) or, very rarely, throughout the portal venous system.

Changes in Margination

Clearly defined ventral and caudoventral hepatic margins rely on the presence of abdominal fat highlighting the soft tissue opacity of the liver; loss of this clear margination may be seen in patients with ascites and in very young or emaciated patients.

Hepatobiliary Ultrasonography

Ultrasound Technique

The location of the liver within the costal arch limits the availability of acoustic windows from which the liver can be evaluated without interference from the ribcage. The use of a transducer with a relatively small contact area is therefore recommended; a curvilinear or microconvex probe operating at frequencies of 5–12 MHz is ideal, with the higher frequencies being used for cats and small-to-medium dogs and the lower frequencies for large- and giant-breed dogs.

Careful patient preparation is important in optimizing image quality. An overnight fast is strongly recommended, as the presence of gas and ingesta within the stomach lumen often reflects and/or attenuates the sound waves, hindering detailed examination. Although not always necessary, sedation will usually facilitate an easier and more thorough examination, especially in deep-chested or tense patients who may resent the firm pressure of an ultrasound probe around their ribcage. A clipped area extending cranially to the level of the xiphisternum and extending dorsally two-thirds of the way up the abdominal wall on either side is required, together with the generous application and reapplication of ultrasound gel to optimize acoustic transmission.

The liver is fixed within the costal arch by a number of ligamentous attachments. This fixed location facilitates a systematic approach to the ultrasound examination. In cats and small-to-medium dogs, it is often possible to examine the entire liver from a subcostal window, usually with the patient in right lateral or dorsal recumbency: the ultrasound probe is placed in the midline just caudal to the xiphisternum and the ultrasound beam is "swept" through the liver in both sagittal and transverse planes. In patients where the liver lies well within the costal margins (typically deep-chested patients and those with a small liver), it can be challenging to get a good image from a subcostal window, and it is often easier to examine each side of the liver by obtaining dorsal and transverse plane images through the adjacent intercostal spaces. The gallbladder, common bile duct, and caudal vena cava all lie to the right of midline; for this reason, evaluation of the biliary tract and screening for possible portosystemic shunts are often performed with the transducer positioned on the right side, either just caudal to the costal arch or within the caudal intercostal spaces.

Recognizing Artifacts

Several artifacts are commonly encountered during hepatic ultrasound. The "mirror-image" artifact (Figure 61.5) is seen as a reflection of the liver beyond the diaphragm, and is caused by the highly reflective interface between the liver and lung. "Acoustic enhancement" is caused by the fact that fluid results in less attenuation of the ultrasound beam than soft tissues, and is recognized as the tissues deep to a fluid-filled structure, such as the gallbladder, appearing artificially echogenic relative to the adjacent tissues.

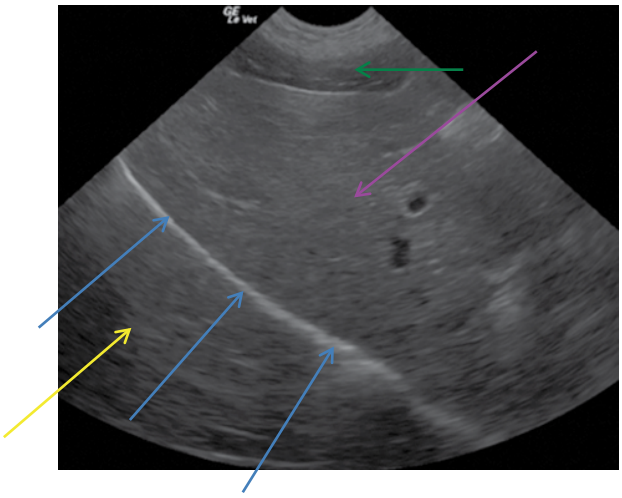


Figure 61.5 A sagittal plane ultrasound image of a normal canine liver. The diaphragm is seen as a curved hyperechoic line (*blue arrows*) demarcating the cranial hepatic margin. The normal hepatic parenchyma (*pink arrow*) is of medium echogenicity with a coarse but even echotexture. In the near field, the ventral border of the liver is separated from the coarser appearing falciform fat (*green arrow*) by a fine hyperechoic line representing the hepatic capsule. A "mirror-image" of the liver is seen beyond the diaphragm (*yellow arrow*).

"Acoustic shadowing" occurs when highly attenuating structures (such as bone and calculi) leave the deeper tissues relatively devoid of echoes, appearing artificially hypoechoic or anechoic. In the normal liver, acoustic shadowing may be recognized deep to the ribs when scanning through an intercostal space. "Reverberation" is recognized as a closely spaced series of parallel hyperechoic bands running across the screen and is caused by sound waves reverberating between the transducer and a very reflective gas interface. When examining the liver, this artifact is most frequently identified deep to a gas-filled stomach.

Ultrasound Evaluation

A consistent, logical approach to ultrasound evaluation is recommended, with an initial assessment being made of the position, size, and shape of the liver, followed by more detailed evaluation of the parenchymal structure, vasculature, biliary system, and lymph nodes.

The *position* of the liver is most easily evaluated relative to the position of the surrounding organs. The diaphragm should be seen as a curved hyperechoic line on the cranial aspect of the liver, demarcating the interface between liver and air-filled lung, with a mirror-image artifact sometimes seen beyond the diaphragm. Caudally, the normal liver is in contact with the spleen on the left, the stomach centrally and the right kidney on the right. Changes in position are more commonly encountered due to changes in the adjacent organs or structures (e.g., rupture of the diaphragm) than due to abnormalities of the liver itself.

Although radiography is usually more useful in evaluating the overall *size* and *shape* of the liver, caudal extension of the liver beyond the costal arch and rounding of the normally sharply pointed caudoventral margin in patients with generalized hepatomegaly may also be identified on ultrasound. Localized hepatomegaly is usually easier to identify with ultrasound than with radiography, and is recognized by distortion and/or bulging of the hepatic margins, often together with a localized change in the appearance of the hepatic parenchyma.

Parenchymal Structure

The normal liver (see Figure 61.5) is of medium echogenicity with a slightly coarse but uniform echotexture, interrupted only by the hepatic vasculature and gallbladder. Although the hepatic margins are generally well defined, the liver lobes are not usually individually identified unless they are separated out by the presence of free abdominal fluid. The liver is bordered on the ventral aspect by variable amounts of falciform fat. This fat is coarser in appearance than the normal hepatic parenchyma and is usually demarcated from the liver by the fine hyperechoic line of the hepatic capsule; however, in some patients the demarcation between fat and liver is not as clear and the falciform fat may be misdiagnosed as hepatomegaly.

Biliary System

The normal gallbladder is seen just to the right of midline as a rounded fluid-filled structure with a thin well-defined echogenic wall. Normal gallbladder size varies widely and is larger in fasted or anorexic patients. The normal gallbladder wall measures up to 1 mm across in cats and up to 2–3 mm in dogs. Gallbladder sludge is a common and often incidental finding, recognized as echogenic, non-shadowing material settled dependently within the gallbladder lumen. The normal intrahepatic biliary tree cannot be identified, although in some patients, especially cats, it is possible to identify the normal common bile duct leaving the porta hepatis ventral to the hepatic portal vein and entering the proximal duodenum at the major duodenal papilla.

Vasculature

Normal hepatic arteries are not identified on ultrasound. The hepatic portal vein enters the liver at the porta hepatis before branching into left and right portal veins and arborizing throughout the liver. The portal vasculature is seen as branching, tapering anechoic tubes with characteristically echogenic walls. The caudal cava enters the liver dorsal to the portal vein, receiving venous drainage via the hepatic veins as it crosses the right side of the liver. Unlike the portal veins, the walls of the hepatic veins cannot usually be seen.

Hepatic Lymph Nodes

The hepatic and splenic lymph nodes receive the majority of lymphatic drainage from the liver and are located respectively at the porta hepatis and along the course of the splenic vein. The normal lymph nodes are small, ovoid, isoechoic to the surrounding mesentery and usually not identified. Enlarged lymph nodes are typically hypoechoic and rounded or irregular.

Imaging Features of Hepatobiliary Disease

Parenchymal Disease

Conditions classified as parenchymal disorders include vacuolar diseases (e.g., steroid hepatopathy, hepatic lipidosis), amyloidosis, acute and chronic hepatitis, cirrhosis, hepatic abscessation, granulomatous disease, and hepatic necrosis (e.g., due to toxic, ischemic or immune-mediated disease).

The radiologic assessment of hepatic parenchymal disease is limited to the evaluation of overall hepatic size and shape; ultrasound assessment provides additional valuable information about parenchymal echotexture and echogenicity and is therefore more sensitive in the detection of parenchymal abnormalities. Hepatic parenchymal disease may be described as diffuse, focal or multifocal, depending on the distribution of changes identified on ultrasound.

Diffuse Parenchymal Disease

Diffuse parenchymal pathology is usually due to generalized infiltrative disease, typically affecting all liver lobes. Unless the disease process results in a fairly marked change in liver size and/or shape, the liver may appear normal on abdominal radiographs. However, in many cases, changes in hepatic echogenicity and/or echotexture can be identified on ultrasound.

Accurate evaluation of hepatic echogenicity is challenging, as apparent echogenicity is influenced by machine settings and transducer choice; this makes the identification of uniform alterations in hepatic echogenicity especially difficult. Comparison of the liver with adjacent organs imaged at the same depth is useful: the normal canine liver is coarser than and hypoechoic to the spleen, but usually isoechoic, or slightly hyperechoic, to the kidneys. A diffusely hyperechoic liver is likely to be similar in echogenicity to the spleen, with decreased contrast between abnormally hyperechoic parenchyma and the hyperechoic portal vessel walls blurring the normally clear definition of these walls. A diffusely hypoechoic liver may be recognized by the unusual prominence of the portal vessel walls, which become highlighted by the abnormally hypoechoic background. Diffuse parenchymal disease may also be seen as an abnormally heterogenous liver of mixed hyper- and hypoechogenicity. This can be difficult to differentiate from a poorly defined multifocal disease process. It is also important to remember that it is possible for significant infiltrative disease to be present without any obvious abnormalities identified on ultrasound examination. Due to the nonspecific nature of the imaging findings, cytologic and/or histopathologic evaluation of tissue will almost always be required to provide a definitive diagnosis.

Vacuolar Disease

Vacuolar hepatopathy (Figure 61.6) is most commonly associated with steroid hepatopathy and hepatic lipidosis.

The liver typically appears diffusely enlarged, with caudal extension of a rounded caudoventral hepatic margin recognized on both abdominal radiography and ultrasound. On ultrasound, the liver is typically hyperechoic and hyperattenuating, with increased attenuation of the ultrasound waves as they pass into the patient resulting in the deeper areas of the liver appearing unexpectedly dark relative to the more superficial areas.

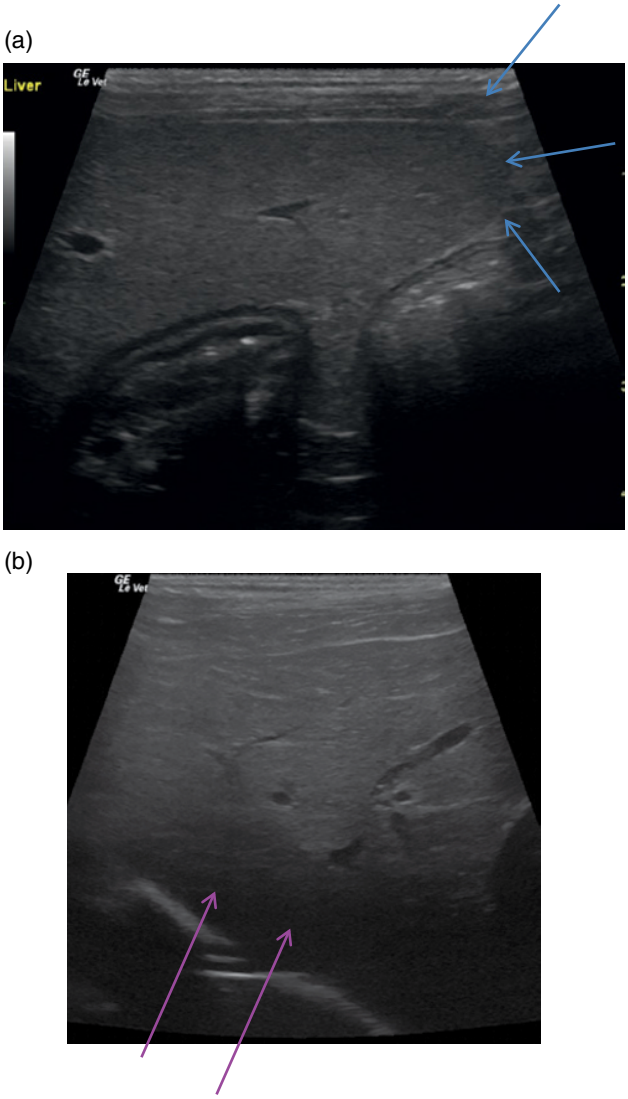


Figure 61.6 Sagittal plane ultrasound images showing the liver of a patient with vacuolar hepatopathy secondary to hyperadrenocorticism. (a) Marked rounding of the caudoventral hepatic margin (*blue arrows*). (b) Hyperattenuation of the hepatic parenchyma, with the deeper areas of the liver appearing unexpectedly hypoechoic (*pink arrows*).

Amyloidosis

Amyloidosis may cause hepatomegaly, with diffusely heterogenous hepatic parenchyma characterized by mixed hyperechoic and hypoechoic foci described in cats. Spontaneous hepatic rupture may occur in patients with severe amyloidosis, resulting in hemabdomen. This would be recognized on abdominal radiographs as loss

of normal serosal detail and on ultrasound as the presence of free abdominal fluid. A breed predisposition to amyloidosis is reported in Shar Peis, Abyssinian and Siamese cats.

Acute Hepatitis

Although acute hepatitis may cause diffuse hepatic enlargement, this is often not obvious on abdominal radiography or ultrasound. A diffusely hypoechoic liver with unusually prominent portal vessel walls may be recognized but in some patients the liver may appear ultrasonographically unremarkable. In cats, there may be evidence of concurrent biliary tract disease (see later).

Chronic Hepatitis and Cirrhosis

Chronic hepatitis (Figure 61.7) is usually associated with a mixed pattern of hepatic fibrosis, inflammation, and hyperplasia; this appears on ultrasound as heterogenous hepatic parenchyma of mixed echogenicity.

Cirrhosis is the end-stage of chronic hepatitis; a small, irregularly marginated liver may be identified on both abdominal radiography and ultrasound; extensive hepatic fibrosis may result in diffusely increased hepatic echogenicity, often with hypoechoic regenerative nodules scattered throughout the parenchyma and bulging from the hepatic margins. Portal hypertension is a common sequel to hepatic fibrosis, resulting in abdominal ascites and the development of acquired portosystemic shunts.

Hepatocutaneous Syndrome

Hepatocutaneous syndrome (Figure 61.8), also known as superficial necrolytic dermatitis, is occasionally seen in older dogs, where it is associated with ulcerative skin lesions.

The hepatic parenchymal lesions are seen as multiple hypoechoic nodules, giving the liver a "honeycomb" appearance. There are no marked changes in hepatic size or shape, making this condition impossible to diagnose from abdominal radiographs.

Focal or Multifocal Parenchymal Disease

Focal or multifocal parenchymal lesions are more easily recognized than diffuse parenchymal infiltration on ultrasound examination and are typically seen as areas of altered echogenicity and/or echotexture that are highlighted by the surrounding normal parenchyma. Large or peripheral lesions may be identified on abdominal radiographs if they result in localized hepatomegaly or distortion of the hepatic margins. The imaging features described are not specific and it is not possible to accurately differentiate the different lesions on imaging appearance alone.

Hepatic Abscesses

Hepatic abscesses are rare in cats and dogs. Although multiple lesions may be seen, solitary lesions, often at least 3 cm in diameter, are more common. On ultrasound, the typical appearance is of a rounded or irregular cavitated lesion, with a relatively echogenic and variably thick capsule around a hypoechoic central area. There

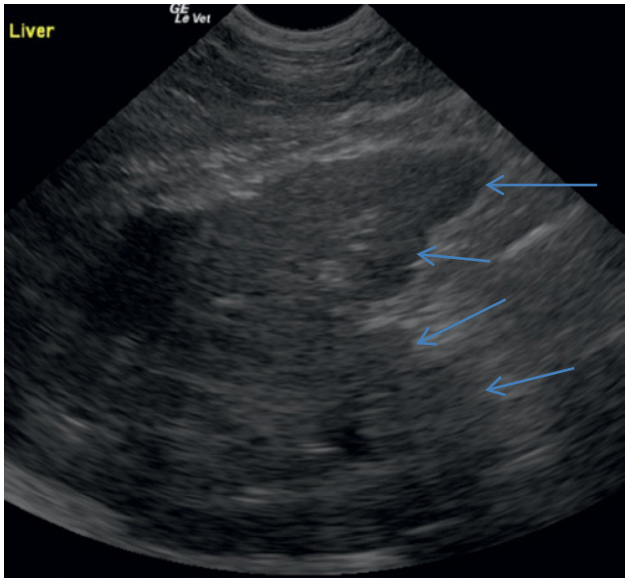


Figure 61.7 Sagittal plane ultrasound image showing the liver of a patient with chronic hepatitis. The liver is small and irregularly marginated (*blue arrows*).

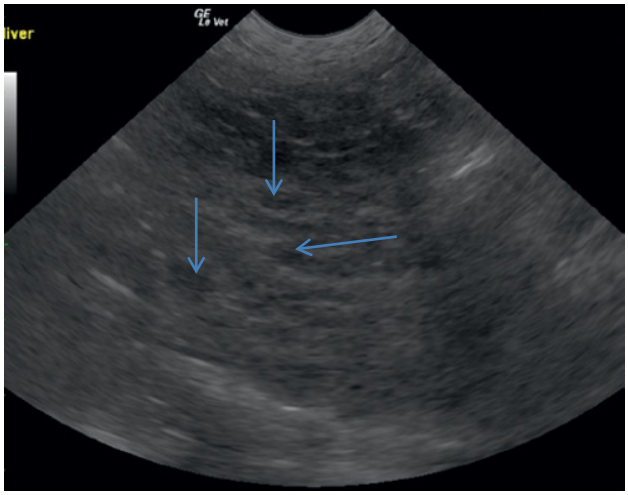


Figure 61.8 Sagittal plane ultrasound image showing the liver of a Cavalier King Charles spaniel presented with ulcerative skin lesions. Multiple poorly defined hypoechoic nodules are seen throughout the hepatic parenchyma (*blue arrows*); hepatocutaneous syndrome was diagnosed from a liver biopsy.

may be acoustic enhancement deep to fluid content, with occasional gas bubbles recognized as brightly echogenic foci with distal reverberation artifact. Mineralization of the abscess capsule may result in echogenic foci with distal acoustic shadowing. Most hepatic abscesses will not be radiographically apparent; however, lesions bulging from the liver surface and lesions with mineralization of the capsule and/or gas within the abscess cavity may be identified. Concurrent hepatic lymphadenopathy, abnormally hyperechoic local mesentery, and free abdominal fluid may be seen in some patients; radiographically, these features would be recognized as a progressive loss of serosal detail.

Cystic Lesions

Hepatic cysts are recognized as well-circumscribed, single or multiple, uni- or multilocular, thin-walled structures, with anechoic contents and distal acoustic enhancement. Congenital cystic diseases of the dog and cat are occasionally seen and may be associated with polycystic kidney disease. These congenital cysts typically arise from congenital dilation of the intrahepatic bile ducts, and strictly speaking should be classified as a biliary disorder. Differential diagnoses include parasitic cysts, focal areas of necrosis, and cystic tumors (e.g., biliary cystadenoma). Cystic lesions that do not distort the hepatic margins will not be recognized on abdominal radiographs.

Hepatic Granulomas and Hematomas

Hepatic granulomas and hematomas are uncommon. Granulomas are occasionally identified in association with *Mycobacterium tuberculosis*, fungal diseases, migrating parasites and, in cats, feline infectious peritonitis. They are usually multifocal and typically appear hyperechoic and well marginated on ultrasound. Abdominal radiographs are often unremarkable but may occasionally show evidence of dystrophic mineralization, with hepatomegaly and possible distortion of the normally smooth hepatic margins seen in patients with extensive disease. Hematomas may be seen following trauma or biopsy procedures, typically appearing anechoic or hypoechoic on ultrasound until an echogenic clot has formed. The subsequent retraction and lysis of the clot results in a variable pattern of mixed echogenicity whose appearance cannot be differentiated from an abscess or necrotic tumor.

Liver Lobe Torsion

Liver lobe torsion is a rare cause of acute abdominal pain and abdominal effusion in the dog. On ultrasound, the affected lobe is typically seen as a hypoechoic mass, often surrounded by free fluid, with color Doppler demonstrating reduced or no blood flow into the area. A loss of serosal detail will be seen on abdominal radiographs due to the presence of free fluid. Depending on the volume of fluid, it may also be possible to appreciate alteration of the normal hepatic shape.

Neoplastic Disease

The WSAVA classification of neoplastic disorders includes primary neoplasia, usually arising from the hepatocytes (hepatocellular adenoma/carcinoma) and/or the biliary system (e.g. cholangiocellular adenoma/carcinoma), primary vascular neoplasia (most commonly hemanigosarcoma), diffusely infiltrative hematopoietic neoplasia (e.g., lymphoma, malignant histiocytosis, and malignant mastocytosis) and metastatic neoplasia. Although benign, nodular hyperplasia, commonly seen in older dogs but less frequently identified in cats, is also included in the classification of neoplastic disease.

Primary Focal Neoplasia

Primary liver tumors arising from the hepatocytes or the biliary system are typically seen as focal, or occasionally multifocal, masses. A wide variety of imaging features may be recognized and it is not possible to differentiate between benign and malignant lesions or between tumor types based on imaging appearance. On ultrasound, lesions are variably well defined and vary in size, shape, and echogenicity (Figure 61.9).

Biliary cystadenomas are uncommon benign tumors of older cats. These lesions, which have a wide range of possible sizes and may be solitary or multifocal, are characterized by the presence of a variable cystic component (Figure 61.10).

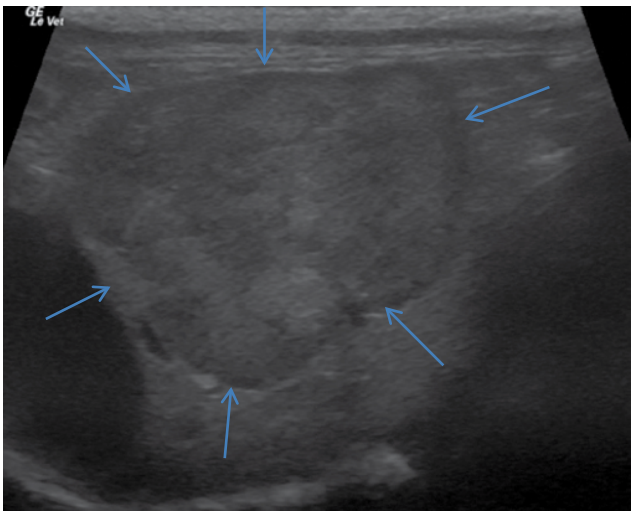


Figure 61.9 Sagittal plane ultrasound image demonstrating a well-defined heterogenous mass in a 10-year-old FN DSH (*blue arrows*). The cytologic diagnosis was hepatocellular carcinoma.

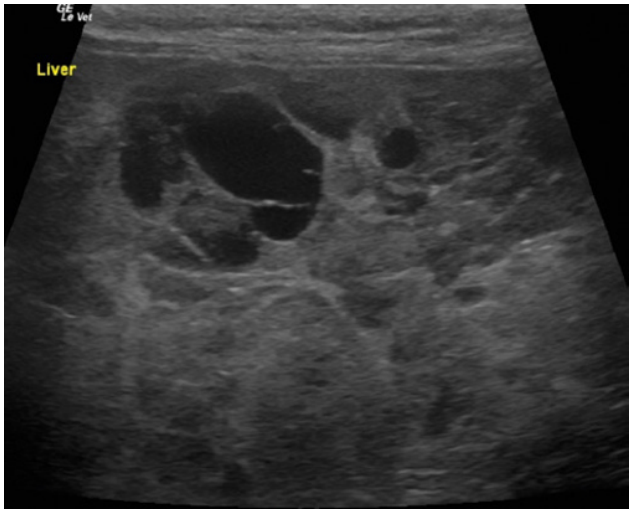


Figure 61.10 Sagittal plane ultrasound image showing a multiloculated cystic hepatic lesion diagnosed as a biliary cystadenoma in a 12-year-old FN DSH.

Hepatic hemangiosarcomas often also have a cystic component and, in cases of rupture, will be accompanied by the presence of free abdominal fluid. Liver tumors will only be recognized radiographically where they cause localized hepatomegaly and/or distortion of the normal hepatic shape (see Figure 61.3). The oral administration of barium may be useful in determining the location of the gastric axis in cases with suspected localized hepatomegaly. Pedunculated liver tumors can be confusing and may be seen as a cranioventral soft tissue abdominal mass, which is not obviously connected to the liver. In patients with tumor rupture and subsequent hemoperitoneum, abdominal radiographs will show loss of serosal detail.

Infiltrative Neoplasia

Lymphoma, histiocytic tumors, and mast cell tumors are typically diffusely infiltrative. On ultrasound, these tumors are most commonly recognized as diffusely hypoechoic or heterogenous hepatic parenchyma, or as multifocal parenchymal nodules or masses. Less commonly, the hepatic parenchyma appears diffusely hyperechoic or, occasionally, ultrasonographically normal. Evaluation of the area around the porta hepatis is important for the identification of hepatic lymphadenopathy, which is often identified in association with infiltrative hepatic neoplasia. Diffuse neoplastic infiltration often results in generalized hepatomegaly, which may be apparent on abdominal radiographs.

Metastatic Neoplasia

Metastatic hepatic disease is most likely to be recognized on ultrasound as multifocal nodules or masses. Although a wide variety of imaging features may be seen, the identification of "target lesions," seen as hypoechoic nodules with a hyperechoic center, is commonly associated with (but not pathognomonic for) metastasis (Figure 61.11).

An important differential diagnosis for multifocal nodules is benign nodular hyperplasia. Unless the metastatic lesions are large enough to cause localized or generalized hepatomegaly, metastatic hepatic disease is unlikely to be identified on abdominal radiographs.

Benign Nodular Hyperplasia

Benign nodular hyperplasia, also referred to as regenerative nodular hyperplasia, appears on ultrasound as multiple nodules of variable size, shape, echogenicity, and definition. It is not possible to distinguish between benign nodular hyperplasia and primary or metastatic neoplasia from the ultrasound appearance. Mild generalized hepatomegaly may occasionally be radiographically apparent in patients with benign nodular hyperplasia.

Disease of the Biliary System

Important disorders of the biliary tract include cholestasis, due to either primary liver disease or obstruction of the (usually extrahepatic) biliary tract, and cholangitis (most commonly neutrophilic or lymphocytic). Diseases affecting the gallbladder include gallbladder mucoceles and cholecystitis (frequently seen in cats, sometimes in association with neutrophilic cholangitis).

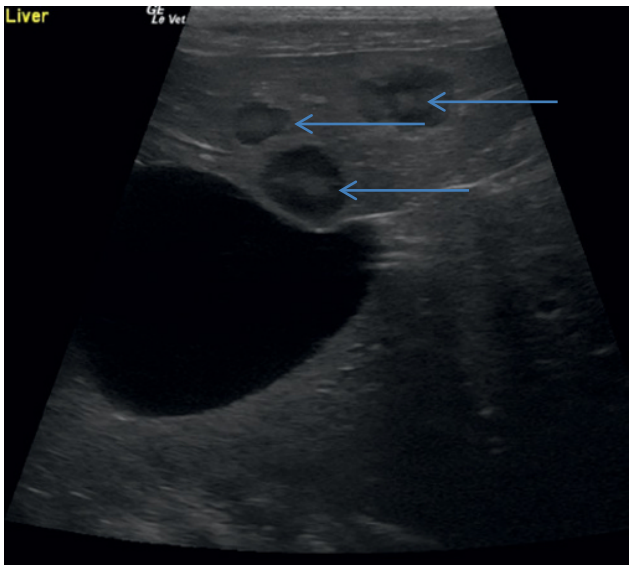


Figure 61.11 Sagittal plane ultrasound images showing target lesions (*blue arrows*) consistent with metastatic liver disease in a 9-year-old JRT with an insulinoma.

Extrahepatic Cholestasis

Causes of extrahepatic biliary obstruction (EHBO) include inflammation or neoplasia of the common bile duct, pancreas or duodenum and obstruction of the duct lumen by choleliths (choledocholithiasis). Dilation of the common bile duct (>5 mm in cats and >4 mm in dogs) is the most consistent ultrasound finding in acute EHBO (Figure 61.12).

Dilation of the extrahepatic and intrahepatic bile ducts may be seen in patients with obstruction of at least 5–7 days duration; these dilated ducts are recognized as the presence of multiple slightly tortuous anechoic tubes with hyperechoic walls, which do not show any evidence of flow on Doppler. Dilation of the gallbladder is an inconsistent finding and the absence of a distended gallbladder does not exclude the possibility of EHBO. Detailed evaluation of the common bile duct is required to identify possible causes of obstruction; obstructive choleliths are most commonly located in the distal common bile duct, highlighted by the dilated bile duct proximal to the obstruction, with an empty bile duct seen distally. In patients with inflammatory or neoplastic disease, an extraluminal mass may be identified causing obstruction; however, it is not possible to determine the nature of the mass (inflammatory or neoplastic) from the ultrasound appearance. Although mineralized choleliths may be identified on abdominal radiographs, EHBO will not be seen.

Cholangitis

Inflammatory liver disease is classified according to the histopathologic features of the disease. Neutrophilic and lymphocytic cholangitis are both commonly diagnosed in cats, but less frequently reported in dogs. On ultrasound, cholangitis is most commonly recognized as diffusely hypoechoic hepatic parenchyma, which highlights the echogenic walls of the portal vasculature (Figure 61.13).

These changes are nonspecific, and it is not possible to make a definitive diagnosis or to distinguish between neutrophilic and lymphocytic disease without tissue sampling. Cholangitis cannot be diagnosed from abdominal radiographs. Concurrent cholecystitis (see later) is identified in a significant number of cats and occasionally dogs with cholangitis.

Gallbladder Mucocele

Gallbladder mucoceles occur in dogs and are caused by an abnormal accumulation of inspissated mucus and bile within the gallbladder lumen, leading to progressive luminal distension and potentially to necrosis and ultimately rupture of the gallbladder wall. Typical mucoceles have a distinctive ultrasound appearance, described as "kiwi-like" or "stellate," with immobile hyperechoic striations seen radiating from a central point (Figure 61.14).

Variations in the appearance include a "mosaic-like" pattern of mixed echogenicity; unlike gallbladder sludge, which is a common and often incidental finding, the contents of a gallbladder mucocele are immobile and do not move with gravity when the patient changes position. Gallbladder wall thickness is variable, although inflammation and/or necrosis may result in wall thickening. Gallbladder rupture may be recognized as discontinuity within the gallbladder wall, together with a localized

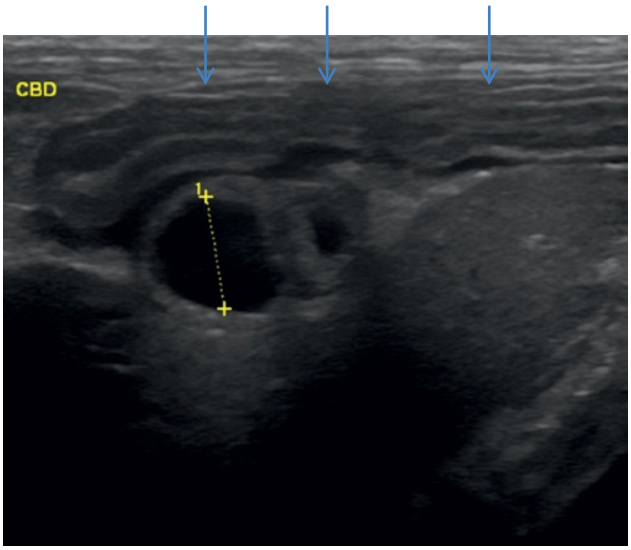


Figure 61.12 Ultrasound image of a 14-year-old MN Siamese showing moderate dilation (7 mm) of the distal common bile duct (*yellow cursors*) just proximal to its termination. The duodenum is seen in the near field of the image (*blue arrows*).

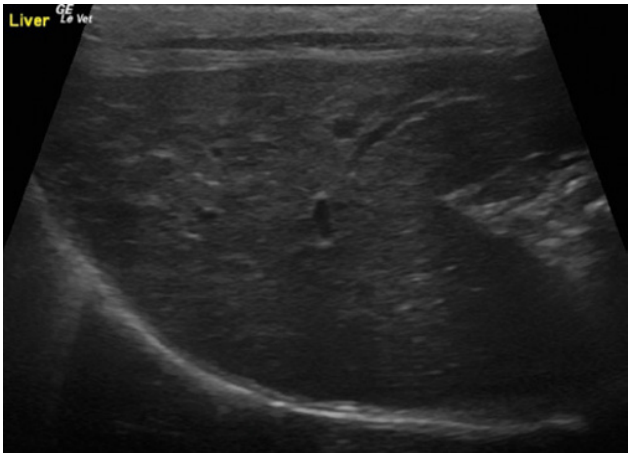


Figure 61.13 Sagittal plane ultrasound image showing the liver of a jaundiced 11-year-old MN DSH. The diffusely hypoechoic hepatic parenchyma highlights the echogenic walls of the portal vasculature. A histopathologic diagnosis of neutrophilic cholangitis was made on examination of an ultrasound-guided tissue-core biopsy.

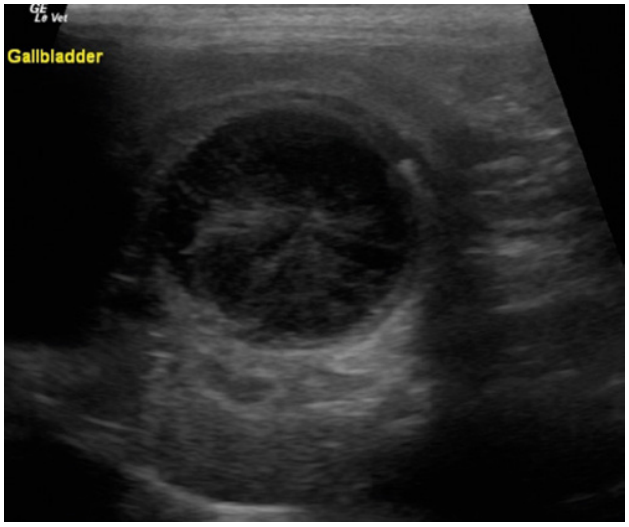


Figure 61.14 Ultrasound image showing the typical "kiwi-like" appearance of a gallbladder mucocele in a 5-year-old FN Chihuahua.

collection of free fluid and abnormally hyperechoic fat around the periphery of the gallbladder.

Cholecystitis

Cholecystitis is more commonly identified in cats than dogs, and is usually associated with bacterial infection. Typical ultrasound features of acute cholecystitis include gallbladder wall thickening (Figure 61.15) (>1 mm in cats, >2–3 mm in dogs), together with thickening of the wall of the common bile duct.

The thickened gallbladder wall may be diffusely hyperechoic or may have a layered appearance, with a hypoechoic central layer sandwiched between hyperechoic layers. Differential diagnoses for gallbladder wall thickening include acute cholecystitis, edema (e.g., in patients with hypoalbuminemia or portal hypertension), cystic mucinous hyperplasia and, rarely, neoplasia. Although commonly considered to be an incidental finding, biliary sludge, sludge balls, and choleliths may be associated with cholecystitis, especially in cats. Biliary sludge is recognized as mobile echogenic nonshadowing debris within the gallbladder lumen. Sludge balls are mobile, rounded, echogenic, nonshadowing luminal structures composed of thick bile. Choleliths are seen as hyperechoic foci of variable size, shape, and number, often casting an acoustic shadow. Ultrasound-guided aspiration of bile (cholecystocentesis) is useful in providing material for bacterial culture in patients with suspected cholecystitis.

Radiographic abnormalities associated with cholecystitis are unusual; however, choleliths may occasionally be identified as small mineralized foci in the area of the gallbladder and/or common bile duct and, rarely, patches

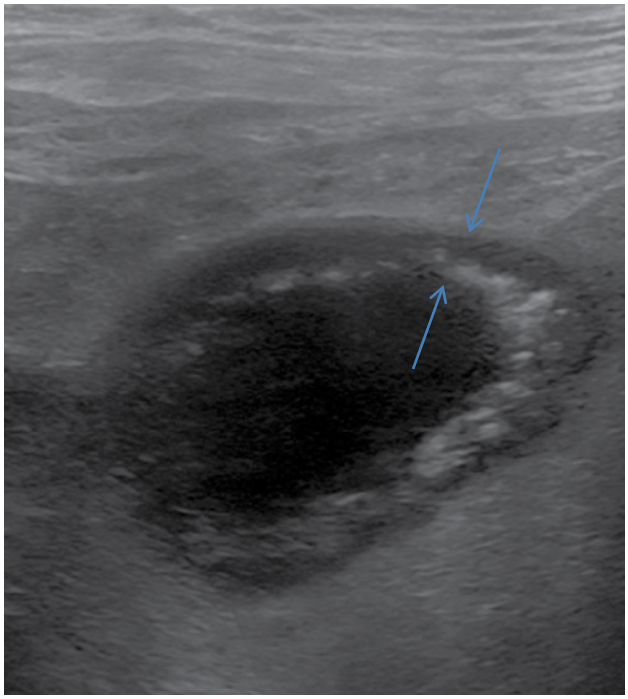


Figure 61.15 Ultrasound image showing thickening of the gallbladder wall (*blue arrows*) in a 10-year-old ME cross-bred dog diagnosed with cholecystitis.

and streaks of gas opacity may be seen in patients with emphysematous cholecystitis.

Hepatic Vascular Disorders

The largest group of hepatic vascular disorders consists of the circulatory disorders, which are subdivided into congenital portosystemic shunts, hepatic congestion due to outflow disturbances, and disorders due to portal hypertension. Other vascular disorders include peliosis hepatis and portal vein thrombophlebitis.

Congenital Portosystemic Shunts (CPSS)

Congenital portosystemic shunting occurs due to an anomalous connection between the portal vasculature and systemic venous system, which allows blood to bypass the hepatic sinusoids. CPSS are usually described according to their location (extrahepatic or intrahepatic) and can be further classified by their anatomic configuration. Extrahepatic CPSS are most commonly identified in smaller breed dogs and in cats, while intrahepatic CPSS are most commonly identified in larger breed dogs. Although studies have demonstrated more than 90% accuracy for experienced operators, the identification of CPSS with ultrasound is challenging.

In addition to evaluating the liver from the standard subcostal acoustic window, the use of a high right dorsal

acoustic window, located just cranial to the right kidney, with the patient positioned in left lateral recumbency, is recommended for visualization of the caudal vena cava (CVC) and the hepatic portal vein (HPV) as they enter the liver; in most patients with an extrahepatic CPSS, this window allows identification of the shunting vessel itself. Subcostal, right dorsal intercostal, and left ventral intercostal windows are all recommended for evaluation of the liver in patients with a suspected intrahepatic CPSS. In anesthetized patients with a very small liver, positive pressure ventilation may be useful in improving visualization by displacing the liver caudally. Although not essential, color and spectral Doppler allow the determination of flow direction, the identification of turbulence and the measurement of hepatic portal velocity, and are therefore very useful in the ultrasound assessment of patients with suspected CPSS.

The majority of extrahepatic CPSS in dogs originate from the splenic or left gastric veins and terminate in the caudal vena cava (usually at the level of the epiploic foramen), the left phrenic vein (at the level of the oesophageal hiatus) or, less commonly, in the azygos vein. In cats, portocaval shunting via the left gastric vein is most frequently reported but cats also appear to have a higher incidence of more unusual shunting loops, which may arise caudal to the confluence of the mesenteric veins. Regardless of the precise anatomy, the ultrasound appearance of an extrahepatic CPSS is usually of a relatively short, dilated and sometimes tortuous vessel, diverting blood away from the hepatic portal vein (Figure 61.16).

Comparison of the diameter of the portal vein at the porta hepatis with the diameter of the aorta and caudal vena cava at the same level is very useful; a portal vein:aortic ratio ≤0.65 is predictive for the presence of an extrahepatic shunt. Conversely, an extrahepatic shunt is considered unlikely with a portal vein:aortic ratio >0.8 and a portal vein:caval ratio >0.75.

Intrahepatic CPSS may be classified as left, central or right divisional. The left divisional shunt, which represents a patent ductus venosus and joins the left portal branch to the intrahepatic caudal vena cava, is the most common (Figure 61.17).

Both right and central divisional shunts arise from the right portal branch; right divisional shunts are long shunts, whereas the central divisional shunt is usually a short aneurysm-like dilation joining the right portal branch with the intrahepatic caudal vena cava.

Microhepatica is common in dogs with both extrahepatic and intrahepatic CPSS, but is less commonly reported in cats. Urolithiasis and mild renomegaly are also fairly common in dogs, but infrequently identified in cats.

Potential abnormalities identified on survey radiographs of patients with CPSS include microhepatica, renomegaly, and limited serosal detail due to poor body condition. In cases with portoazygos shunting, a dilated azygos vein is occasionally recognized as a soft tissue band crossing the thorax adjacent to the aorta. Although hematogenous osteomyelitis of the lumbar vertebrae has occasionally been reported in patients with CPSS, this is not a common finding. The uroliths associated with CPSS are ammonium biurate and are typically radiolucent.

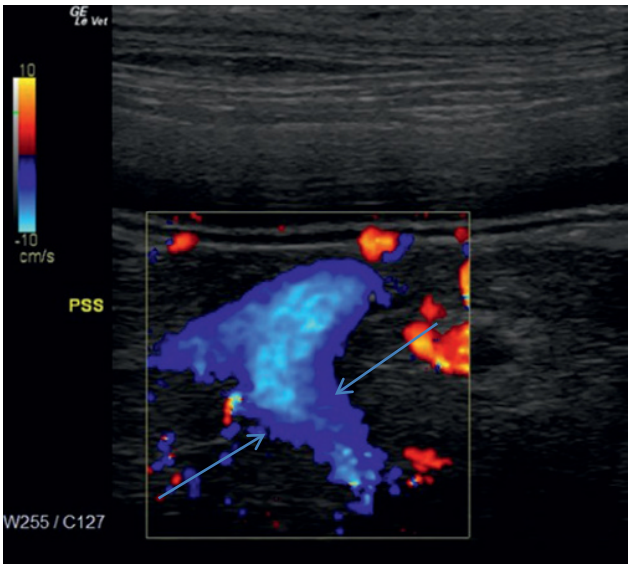


Figure 61.16 Color Doppler ultrasound image showing an extrahepatic portocaval shunt (*blue arrows*) in a 6-month-old ME Bichon × Yorkshire terrier. The blue color indicates that the direction of blood flow is away from the hepatic portal vein.

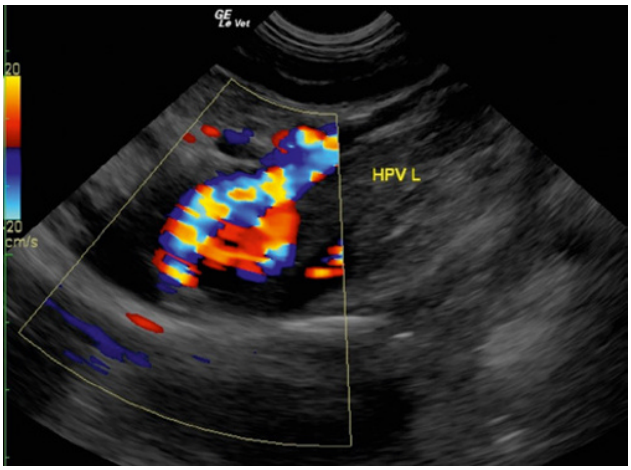


Figure 61.17 Color Doppler ultrasound image showing a left divisional intrahepatic portocaval shunt in a 6-month-old FE golden retriever. The mosaic pattern of the color Doppler indicates turbulence at the point that the shunt joins the intrahepatic caudal vena cava.

Historically, mesenteric portovenography was widely used for the definitive confirmation of a suspected portosystemic shunt and for the differentiation between intra and extrahepatic shunts. The most popular technique for portovenography is the intravenous injection of nonionic iodinated contrast media through a catheter preplaced into a mesenteric vein. This involves a laparotomy and is an invasive procedure. Alternative and potentially less invasive, but less commonly used, techniques for contrast administration include percutaneous ultrasound-guided catheterization of the splenic vein, catheterization of the cranial mesenteric artery via the femoral artery and transvenous retrograde portography. In many cases, mesenteric portovenography has been superseded by contrast Computed Tomographic examination. However, during surgical occlusion of a shunt, portovenography is still used to verify that the correct vessel has been occluded, to check that there are no additional shunting vessels and to assess the degree of portal vascularization post-ligation. Fluoroscopic imaging of the contrast injection provides useful real time information (Fig 61.18): if this is not available, then standard radiographic views (ideally both lateral and VD views, each exposed at the end of a separate contrast injection) should be taken.

Hepatic Congestion

Disturbance of the normal venous outflow results in passive hepatic congestion. Causes include right-sided heart failure and obstruction or compression of the cranial part of the caudal vena cava (between the hepatic veins and right atrium), for example by thrombosis, neoplasia or inflammation. Ultrasound findings include hepatomegaly, reduced hepatic echogenicity, dilation of the hepatic veins and caudal vena cava and, in some cases, the presence of free abdominal (+/– pleural) fluid. Radiographs may show hepatomegaly and loss of serosal detail in patients with ascites, possibly with evidence of a pleural effusion and cardiomegaly in patients with right-sided heart failure.

Portal Hypertension

Chronic portal hypertension resulting in the development of portosystemic collaterals (acquired portosystemic shunts) is relatively common in dogs, but rarely identified in cats. Causes of portal hypertension include advanced chronic liver disease (cirrhosis), intrahepatic arterioportal fistulae, congenital hypoplasia of the portal vein and portal vein obstruction. Ultrasound evaluation of patients with portal hypertension will typically demonstrate ascites, often with edema of the gallbladder wall and pancreas. Spectral Doppler is useful in measuring portal velocity; the identification of reduced flow velocity (from a normal velocity of approximately 17+/-5cm/s to <10 cm/s in the dog), and occasionally reversed portal flow, is very suggestive of portal hypertension. The portosystemic collaterals open in response to sustained portal hypertension and connect the portal system directly to the systemic circulation. These acquired shunting vessels can be challenging to identify on ultra-

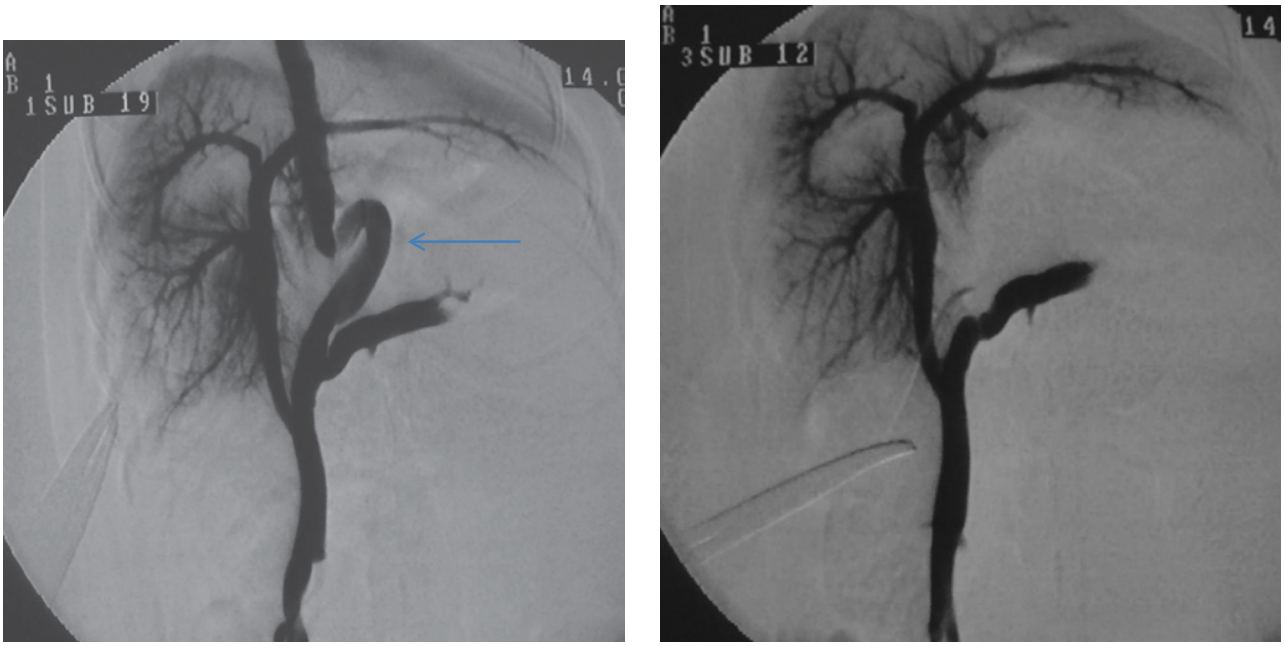


Figure 61.18 Ventrodorsal intraoperative fluoroscopic image acquired immediately after the administration of nonionic contrast medium into a mesenteric vein. The contrast highlights a left gastro-azygos extrahepatic portosystemic shunt (blue arrow). *Source:* Rob White, School of Veterinary Medicine and Science, University of Nottingham

sound; in dogs, the opening of splenorenal collaterals, with enlargement of the left gonadal vein and development of a complicated plexus of vessels adjacent to the left kidney, has been most commonly documented.

Ultrasound examination may be useful in documenting the cause of portal hypertension. A small, hyperechoic, irregular liver with multiple hypoechoic regeneration nodules may be identified in patients with *cirrhosis*. Intrahepatic *arterioportal fistulae* are direct connections between the hepatic arteries and the portal vessels. These vascular anomalies may be congenital or acquired and may be seen on ultrasound as distended, tortuous intrahepatic vessels. The high arterial pressure results in portal hypertension and dramatic ascites, with spectral Doppler demonstrating reversed, often pulsatile flow within an enlarged hepatic portal vein. *Congenital hypoplasia* of the hepatic portal vein is thought to affect both extrahepatic and intrahepatic portal vasculature and includes the condition of portal vein hypoperfusion previously referred to as microvascular dysplasia.

Although hypoplasia of the extrahepatic portal vein may be seen as a reduction in vessel diameter, the lack of objective measurement criteria makes this difficult to identify definitively. A small liver may be identified in patients with mild portal vein hypoplasia; ultrasound examination is often otherwise unremarkable. However, evidence of portal hypertension and acquired portosystemic shunting may be identified in patients with more severe changes. The most common cause of portal vein obstruction is *portal thrombosis*, which may occur secondary to hypercoagulability, vascular stasis or damage to the vascular endothelium (for example, due to local neoplasia or inflammation). Portal thrombosis is recognized as an intraluminal immobile echogenic structure, with color Doppler highlighting the thrombus as filling defects in the normal pattern of flow (Figure 61.19).

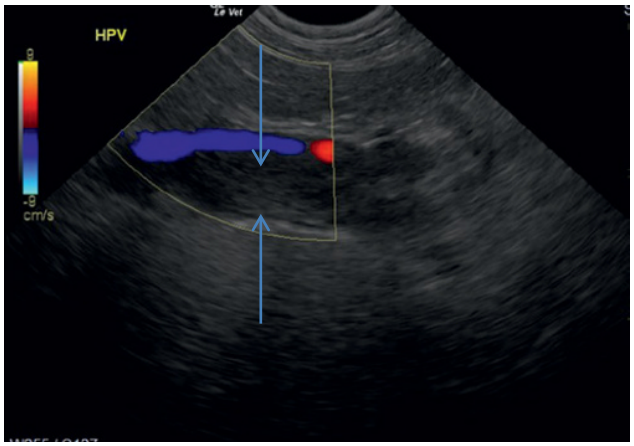


Figure 61.19 Color Doppler ultrasound image highlighting a portal thrombus as a filling defect within the hepatic portal vein (*blue arrows*).

Larger thrombi can extend from the extrahepatic portal vein into the portal branches, resulting in portal hypertension and acquired shunting.

Radiographic examination of patients with portal hypertension is often unrewarding. Many will have evidence of ascites, obscuring the serosal detail of the abdomen. In patients with chronic liver disease, it may be possible to identify microhepatica, even in the presence of ascites, by the cranial displacement and clockwise rotation of the gastric axis.

Peliosis Hepatis

Peliosis hepatis is seen as randomly distributed cystic and blood-filled spaces within the liver, thought to be formed due to either focal hepatocytic necrosis or local obstruction of small portal branches with hepatic atrophy and subsequent sinusoidal dilation. The condition is rare in dogs and more commonly identified in older cats. On ultrasound, the the abnormal sinusoidal dilation may be seen as multiple cystic lesions that may mimic vascular tumors, such as hemangioma or hemangiosarcoma.

Advanced Imaging Techniques

Contrast-Enhanced Ultrasound

Contrast-enhanced ultrasound is a non-invasive imaging technique that enables the functional assessment of organ perfusion patterns. The contrast media consist of microscopic (2–6 μm) inert gas-filled microbubbles that are injected intravenously. When subjected to ultrasound waves, these bubbles respond with a nonlinear oscillation, generating strong harmonic frequencies that can be detected using specialized transducers and dedicated contrast imaging software. In the liver, two phases of contrast enhancement may be recognized: the early phase of enhancement is equivalent to the blood pool phase and is composed of arterial (wash-in) and portal (wash-out) stages, with the enhancement peaking at the same time as peak portal blood flow (typically 15–60 seconds in dogs), and disappearing by 150–200 seconds in most dogs. This early phase allows the detection of hepatic arteries and small vessels that would not be apparent with conventional gray-scale B-mode imaging. The late phase is only recognized with contrast media that are able to leave the blood pool; this phase corresponds to intracellular contrast uptake and enables the assessment of parenchymal perfusion.

Contrast-enhanced ultrasound has been demonstrated as a safe and accurate technique for differentiating between benign and malignant liver lesions. Malignant lesions do not have a portal venous supply and are perfused only via the hepatic arterial supply. At peak

(portal) early phase enhancement, malignant nodules therefore appear show hypoenhancement in comparison to the surrounding liver, while benign nodules typically show isoenhancement or slight hyperenhancement. A similar pattern is reported during late-phase enhancement, with most malignant lesions appearing relatively hypoechoic.

Nuclear Scintigraphy

Although nuclear scintigraphy is a well-established imaging technique, its availability is limited by the strict regulation of radiopharmaceuticals. Nuclear medicine is most widely used as a very sensitive and minimally invasive technique for the diagnosis of PSS. The best documented protocol involves the per-rectal administration of ^{99m}technetium pertechnetate (^{99m}Tc), which is rapidly absorbed from the colonic mucosa. The ^{99m}Tc subsequently enters the mesenteric vessels, from where it should pass through the hepatic portal vein into the hepatic parenchyma before filtering through the hepatic microcirculation to enter the hepatic caudal vena cava and then the heart. In a patient with a PSS, the ^{99m}Tc bypasses the liver and is delivered directly to the heart. Regions of interest (ROIs) drawn over the heart and liver are used to calculate the shunt fraction by comparing the intensity of radioactive counts over the heart with the intensity of counts over the liver.

$$\text{Shunt fraction} = \frac{\text{Total heart counts over first 12 seconds}}{\left[\text{Total heart and liver counts over first 12 seconds}\right]}$$

A normal shunt fraction is less than 15%. In dogs with PSS (extra- or intrahepatic), shunt fractions of 80%+ have been reported; lower shunt fractions (approximately 50%) have been reported in cats with PSS. Unfortunately, there does not appear to be a good correlation between the calculated shunt fraction and the physical size of the shunt. Direct ultrasound-guided injection of the ^{99m}Tc into the splenic parenchymahas been described as an alternative to per-rectal administration; this results in significantly decreased radiation exposure and provides superior image quality, in many cases allowing the differentiation between single congenital and multiple acquired shunts. Although useful both in confirming the presence of a PSS and identifying the presence of continued shunting after an unsuccessful or partial surgical ligation, disadvantages of nuclear scintigraphy include the lack of specific anatomic information (especially with per-rectal scintigraphy), as well as the potential inconvenience and hazards of working with radioactive isotopes. Portal vein hypoplasia (microvascular dysplasia) will not be identified with nuclear scintigraphy.

Following the intravenous administration of the radiopharmaceutical ^{99m}Tc-mebrofenin, hepatobiliary scintigraphy may also used for the evaluation of liver function, detection of cholestasis and biliary tract obstruction, and diagnosis of cholecystitis. In the normal patient ^{99m}Tc-mebrofenin is extracted from the blood pool by the liver, with peak liver radioactivity observed 6–8 minutes after injection. The hepatic extraction fraction (HEF) is used as a measure of hepatocyte function. Following extraction by the hepatocytes, the radiopharmaceutical is excreted into the biliary tree with a half-life of 19 minutes, resulting in detectable radioactivity in the gallbladder and small intestines within one hour of injection. A prolonged clearance time indicates extrahepatic biliary obstruction and in dogs may allow the detection of abnormalities before any ultrasound changes are identified.

Computed Tomography

Computed tomography (CT) is an increasingly widely available, rapid and noninvasive diagnostic imaging technique that is especially useful in the evaluation of hepatic vascular abnormalities and hepatic mass lesions. Multidetector row CT angiography enables very detailed anatomic evaluation of the hepatic arterial, portal and venous architecture and should facilitate the identification of both intra- and extrahepatic portosystemic shunts, arterioportal fistulae, and portal vein obstruction. Using three-dimensional reconstructions, it should be possible to accurately identify and trace the hepatic portal vein and its tributaries and to accurately identify the origin and termination of both intra- and extrahepatic shunts.

In patients with hepatic masses, CT provides important information about the exact size and extension of a mass, allows identification of significant vascular involvement, and facilitates evaluation of the rest of the abdomen and the thorax for the presence of metastatic disease; this information is invaluable both in determining the feasibility of surgical resection and in planning surgical margins. More recently, the use of dynamic contrast CT in dogs has shown potential in the differentiation of benign and malignant hepatic masses.

Disadvantages of CT include its relatively limited availability, the requirement for general anesthesia, and the relatively high doses of ionizing radiation involved.

Magnetic Resonance Imaging

Contrast-enhanced magnetic resonance imaging (MRI), usually referred to as magnetic resonance angiography (MRA), is routinely used in humans for imaging the portal venous system. Although the acquisition of good-quality images is technically difficult and accurate interpretation of the images requires experience, this

technique is being successfully used in dogs and cats and can provide a rapid and accurate diagnosis with excellent anatomic resolution. In dogs with liver masses, MR imaging findings have also been successful in differentiating benign and hepatic lesions.

Image-Guided Sampling

Although diagnostic imaging provides useful information, the imaging features of canine and feline hepatobiliary disease are rarely specific for a single disease process. Despite the potential offered by newer techniques such as contrast-enhanced ultrasound, CT and MRI, in most cases it is still not possible to definitively characterize the underlying disease process or to differentiate benign from malignant disease from the imaging appearance alone. Obtaining samples of material for cytology and/or histopathology is therefore important in providing additional information and, in many cases, a definitive diagnosis.

The most commonly used image-guided sampling techniques are percutaneous ultrasound-guided aspiration and tissue-core biopsy. These well-established techniques are routinely used in dogs and cats, and are considered safe and minimally invasive. Fine needle aspiration (FNA) is cheaper, easier and has fewer potential complications than tissue-core biopsy. However, cytopathologic (FNA) and histopathologic (core biopsy) diagnoses from the same tissue do not always agree. FNAs inevitably result in disruption of the normal structural relationship between cells within a tissue and are therefore most useful in diagnosing diseases that can be identified from individual cells (e.g., lymphoma) and in differentiating between inflammatory, neoplastic, and degenerative/necrotic change. In conditions where preservation of tissue architecture is more important, for example vascular disorders and chronic hepatopathies, a tissue-core biopsy is more likely to provide useful diagnostic information.

When obtaining samples, the most important guidelines are to use the *shortest distance* and the *safest path* to reach the site of interest. The needle should not pass through more than one body cavity or more than one organ and for both FNA and tissue-core samples, it is important to visualize the needle tip as it is advanced into the tissue, keeping the entire needle length visible within the plane of the ultrasound beam. Accurate needle placement is usually easier using a curvilinear (or micro-convex) transducer. For superficial lesions, linear transducers have the advantage of superior near-field resolution, but needle placement may be more challenging. 1" or 1.5" 20–22 ga standard injection needles are most commonly used for FNA, with 2.5" or 3.5" spinal needles occasionally used for sampling deeper lesions. For tissue-core biopsies, either manual or automated biopsy devices may be used. A 14, 16 or 18 ga needle (depending on the size of the patient and of the liver) and a 2 cm tissue sample notch are usually selected. Depending on the patient's clinical status and the tissue being sampled, a coagulation profile is not usually required before obtaining FNAs; however, it is strongly recommended prior to tissue-core biopsy.

Although many conscious patients will tolerate ultrasound-guided FNAs, sedation is recommended and general anesthesia is indicated for patients undergoing tissue-core biopsy. When obtaining FNAs, the skin overlying the aspiration site should be clipped and cleaned prior to sampling; ultrasound gel can confuse the cytologic interpretation and should be avoided. For a tissue-core biopsy, aseptic preparation is required. Ultrasound gel may be used, but should be sterile.

Serious complications associated with FNAs are rare, but include hemorrhage, tumor seeding, and, following gallbladder aspiration, bile leakage and potential peritonitis. The risk of hemorrhage is increased with tissue-core biopsy; however, although small amounts of free fluid are not uncommon post biopsy, in patients with normal coagulation status any bleeding should be self-limiting.

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62

Metabolic, Toxic, and Neoplastic Diseases of the Liver

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Metabolic Diseases

The liver displays a multitude of metabolic functions, which may fail when the liver becomes diseased. The most important functions which may cause immediate clinical signs with a failing, diseased liver are bilirubin metabolism and metabolism of neurotransmitter precursors. Failing liver function may then lead to hyperbilirubinemia with icterus, and hepatic encephalopathy, respectively. Furthermore, the liver is involved in many metabolic and detoxification processes, and may therefore be the principal organ to develop secondary damage. The most important examples are secondary nonspecific (reactive) hepatitis, steroid or vacuolar hepatopathy, and hepatotoxicity of drugs such as acetaminophen, carprofen, and sulfonamides. Hepatic lipidosis (steatosis) in cats deserves specific mention, as this is the most common metabolic disorder of the liver in cats. The final group of metabolic liver diseases are the inherited metabolic diseases. Some are very frequent, such as copper storage diseases in many dog breeds, while others are rare (amyloidosis) or very rare (lipoprotein lipase deficiency, lysosomal storage diseases).

Vacuolar Hepatopathy, and Liver Changes in Cushing Disease

Etiology/Pathophysiology

Both spontaneous hyperadrenocorticism (Cushing disease) and the administration of glucocorticoids cause specific abnormalities in the liver. A similar hepatic change may occur without any known cause. There is glycogen accumulation in the hepatocytes that results in large vacuoles (ballooning). This leads to varying degrees of hepatomegaly. These changes can cause elevation of the plasma levels of liver enzymes, mainly alkaline phosphatase (ALP), and bile acids. Alanine aminotransferase (ALT) may be elevated but usually much less than the cholestasis indicators. Increased ALP is caused not only by hepatocellular damage but also by induction of an isoenzyme of ALP by glucocorticoids.

History and Clinical Signs

The clinical signs are those of Cushing disease if this is the underlying cause. Steroid hormones other than cortisol may also cause these liver effects. The above-mentioned changes in the liver can result in hepatomegaly, which may be detectable by abdominal palpation. The histologic changes occur long before signs suggestive of Cushing disease, as do the elevations of ALP and ALT. It is important to remember that a number of signs that occur in Cushing disease also occur in primary liver diseases: lethargy, exercise intolerance, polydipsia, hepatomegaly, and elevated ALP, ALT, and bile acids.

Diagnosis

It is important to know whether elevated liver enzyme levels and bile acids are due to exogenous corticosteroid use or Cushing disease. The typical liver changes can always be determined by histologic examination of a liver biopsy; the histologic changes are specific. These diffuse changes are also detectable in cytologic smears taken by way of fine needle aspiration. The corticosteroid-induced ALP isoenzyme can be distinguished because most of it is still active after heating the plasma to 65° for 2 minutes. Readers are referred elsewhere for discussions on the diagnosis and management of Cushing disease.

Therapy

The glucocorticoid-induced changes in the liver are reversible within a few weeks to months after removing the cause. However, in other cases, the prognosis depends

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on the cause of the glucocorticoid excess. In cases in which it is not possible to identify the cause of glucocorticoid excess, over time fibrosis may develop, leading to worsening liver disease.

Hepatic Lipidosis Secondary to Diabetes Mellitus

Etiology/Pathophysiology

The liver plays a central role in fat metabolism. In diabetes mellitus, there is increased lipolysis in adipose tissue and therefore increased delivery of fatty acids to the liver, while the production of triglycerides is also increased. Fat accumulates in the liver cells and in the dog it is microvesicular, mainly caused by accumulation of triglycerides. This fatty change begins around the central veins and progresses toward the periphery of the lobule. This results in the development of hepatomegaly. Sometimes there is cholestasis, which can be quite severe. There is much more severe liver dysfunction with fatty change than with glycogen accumulation. In humans, the chronic fatty change that occurs in diabetes mellitus can lead to hypertrophic liver cirrhosis, but in dogs and cats this is very rare.

History and Clinical Signs

Fatty change in the liver is usually present in diabetes mellitus and it can occur without causing clinical signs. It can also cause mild to severe intrahepatic cholestasis. In this case, physical examination reveals hepatomegaly and icterus. All of the liver enzymes can be mildly to severely increased. The clinical signs are those related to diabetes mellitus, namely polyuria, polydipsia, weight loss, and an increased appetite.

Diagnosis

Liver histology demonstrates the fatty change, which is confirmed in combination with the diagnosis of diabetes mellitus (persistent hyperglycemia, glucosuria).

Therapy

Therapy of fatty change in the liver of dogs is not necessary. Regulation of the diabetes mellitus leads to a gradual disappearance of the fatty change.

The Liver in Hyperthyroidism

Hyperthyroidism is associated with fatty infiltration of the hepatocytes. This does not cause clinical signs of liver dysfunction, but in many cases the liver enzymes and bile acid levels are abnormally high. The fatty changes are not severe and there is no liver enlargement. A number of clinical signs associated with hyperthyroidism mimic those of primary liver diseases: polyuria, vomiting, diarrhea, and weight loss.

Hepatic Lipidosis (Steatosis) in Cats

Etiology/Pathophysiology

One important difference between dogs and cats is the relatively low capacity of the liver enzymes responsible for conjugation of cholephilic substances, used to make them more polar prior to biliary or urinary excretion, in the cat. The low hepatic glucuronyl transferase capacity is important for the metabolism of endogenous products such as bilirubin and exogenous compounds, either drugs or toxins. The elimination of drugs like chloramphenicol, nonsteroidal antiinflammatory drugs and anticonvulsants depends on this function. Hence, toxic side-effects develop much more easily in cats in cases of overdosage or reduced liver function.

Cats also have different amino acid requirements from dogs, as they cannot synthesize a sufficient number of the essential amino acids (arginine, taurine, and carnitine). Arginine is an important intermediate metabolite in the hepatic urea cycle in which ammonia is being converted into urea. This causes a relatively high susceptibility to develop hyperammonemia and hepatic encephalopathy in cases of inadequate protein intake, for example anorexia. Cats, unlike dogs, may have hepatic encephalopathy with parenchymal liver disease without portosystemic collateral circulation. Arginine and taurine are involved in the hepatic production of apoproteins, which are used to form the very low-density lipoproteins. These lipoproteins are the form in which the liver can secrete triglycerides into the circulation for further metabolism. Insufficient availability of arginine and taurine may lead to accumulation of triglycerides in the liver, for example in the case of fasting. Taurine also plays a role in detoxification, as it is used by the liver as a conjugating group to make substances such as bile acids more hydrophilic. Taurine is also involved in glutathione metabolism, which is one of the major routes of hepatic detoxification. Carnitine is an intermediate enabling beta-oxidation of long chain fatty acids in mitochondria, and this function may be impaired in anorexia.

Fat accumulation in the liver occurs in different species, as a result of metabolic conditions in which there is increased deposition or impaired removal of triglycerides in the liver. Clinically, this may be of importance in diabetes mellitus as discussed for dogs. Subclinical fat accumulation, only detectable with histologic examination of the liver, occurs in many other conditions such as high intake of calories, hypoxia of the liver and induction by a number of toxic substances. Cats, however, display an idiopathic form of hepatic lipidosis that may become life-threatening. Accumulation of triglycerides is the result of a disturbed balance between triglyceride uptake by the liver and their removal. The latter is normally achieved by formation of lipoproteins (especially very

low-density lipoproteins, VLDL), which allows for secretion of fatty acids into the circulation for further metabolism in other tissues. Another route for the liver to metabolize fatty acids is via beta-oxidation.

Fat cats seem to be predisposed, but lean cats may also develop lipidosis. It is generally appreciated that prolonged fasting is the most important factor inducing lipidosis. Fasting may affect hepatic fatty acid metabolism in three ways. First, fasting induces peripheral lipolysis and increased delivery of fatty acids to the liver. The intake of essential amino acids may also become inadequate. Deficiency of arginine and taurine may inhibit the apoprotein formation necessary to form resulting in the accumulation of triglycerides. Finally, carnitine deficiency may result in impairment of beta-oxidation, which is a major pathway for hepatic fatty acid catabolism.

Most cats with lipidosis have slight hyperglycemia as a result of impaired glucose tolerance. It is not known what underlying mechanism leads to deranged glucose metabolism. There is no tendency to develop overt diabetes mellitus. There is no consistency with respect to the level of insulin and glucagon; both high and low values have been reported. In cats with concurrent diabetes mellitus, very high doses of insulin are required to lower the blood glucose in these cats, suggesting insulin resistance. We have measured high growth hormone concentrations in a few patients, which could explain insulin resistance, but this could not be related to progestin administration or other factors known to induce growth hormone excess. Whatever the cause, hyperglycemia is a possible factor further contributing to accumulation of triglycerides.

Lipidosis results in hepatomegaly with yellow discoloration and a friable texture. As in all types of hepatomegaly, the margins of the lobes become rounded. Accumulated fat is concentrated in micro- or macrovesicular vacuoles in the hepatic cytoplasm. Swelling of cells can easily produce intrahepatic cholestasis. Reduced liver function and fasting may trigger hepatic encephalopathy.

Signalment

Lipidosis may occur at any age in both males and females, although there seems to be an increased incidence in middle-aged cats. There appear to be individual differences in susceptibility; some cats sustain prolonged fasting without developing lipidosis, and others develop recurrence with every episode of prolonged fasting. It is interesting to note that hepatic lipidosis occurs regularly in the United States but less frequently in Europe, and is very uncommon in the United Kingdom. It is not known whether these regional differences reflect variations in genetic make-up of the populations or differences in composition of cat food.

History and Clinical Signs

Cats often present with anorexia and lethargy. There may be occasional vomiting, and icterus is a common finding. Clinical signs consistent with hepatic encephalopathy may also occur. Clinical signs related to an underlying disease resulting in anorexia may also be present.

Diagnosis

The clinical signs and findings on physical examination (icterus and hepatomegaly) are not specific, and neither are elevated serum bile acids and liver enzymes. Slight or moderate hyperglycemia is often present but this is not diagnostic. Remember that stress during blood sampling often results in hyperglycemia in cats. On ultrasonographic examination, an enlarged and obviously hyperechoic liver is commonly seen. The diagnosis can only be made by evaluation of liver tissue. However, due to the diffuse nature of the disease, fine needle aspiration cytology is usually diagnostic.

Therapy

The most important management strategy is to get the cat out of the catabolic condition, and to supply the amino acids essential to prevent further fat accumulation and development of hepatic encephalopathy. Forced feeding of semiliquid food may be required, and this can be achieved in most cases by slow oral feedings with a syringe. However, this method of feeding is unsuitable for the long term and can be very difficult in some cats. Other forms of enteral feeding are therefore preferred, and esophagostomy or gastrostomy tubes are sensible first choices. These feeding tubes can be left *in situ* for prolonged periods, and also enable sufficient calories to be fed to meet the cat's daily need. Alternatively, a nasoesophageal feeding tube can usually be placed with relative ease, although these are not suitable for the long term, nor adequate for meeting the daily nutritional requirements.

Since protein is the most important component in the treatment of the metabolic derangements leading to lipidosis, 30–40% of the total calories should be administered as protein. Moreover, diets should contain the essential amino acids arginine and taurine. Recovery formula commercial diets are available to meet these requirements. It may be advisable to give vitamin B12 supplementation as well. There is little indication for the use of glucose as an energy source, since cats tend to have glucose intolerance and cannot adequately utilize it. So-called lipotrophic compounds, such as methionine, are also not recommended. It also is not recommended to administer insulin, because of the risk of life-threatening hypoglycemia, whereas hyperglycemia appears to be a secondary instead of a primary phenomenon.

Supportive care includes restoration of the fluid and electrolyte balance. Ammonia (if available), electrolytes (sodium and especially potassium), and pH should be monitored to permit supportive care directed at hepatic encephalopathy if indicated.

Prognosis

Owners need to be warned that the prognosis is generally guarded, with roughly half of cats surviving. Moreover, therapy can be prolonged, sometimes consisting of several weeks to months of enteral nutrition. The prognosis is quite good if the condition is diagnosed and treated early. However, cats with severe hepatic encephalopathy have a worse prognosis.

Liver Changes Due to Anemia and Shock (Acute Hypoperfusion)

Etiology/Pathophysiology

Liver degeneration or necrosis can occur with acute hypoxia of the liver. In this context, it is important to remember that the blood supply of the liver is predominantly venous and therefore any adaptation to hypoxia requires time. Possible causes for such lesions are acute hemolysis or massive blood loss. Histologically, there is necrosis of the centrilobular zone 3 (the oxygen-poor part of the liver lobule). Extensive necrosis may occur in rare cases with confluent and bridging necrosis, forming connections between necrotic centrilobular areas. Necrosis induces a secondary inflammatory reaction of polymorphonuclear cells, and there is usually widespread cholestasis. In cases of hemolysis, there is erythrophagocytosis and/or accumulation of iron pigment in the reticuloendothelial system, and sometimes extramedullary hematopoiesis is seen. In addition to the general illness and icterus, hepatic encephalopathy can also occur in severely affected cases.

These changes explain why hemolytic anemia is so often accompanied by an increase in conjugated bilirubin, and this is sometimes marked. It is the cholestasis, rather than the hemolysis, that determines the degree of icterus. Hence, bilirubin is predominantly the conjugated direct reacting type. ALT, AST, ALP, and gamma-glutamyl transferase (GGT) can be severely elevated. Sometimes, the liver dysfunction is so severe that, in spite of adequate treatment of the hemolysis, it leads to death.

History and Clinical Signs

Clinical signs are usually acute in onset, and a history of recent shock may be present. In hemolytic anemia, the mucous membranes may be jaundiced and are usually pale. Clinical signs are in part those of anemia, namely lethargy and exercise intolerance. Subsequent signs resulting from liver dysfunction depend on the extent of liver necrosis, and vary from general illness and lethargy to hepatic encephalopathy. Anorexia and vomiting may occur as a result of impaired detoxifying function of the liver.

Diagnosis

The presence and severity of any liver changes can only be confirmed by histologic examination of a liver biopsy. These changes are specific and therefore confirmatory. An impression of the severity and course of the liver necrosis is provided by measurements of the liver enzymes and bile acids in serum, but they may also be elevated in any other hepatobiliary disease and are by no means specific. The diagnosis of the underlying disease causing anemia or shock is not discussed here.

Therapy

Management primarily involves treatment of the underlying cause of hypoxia. There is no specific treatment possible for the hepatic lesions, and the liver will recover spontaneously in most cases after resolution of the underlying condition. In cases of severe damage, the impaired liver function may become life-threatening. Only symptomatic supportive therapy for liver dysfunction can be given, to allow time for the liver to regenerate. Specific measures to prevent or reduce hepatic encephalopathy may be important. Remember that the course of liver regeneration cannot be evaluated by the degree of icterus.

Prognosis

The prognosis is very variable and primarily depends on the underlying cause of hypoxia. If the underlying cause can be addressed, hepatic changes are likely to be reversible.

Amyloidosis

Etiology/Pathophysiology

Amyloidosis of the liver is very rare in dogs or cats. Amyloidosis is often a systemic disease involving a number of organs. In cases of generalized amyloidosis, there is usually also deposition of amyloid in the liver and kidneys, but this seldom leads to clinical signs relevant to the liver. The severe glomerular damage leading to urinary protein loss is almost always the most important clinical phenomenon. In the liver, deposits of amyloid are visible as amorphous hyaline and eosinophilic material in the space of Disse when Congo red staining is used. Depending on the amount of amyloid, the liver may be enlarged on abdominal palpation. However, it is often a normal size. Liver enzymes and bile acids may be increased, although sometimes they are within the normal reference interval.

Signalment

Amyloidosis is frequently identified in the shar-pei dog, although other breeds can be affected. In cats, the Siamese, Oriental shorthair, Devon Rex and Burmese are predisposed.

History and Clinical Signs

Overt liver dysfunction is rare in amyloidosis, even when the liver is grossly enlarged. Nephrotic syndrome is the most common finding in these patients due to severe and prolonged proteinuria resulting from renal amyloidosis. Other possible signs of renal dysfunction are vomiting, anorexia, and polyuria. Spontaneous rupture of the liver may occur in severe cases, resulting in acute blood loss, shock, and death.

Diagnosis

The deposition of amyloid can only be detected by cytologic or histologic examination of relevant biopsy material (liver or kidney). Taking biopsies is not without risk as the liver may rupture, resulting in severe abdominal hemorrhage.

Therapy

There is no specific treatment available for amyloidosis. The deposition of amyloid is progressive and in animals with end-stage disease, the prognosis is very poor.

Copper Storage Diseases Leading to Chronic Hepatitis and Cirrhosis

The accumulation of copper in liver tissue has been described in several breeds of dog. Excessive accumulation includes that seen in true "copper storage" disease, where the primary initiating event is a defect in copper excretion leading to secondary hepatocyte damage, and "copper-associated" disease, in which copper accumulates secondary to an underlying inflammatory liver disease.

Copper storage diseases probably occur in several breeds of dog, although there appear to be differences in prevalence between countries. Copper storage disease was suspected in about 30% of all dogs with hepatitis in one study from The Netherlands, but is relatively uncommon in the UK. The Bedlington terrier, Labrador retriever, Dalmatian, Anatolian shepherd, Airedale terrier, and spaniel breeds appear to be predisposed.

In primary copper storage disease, copper accumulates in the liver when the excretion of excessive copper into the bile is deficient. This is a gradual process and usually toxic levels leading to chronic hepatitis and cirrhosis are reached at an age of 4–7 years. Copper first accumulates in the centrolobular region of the liver (zone 3 around the central vein); in later stages, zone 2 and zone 1 (periportal zone) may also become gradually affected. This differs from copper-associated disease, which is the predominant form in all dogs, in which cholestasis causes periportal copper accumulation (zone 1), with copper later accumulating in zones 2 and 3.

Copper Storage-Induced Hepatitis and Cirrhosis in the Bedlington Terrier

Etiology/Pathophysiology

This disease occurs in Bedlington terriers, resulting in an accumulation of copper in the liver, usually due to an autosomal recessive mode of inheritance. In many affected dogs, the disease is caused by a deletion in the COMMD1 gene, resulting in lack of production of a specific protein. This protein is an important chaperone for the copper-transporting protein ATPase 2, encoded by the human Wilson disease gene ATP7B, the principal hepatocyte exporter of copper into bile. Only homozygotes become ill; heterozygotes have a normal liver.

Normally, some of the copper ingested is absorbed in the intestine and transported to the liver in the portal blood, where it is loosely bound to albumin. Most of this is taken up by the hepatocytes and excreted in the bile via the liver cell lysosomes. A small part is incorporated in ceruloplasmin in the liver, and copper incorporated in this protein is released in the plasma. Copper in ceruloplasmin is used for incorporation in a number of enzymes and proteins, essential for normal function. Most of the copper is bound to the protein metallothionein. Copper then moves to the lysosomes of the hepatocytes and is excreted into the bile bound to an unidentified protein. In this form, it leaves the body in the feces. In Bedlington terriers with copper storage disease, the hepatocytes are almost completely unable to excrete copper in the bile and hence there is an increasing accumulation of copper in the liver. The exact nature of the defect is not known, but it is a lysosomal disorder. Because the copper accumulation begins gradually, the clinical signs usually only begin to appear after around 4 years of age. The increased copper concentration in the liver can be confirmed after 1 year of age; before then, some dogs with the disease have not yet stored sufficient copper to distinguish them from normal animals.

There is a chronic form in which the copper accumulation leads to liver cell necrosis and secondary hepatitis, cumulating in cirrhosis. Some dogs also have an acute form of copper storage disease, with a hemolytic crisis. The hemolysis is probably the result of a sudden release of a large amount of copper from hepatocytes into the blood. The mechanism for this is not clear. The sudden increase in blood copper concentration causes acute hemolysis, and because liver function is already reduced, this leads to severe icterus. Tubulonephrosis may occur and can lead to uremia. The hemolysis in turn results in

centrilobular liver necrosis as a result of hypoxic damage. In dogs surviving the hemolytic crisis, cirrhosis occurs much more often than in other animals.

History and Clinical Signs

With chronic copper accumulation, the clinical signs are those of chronic hepatitis or cirrhosis. The reader is therefore referred to the relevant sections for further details. In the acute form there is acute hemolysis, anemia, severe icterus, and sometimes uremia. The acute form is often lethal within a few days.

Diagnosis

Laboratory examination may reveal any of the changes seen in chronic hepatitis and cirrhosis, such as increased ALT, ALP, GGT, bile acids, and bilirubin. Hypoalbuminemia and hepatic encephalopathy with increased ammonia concentrations occur only in late stages. There are no specific laboratory parameters that are specific for copper accumulation. Ceruloplasmin and free copper concentrations are not different from healthy dogs, whereas Wilson disease in humans is associated with decreased ceruloplasmin levels.

On the basis of the clinical examination and result of blood tests, it is not possible to differentiate copper storage disease from chronic hepatitis or cirrhosis. The diagnosis can only be made by demonstrating increased copper accumulation in a liver biopsy in animals older than 1 year. Histologically, copper in a liver biopsy may be detected with specific stains such as rubeanic acid. The same staining may be used on cytologic preparations collected by fine needle aspiration. Copper accumulation begins in hepatocytes around the central veins (zone 3) and gradually spreads outwards toward the portal areas. The copper is stored in the hepatic lysosomes. The copper-induced liver cell damage only occurs when a certain level is exceeded. The damage leads to ongoing liver cell necrosis and secondary inflammation that can eventually result in fibrosis and cirrhosis. The normal concentration of copper in the canine liver is between 50 and 300 µg/g dry weight. Dogs with copper accumulation have levels exceeding 1000 µg/g dry weight at 1 year of age, but most cases have higher concentrations. With time, levels of 12 000 µg/g dry weight may be reached. At 1 year of age, a few dogs have concentrations between 300 and 1000 µg/g dry weight, and most of them appear not to accumulate when reexamined later.

A genetic test for the mutated COMMD1 gene is available, although not all dogs with the disease have this defect. However, heterozygote carriers cannot be distinguished from homozygote healthy animals. A few decades ago, the incidence of the disease in Bedlington terriers was about 30–50%. However, with the availability of a reliable genetic test, the incidence of the disease has dramatically declined, with clinical cases becoming quite rare.

Therapy

Once signs of chronic hepatitis or cirrhosis are present, or those of an acute hemolytic crisis have developed, specific therapy is usually not possible. Symptomatic and supportive care is therefore important. In chronic hepatitis or cirrhosis, management of hepatic encephalopathy, portal hypertension, and ascites is vital. Readers are referred to Chapter 65 for further details regarding therapy.

Hemolytic crisis is a very serious event. Administration of penicillamine, which is a chelating drug that binds metals, preferentially copper, is indicated. The penicillamine–copper complex is excreted from the kidneys into urine, resulting in free copper being removed from the circulation. Intravenous infusion of fluids with diuresis may also be helpful to enhance urinary copper excretion.

It is important to try to prevent the development of clinical signs in dogs at risk for copper storage disease. Hence, asymptomatic dogs should be examined at a young age, and if there is copper accumulation, life-long medication with drugs that prevent further accumulation of copper is essential. There are two drugs available, and both are given orally in a capsulated form. Penicillamine may be given 30 minutes before each meal at a total daily dose of 25 mg/kg. Penicillamine binds copper in the circulation and the bound complex is excreted in the urine. Another drug is zinc, which may be given as zinc gluconate at a dosage of 30 mg/kg/day in divided doses immediately before each meal. The action of zinc is at the level of the intestinal mucosa, as it induces the formation of copper-binding metallothionein, thus preventing the absorption of copper. The two drugs should not be combined since they form complexes and inactivate each other. These medications are unable to reduce hepatic copper levels in most cases, but they prevent further accumulation and development of the symptomatic stage. Another measure to prevent further accumulation is to reduce the copper content of the food. Commercial foods have been developed to treat and prevent copper storage diseases, and have been proven to be very effective. These are veterinary-formulated liver diets containing low copper and high zinc.

Copper Storage-Associated Hepatitis and Cirrhosis in Labrador Retrievers

Since 2006, Labrador retrievers have been reported to have a form of copper storage disease causing hepatitis, which if untreated results in cirrhosis. Much of the description pertaining to the Bedlington terrier applies to the disease in Labradors. Like all forms of copper storage, the disease develops gradually due to the slow accumulation of copper in the centrilobular area of the liver. Therefore, the typical age of onset of clinical signs in this

breed is also 4–7 years. The copper concentrations in Labrador retrievers remain much lower than in Bedlington terriers (by a factor of 10), and liver samples from Labrador retrievers usually do not exceed 2000 µg/g dry weight, whereas Bedlington terriers may have concentrations exceeding 15000 µg/g dry weight. Another difference is that Labrador retrievers do not develop a hemolytic crisis as easily as Bedlington terriers. The hepatitis may remain "hidden" for a long period since the most sensitive marker, ALT, may stay within normal limits for years, even when copper accumulation and hepatitis are already present. In more advanced cases, fibrosis and cirrhosis may develop, similar to other breeds with copper storage disease.

The diagnosis is made in the same way as the Bedlington terrier, and prevention and therapy are also comparable. Commercial hepatic diet has proven very effective in this breed. Although it is a proven genetic disease, it appears to be much more complex than in the Bedlington terrier, and as such a reliable genetic test is not yet available. Due to the complexity of the disease, it is difficult to give good advice to breeders to aid in prevention of the disease.

Toxic Diseases

Nonspecific Reactive Hepatitis Due to Endotoxins

Etiology/Pathophysiology

Nonspecific reactive hepatitis is a diffuse or focal liver disease with secondary inflammatory reaction resulting from toxemia or sepsis. Reactive hepatitis can occur with every toxemia, sepsis, inflammation, and necrotizing process (including necrosis in tumors). When the process is in tissues drained by the portal system, toxins are transported exclusively to the liver. Toxins and bacteria from processes elsewhere are first diluted in the general circulation before reaching the liver. It is therefore logical that reactive hepatitis is most often caused by processes within the abdomen.

Reactive hepatitis develops in most cases of gastroenteritis and extensive gastric or intestinal tumours (e.g., lymphoma), as a result of increased endotoxin absorption. It also develops in peritonitis, including local peritonitis resulting from abdominal surgery, and in other inflammatory processes in the organs drained by the portal vein. Reactive hepatitis is thus most often caused by gastrointestinal disorders. On the other hand, vomiting and/or diarrhea often occur with primary liver disorders. Hence, when a patient with gastrointestinal problems is found to have high liver enzyme levels, the classic chicken-or-egg situation is encountered, and this problem may only be solved with liver histopathology. However, the reaction pattern in the liver to endotoxins primarily involves the development of canalicular cholestasis, and therefore the cholestatic enzymes ALP, GGT, and bile acids are the most important markers. In many primary liver diseases, the hepatocellular enzymes ALT and AST are the predominant markers, with cholestatic markers less affected. However, there are many exceptions to this general rule.

The circulating toxins, inflammatory mediators, and microbes cause reticuloendothelial proliferation and infiltration of neutrophils into the liver. There can also be focal liver necrosis. In chronic cases, there is also lymphocytic and plasmacytic inflammation. There can be mild to severe cholestasis in the canaliculi. In some cases associated with sepsis, there are diffuse foci of necrosis, microabscesses, or granulomas (e.g., infection with *Herpes canis*, toxoplasmosis, brucellosis, tuberculosis, *E. coli* and migrating larvae of *Toxocara canis*).

Hepatocellular functions usually remain intact in this group of secondary liver diseases. Therefore, hypoalbuminemia, coagulopathies and hepatic encephalopathy are not seen in animals with nonspecific reactive hepatitis.

History and Clinical Signs

The clinical signs are often determined by the primary disorder. Hence, there is often vomiting and/or diarrhea, and sometimes fever. When reactive hepatitis is severe, there can be icterus, general lethargy, and sometimes reduced exercise intolerance.

Diagnosis

Differentiation between primary liver diseases and reactive hepatitis is only possible by histologic examination of a liver biopsy. The abnormalities described under pathogenesis are characteristic. Once the diagnosis of reactive hepatitis is made, it can be very difficult to localize the primary process. Further examination and investigation of the gastrointestinal system are usually therefore indicated.

Therapy

Therapy and prognosis depend on the primary disorder. Reactive hepatitis itself requires no treatment, since it resolves spontaneously after removal of the cause. The underlying, likely gastrointestinal disease should therefore be treated.

Drug Toxicity

Many toxins and drugs are concentrated in the liver and may cause direct toxic damage (intrinsic toxicity), and rarely cause idiosyncratic (very acute and severe) toxicity. Direct toxic damage may primarily involve the hepatocytes, causing necrosis and/or steatosis, or bile canaliculi, causing intrahepatic canalicular cholestasis. In veterinary medicine, documented idiosyncratic liver toxicity is

restricted to sulfonamides causing severe intrahepatic bile duct necrosis and irreparable cholestasis. Anecdotally, although not well documented, liver toxicity has also been reported for azathioprine, ketoconazole, fen/oxibendazole, phenobarbital, halothane, methoxyflurane, cephalexin, amoxicillin, oxacillin, nafcillin, erythromycin, clindamycin, and several other drugs. The hepatic lesions may include canalicular cholestasis and/or liver cell vacuolization and in severe cases liver cell necrosis. There are no large studies to document the true risk and toxicity of these drugs. Relatively well-documented toxicity is reported for diazepam (cats), acetaminophen (paracetamol) in dogs and cats, and carprofen in dogs.

Specific Toxins

Diazepam Toxicity in Cats

This toxicity has all the features of an idiosyncratic reaction, and has only been reported in cats receiving several doses of diazepam. Toxicity results in severe necrosis of the entire liver lobule, leading to fulminant liver failure and severe signs including inappetence, vomiting, severe lethargy, hepatic encephalopathy, coagulopathy, and jaundice. Liver enzymes, including the transaminases ALT/AST, and also ALP and bile acids are significantly elevated. Only symptomatic treatment is possible and the prognosis is poor in most cases.

Acetaminophen (Paracetamol) Toxicity in Dogs and Cats

Too high a dose of acetaminophen may cause severe oxidative hepatic damage. The result is hepatocellular necrosis which, depending on the dose, may involve the entire liver lobule and cause complete liver failure. Acetaminophen has been used as an experimental drug to induce reproducible acute liver failure in dog models, and it is one of the most used suicide drugs in humans.

If acetaminophen toxicity is suspected, antioxidative drugs such as SAM-e and N-acetylcysteine are advised. However, the proven effect of these drugs was tested in experimental situations in which the drug was given together or before the toxic drug. Treatment after the occurrence of the toxicity, as occurs naturally, may be less successful. The most important treatment is immediate gastric lavage. Supportive care with intravenous fluids and enteral feeding may also be required. If hepatic encephalopathy with severe hyperammonemia is present, the prognosis is often very poor.

Carprofen Toxicity in Dogs

This nonsteroidal antiinflammatory drug (NSAID) may cause idiosyncratic hepatic toxicity. The toxicity usually occurs after prolonged or repeated treatments, and may cause very severe liver damage. Immediate drug withdrawal and supportive care, with intravenous fluids and intensive therapy, result in a favorable outcome for most cases, although several weeks of treatment may be required. Carprofen may also cause simultaneous renal toxicity. Carprofen toxicity causes marked elevation of all liver enzymes, bile acids, and bilirubin. It is not known if other NSAIDs can cause similar hepatotoxicity.

Sulfonamide Toxicity in Dogs and Cats

Repeated or prolonged treatment with sulfonamides (including trimethoprim/sulfa) may occasionally lead to an idiosyncratic toxicity of the liver in both dogs and cats. The intrahepatic bile ducts appear to be targeted, especially the collecting bile ducts receiving bile from the smaller liver lobules. In most cases, these intrahepatic components of the biliary tree undergo complete necrosis, leading to very severe intrahepatic cholestasis. The degree of cholestasis is comparable to that of complete extrahepatic bile duct obstruction. Clinical signs include a sudden onset of anorexia, depression, vomiting, polyuria, and occasionally acholic stool, in combination with marked icterus. Sometimes the liver is moderately enlarged. The resulting clinical signs are those of severe cholestasis with preservation of liver function. At ultrasonography, the gallbladder may be entirely empty. The diagnosis requires careful histologic examination of the liver, since the lesions have a specific pattern. Management includes immediate withdrawal of the drug, and therapy with the choleretic drug ursodeoxycholic acid. Complete recovery has never been documented and surviving cases need to be treated lifelong with ursodeoxycholic acid.

Biologic Toxins

Amanita mushrooms and blue algae are the two important producers of biologic toxins, which may cause very severe liver damage. Both toxic mushrooms and blue algae cause severe necrosis of hepatocytes, and this is dose dependent. In most cases, the damage is very severe and associated with complete liver necrosis (fulminant hepatitis). This leads to massive increases of all liver parameters (enzymes, bile acids, ammonia, etc.). Clinical signs are comparable to those of the drug toxicities, and may include hepatic encephalopathy, jaundice, spontaneous bleeding, and severe lethargy. Therapy is supportive, with antiemetics and intravenous fluid administration, and normalization of blood pH and electrolytes. Forced diuresis may help to relieve the signs of hepatic encephalopathy.

Neoplasia

Primary Tumors

Hepatocellular Carcinoma

Etiology/Pathophysiology

Among epithelial tumors, hepatocellular carcinoma (HCC) occurs more frequently than hepatocellular adenoma. Both tumors are usually solitary and can become

very large, leading to focal enlargement of a liver lobe. Hepatocellular carcinomas do not commonly metastasize and they grow slowly. They seldom lead to reduced liver function as they only arise from one liver lobe, leaving the rest of the liver intact. Hepatocellular carcinoma is associated with chronic hepatitis and cirrhosis in humans, but such a relation does not appear to exist in dogs though they appear to occur more frequently in Scottish terriers with hyperphosphatemia.

Signalment

Hepatocellular carcinomas are generally seen in older dogs, and some studies have shown a breed predisposition in the poodle, fox and Scottish terrier, and Labrador retriever.

History and Clinical Signs

Hepatocellular carcinomas lead to the development of clinical signs only when they have attained a significant size, at which time they may be palpable. With increasing size, they can also displace the stomach and cause vomiting. Abdominal palpation reveals a mass in the cranial abdomen in most cases, and the tumor may be so big that the abdomen is distended. It may be difficult to distinguish such masses from those arising from the spleen.

Hypoglycaemia occurs relatively commonly (about 50% of cases), and may be a paraneoplastic phenomenon due to tumor production of insulin-like peptides (IGF-2). In some cases, hypoglycemia induces exercise intolerance or episodic weakness.

Diagnosis

The liver enzymes are variably elevated, and sometimes may be within the reference interval. Focal enlargement of the liver, often combined with displacement of the stomach, can often be identified on plain abdominal radiographs. Ultrasonography reveals a mass with an echogenicity similar to that of normal liver, although sometimes echogenicity is abnormal. Histology of a liver biopsy may be diagnostic, but sometimes these tumors are well differentiated and may be very hard to distinguish from normal liver or an adenoma. Cytologic diagnosis is therefore impossible in most cases.

Therapy

Surgical removal of the affected liver lobe is the only definite treatment. This may be successful if the tumor is not located near the hilus, the large hepatic vessels or major bile ducts. Peripherally located carcinomas are resectable, and in most cases, resection is curative. It is important to monitor the blood glucose concentration during or directly following surgery. Moreover, no anticancer chemotherapeutic drugs have been shown to be effective in the management of this tumor type although tyrosine kinsase inhibitors are being investigated.

Bile Duct Carcinoma

Etiology/Pathophysiology

This is a relatively infrequent primary tumor of the biliary epithelium. In the dog, it usually arises from intrahepatic bile ducts and readily metastasizes to the liver parenchyma and other organs. The multiple metastases throughout the biliary system often lead to signs of cholestasis. In the cat, bile duct carcinomas occur more often in the large bile ducts and result in obstruction. The disease tends to be rapidly progressive.

History and Clinical Signs

Icterus is a common clinical sign. Other clinical signs depend on the amount of hepatic involvement, and signs may be those of acute or chronic liver disease. There is often widespread infiltration of the tumor in the liver and thus hepatomegaly.

Diagnosis

Physical examination and laboratory findings usually only indicate extrahepatic cholestasis. Fine needle aspiration cytology is generally not useful for diagnosis. Bile duct carcinoma is best diagnosed by liver biopsy, either under ultrasound guidance or at laparotomy/laparoscopy.

Therapy

The tumor usually is usually very infiltrative. However, if localized to a single liver lobe, lobectomy of that lobe can be curative. In most cases, no treatment is possible by the time clinical signs occur. Moreover, no anticancer chemotherapeutic drugs have been shown to be effective in the management of this tumor type.

Hemangiosarcoma

Etiology/Pathophysiology

This is the only common mesenchymal type of hepatic tumor. They are usually smaller (up to a few centimeters) and multiple. Because they occur as multiple masses, their presence often results in more extensive hepatic dysfunction and cholestasis than are seen with epithelial tumors. Apart from being primary liver tumors, they may also be metastatic from other organs such as the spleen, kidneys, and skin.

Signalment

Hemangiosarcomas usually occur in older dogs and there appears to be a breed predisposition in the German shepherd dog, golden retriever, boxer, Great Dane and English setter.

History and Clinical Signs

Mesenchymal tumors usually have a severe and rapid course, with anorexia, vomiting, weight loss, and sometimes icterus. Abdominal distension and hemorrhagic ascites due to ruptures of the tumor may be present.

Diagnosis

There may be palpable liver enlargement but this is not always the case. Biochemical examination usually reveals high liver enzymes and bile acids but this is nonspecific. Ultrasonography allows visualization of any tumors, and these appear as dark hypoechogenic masses due to their rich vascularization. The diagnosis may also be confirmed by laparoscopy/laparotomy. Ultrasound-guided biopsy can be used in diagnosis, although there is a risk of bleeding and also tumor seeding. Fine needle aspiration cytology is not recommended for diagnosis.

Therapy

Mesenchymal tumors are usually inoperable and rapidly progressive. See discussion of hemangiosarcoma in Chapter XX. Survival times are usually in the area of weeks to months, and the owner should be warned about the risk of acute bleeding into the abdomen.

Secondary Tumors (Metastatic)

Etiology/Pathophysiology

Tumors of organs in the portal drainage area usually metastasize to the liver in the course of the disease. Hemangiosarcomas of the spleen are by far the most frequent, followed by pancreatic carcinomas and gastrointestinal tumors. Tumors from outside the portal drainage area can also metastasize to the liver. Tumor metastases are almost always multiple and distributed throughout the liver. Depending on their number and size, there can be varying amounts of liver damage.

History and Clinical Signs

The clinical signs may originate chiefly from the primary organ: vomiting in the case of gastric tumors, extrahepatic cholestasis with pancreas tumors, and ascites resulting from hemorrhage from splenic hemangiosarcoma. The main clinical signs caused by liver damage from metastatic disease include lethargy, anorexia, vomiting, and icterus. There may also be palpable hepatomegaly, although this depends on the number and size of masses.

Diagnosis

Physical and laboratory signs of liver damage and/or cholestasis are not specific. The diagnosis is made by histologic examination, although this may be missed by a percutaneous liver biopsy. The chances of a representative liver biopsy are increased when this procedure is performed under ultrasound guidance.

Therapy

Because of the multiple sites of metastases, surgery is virtually never possible and the prognosis is extremely guarded.

Generalized Systemic Tumors: Malignant Lymphoma

Etiology/Pathophysiology

Hepatic lymphoma is relatively commonly seen in dogs and cats, usually as part of a generalized disease. However, in some cases lymphoma may only be present in the liver. Infiltration of tumor cells causes hepatomegaly, and intrahepatic cholestasis can also occur. Because the liver damage is diffuse and widespread, there is often severe liver dysfunction. The tumor infiltration is usually more severe in the portal areas and around the central veins, which sometimes causes severe portal hypertension. Portal hypertension then results in the development of ascites and acquired portosystemic shunting vessels. In such cases, hepatic encephalopathy may develop.

History and Clinical Signs

The signs are highly variable, depending on the organ systems involved. With respect to the liver, clinical signs of icterus, lethargy, anorexia, and vomiting may occur. Sometimes there is ascites and hepatic encephalopathy. Hepatomegaly and splenomegaly may result in abdominal distension.

Diagnosis

The diagnosis can always be confirmed by a percutaneous liver biopsy. The diffuse hepatic involvement also means that the diagnosis can usually be made by fine needle aspiration cytology; this is one of the few indications for performing this test for the diagnosis of liver disease.

Therapy

A variety of anticancer chemotherapy protocols for lymphoma are available, and the reader is referred to Chapter 134 for details of these.

Further Reading

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63

Feline Inflammatory Liver Disease

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Etiology/Pathophysiology

Inflammation of the liver in cats may occur with infectious diseases such as feline infectious peritonitis, toxoplasmosis or bartonellosis although other systems may be more significantly affected than the liver. Hepatitis may also be seen in association with toxic damage from drugs such as diazepam, paracetamol (acetaminophen), methimazole and carbimazole, potentiated sulfonamides, tetracyclines, griseofulvin, and phenobarbitone.

Most commonly, however, feline inflammatory liver disease refers to the cholangitis/cholangiohepatitis complex, which is primarily an inflammatory disease of the biliary system. When the inflammation breaches the fibrous tissue of the periportal limiting plate, the term *cholangiohepatitis* may be used. However, as this is uncommon, cholangitis is usually the more correct term.

Cholangitis may be further classified, according to the WSAVA Liver Standardisation Group, into neutrophilic cholangitis (NC), lymphocytic cholangitis (LC), and chronic cholangitis associated with liver fluke infestation. The last of these is due to ingestion of raw fish containing metacercariae of the family Opisthorchiidae, and is associated with mixed inflammation around dilated bile ducts and development of periductal and portal fibrosis.

Neutrophilic cholangitis is proposed to be due to bacteria ascending into the biliary system from the intestines, as common bacteria identified include *E.coli* and *Enterococcus*. Acute neutrophilic cholangitis (ANC) shows a predominantly neutrophilic infiltrate in the epithelium and lumen of the bile ducts, and edema may be present in the portal areas. In more severe cases, the inflammation extends into the hepatic parenchyma and may potentially lead to development of hepatic abscesses. In more chronic cases (chronic neutrophilic cholangitis – CNC), the infiltrate becomes more mixed in nature, comprising lymphocytes, plasma cells and fibrosis in addition to neutrophils.

Concurrent inflammation is commonly identified in other organs such as the pancreas (60%), intestines (50%), and kidneys (60%). The combination of cholangitis, pancreatitis, and inflammatory bowel disease is commonly known as triaditis, and occurs in approximately 25% of NC cases.

Lymphocytic cholangitis is attributed to an immune-mediated process although some authors have suggested that it may be a more chronic form of NC. The inflammatory infiltrate is predominantly T lymphocytes in the portal region, and in some cases the biliary ductular epithelium. With chronicity, portal bridging fibrosis can develop, severe forms of which have been referred to as sclerosing cholangitis. Proliferation of bile ducts or ductopenia can develop and ductopenia is also considered to reflect an immune-mediated process.

The pathogenesis of this disease complex is incompletely understood. Recent work has suggested that bacteria may play a role in LC, as bacterial DNA has been found in the bile of 38% of cats affected with LC. Although this may support the theory that this is a chronic form of NC, it could also be the consequence of the disease, with dilation of the bile ducts and decreased peristalsis permitting retrograde ascent of bacteria from the duodenum. Whether or not *Helicobacter* spp. play a role in triggering initiation of this disease also remains speculative. Another recent study has also documented bacteria within the hepatic parenchyma but not the bile ducts in cats with NC, questioning the traditional hypothesis of ascending infection and suggesting hematogenous entry via the portal vein.

Epidemiology

Cholangitis-cholangiohepatitis was first described in cats in the 1980s. It is the second most common feline hepatic disorder after hepatic lipidosis in the USA, with

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hepatic lipidosis being diagnosed twice as often as cholangitis, although prevalence within a necropsy population is only documented at 0.86%. The prevalence of the different forms of cholangitis is difficult to establish, due to different classifications in older publications. In the UK, cholangitis anecdotally may be more common than hepatic lipidosis.

Signalment

Neutrophilic cholangitis has been reported in a wide age range, although most commonly young to middle-aged cats are affected and a recent study documented a median age at diagnosis of 110 months (9.2 years). No breed or sex predispositions are reported. LC was previously reported to affect primarily young cats, and Persians were suggested to be overrepresented. More recent studies, however, have suggested that this disease affects mainly middle-aged to older cats, with a median age of around 10.5–11 years. Again, no breed or sex predisposition has consistently been identified.

History and Clinical Signs

Cats suffering from NC often present more acutely ill with a shorter history than those with LC. Signs reported by owners include anorexia or inappetence, vomiting and/or diarrhea, lethargy, weight loss, and ptyalism (excessive production of saliva). Physical examination findings can include dehydration, icterus, hepatomegaly, abdominal pain, and pyrexia.

Cats suffering from LC often remain bright, and some may show polyphagia rather than anorexia, although either is possible. Vomiting and diarrhea tend to be more intermittent, hence a more insidious history prior to seeking veterinary attention. Acholic feces can occur in cats with biliary obstruction, for example from cholelithiasis or with ductopenia due to sclerosing cholangitis (Figure 63.1).

Pyrexia is less common on physical examination although hepatomegaly and, in advanced cases ascites can be present.

It is not possible to differentiate the two conditions based on history and physical examination findings alone, as there can be significant overlap in presentation.

Diagnosis

Routine hematology is often nonspecific. Neutrophilia may be more commonly seen with NC than LC, and neutrophils can have a toxic appearance. Lymphopenia is also a nonspecific finding. While significant (10–40× reference range) increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) can be seen, not all cases of cholangitis (NC or LC) will have elevated values. Hyperglobulinemia may be seen with LC. Electrolyte abnormalities, most commonly hypokalemia, may be present as a consequence of vomiting and/or diarrhea.

Bilirubin is frequently, but not always elevated. The effect on bile acids is likely to be similar to bilirubin, as both substances are excreted in bile and affected by cholestasis (see Figure 63.1). Intrahepatic cholestasis results with reduced flow of bilirubin from the hepatocytes into the bile canaliculus, as a result of periportal edema and inflammation. Obstruction of larger bile ducts due to inflammation or cholelithiasis also causes extrahepatic cholestasis.

Urinalysis should be performed to add further information. The specific gravity can be useful to assess for concurrent renal involvement if azotemia is identified. In acutely ill patients it is often high due to dehydration. The finding of bilirubinuria is abnormal in cats, so if identified, it reflects hyperbilirubinemia. It does not help differentiate between the causes of icterus, but if urobilinogen is absent, this may indicate abnormal enterohepatic recirculation, suggestive of extrahepatic bile duct obstruction (see Figure 63.1).

Although imaging can add further information, findings may be normal or nonspecific for cholangitis. Radiography can identify hepatic enlargement, and with chronic inflammatory changes, mineralization of the biliary system can be seen. Presence of ascitic fluid will reduce the utility of this imaging modality.

On ultrasonographic examination, the liver often appears normal although it may be enlarged and have a normal, hypoechoic or hyperechoic texture. Due to the potential for "triaditis," it is also important to evaluate the remainder of the abdomen fully, especially the pancreas, intestines, and kidneys. Free fluid may be sampled for biochemical analysis, cytology, and culture to rule out some other differential diagnoses such as feline infectious peritonitis or neoplasia.

The biliary system should be closely evaluated, although no differentiation can be made between NC and LC based on ultrasound findings. The gallbladder can contain echogenic debris, although this may be seen in normal cats as well. If the common bile duct is found to be distended (>4 mm), it should be checked closely for intraluminal (e.g., choleliths) or extraluminal (e.g., pancreatic mass effect) obstructive lesions that require surgical correction (Figure 63.2). Thickening of the gallbladder wall (>1 mm) is suggestive of cholecystitis.

Ultrasound guidance may be used to obtain bile for culture, although this can be problematic if the bile is

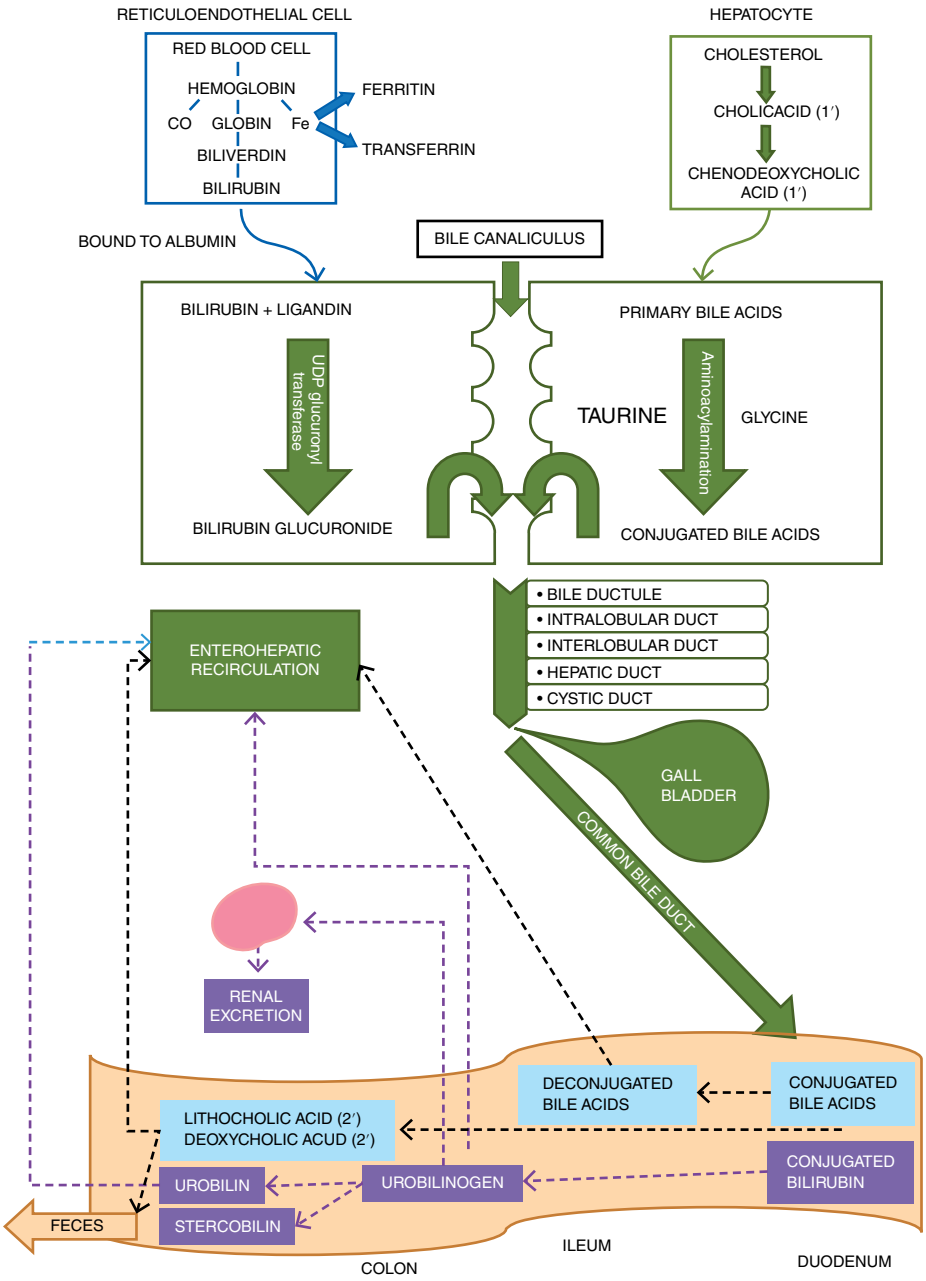


Figure 63.1 Diagrammatic representation of normal biliary physiology. Cholestasis results in hyperbilirubinemia and elevated bile acids. With complete obstruction of the biliary system, urobilinogen will not be available for urinary excretion, and stercobilin will not be present in the feces (acholic feces). Bacteria are responsible for deconjugation of bile acids and bilirubin, therefore these processes may also be affected by abnormal gut flora.

inspissated, requiring use of a larger gauge needle and hence potentially increased risk of bile peritonitis.

Coagulation times may be prolonged due to vitamin K deficiency, both as a result of anorexia but also because cholestasis reduces passage of bile acids into the intestine where they are required for absorption of this fat-soluble vitamin. Coagulation times should therefore always be evaluated prior to liver biopsy. Liver biopsy is required for a definitive diagnosis. Due to the patchy distribution of lesions, the larger samples obtained via laparoscopy or surgical wedge biopsies may be preferable to needle ("Tru-cut") biopsies. Ideally, both liver and bile should be cultured, as different organisms may be cultured from each site, although culture of bile yields higher recovery of organisms than culture of liver. Anaerobic as well as aerobic culture should be performed.

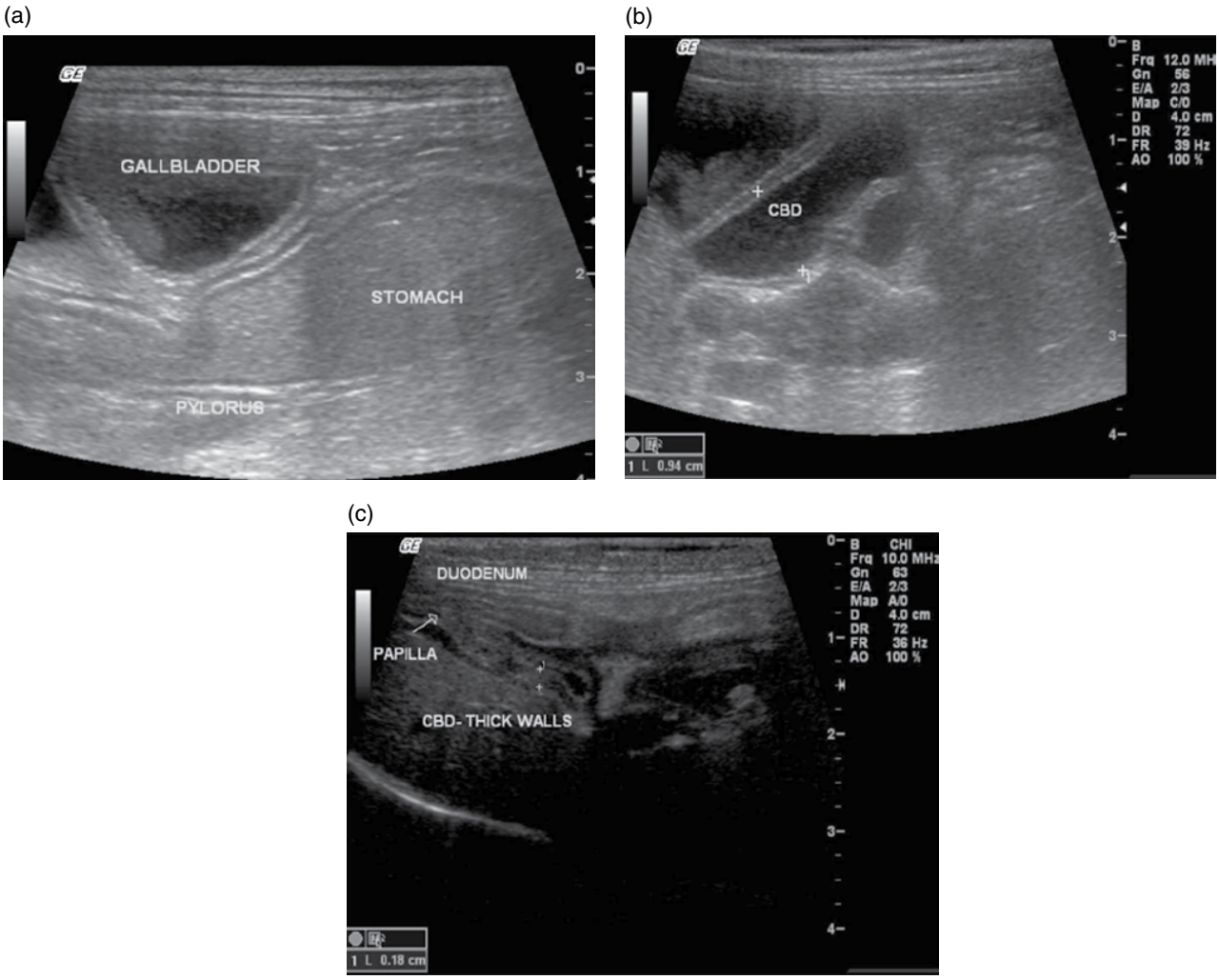


Figure 63.2 Ultrasound images from a cat diagnosed with neutrophilic cholangitis. Cytology of an aspirate of bile showed large numbers of predominantly degenerate neutrophils, many of which contained intracellular bacteria. A profuse growth of *E.coli* was cultured. (a) The gallbladder is distended and contains hyperechoic sludge. (b) The common bile duct is markedly dilated at 0.94 cm (normal <0.4 cm). (c) The walls of the common bile duct (CBD) are thickened.

Lymphocytic cholangitis needs to be differentiated from lymphoma, and immunophenotyping or T cell receptor polymerase chain reaction (PCR) for gene rearrangement may need to be considered if the diagnosis is in doubt.

Therapy

If chronic cholangitis is identified to be due to liver flukes, treatment involves the administration of praziquantel (30 mg/kg PO q24h for 5–10 days). Treatment of necroinflammatory hepatitis primarily involves withdrawal of any hepatotoxic drugs and use of supportive and hepatoprotective therapies as described later.

Patients with ANC can be seriously ill, potentially in septic shock from bacteremia. Fluid therapy should therefore be administered at rates appropriate to the degree of dehydration or shock present. Potassium supplementation at 20 mmol/L fluid is likely to prevent development of hypokalemia with rehydration; however, if hypokalemia is already documented, higher rates may be required.

Analgesia should be administered as abdominal pain is a common finding in these patients. Opioids are preferred over nonsteroidal antiinflammatories, especially in hypovolemic patients.

Antibacterial therapy should ideally be based on culture and sensitivity results, but pending these, empiric choices may be made based on the likely bacteria present (gram negative and anaerobes – see Table 63.1). Combination therapy may be required (e.g., fluoroquinolone plus metronidazole). Intravenous antibacterial therapy should be used initially in systemically ill patients. Antibacterial therapy is typically administered for a minimum of four weeks, or until values of hepatic

Table 63.1 Antibacterial agents used in the management of feline hepatobiliary disease

Drug	Dose	Comments
Amikacin	10–15 mg/kg IV, SC, IM q24h	Gram-negative bacteria. Nephrotoxic (less so than gentamicin), therefore only used if resistance patterns merit its use
Amoxicillin-clavulanate	12.5–25 mg/kg IV, PO q8–12h	Broad-spectrum antibacterial but may not be effective against *Pseudomonas* or *Klebsiella*. Oral absorption reduced in systemically ill patients
Cephalexin (first generation)	10–35 mg/kg PO q8–12h	May not be effective against *Pseudomonas* or *Proteus*. Poor efficacy against anaerobes
Cefotaxime (third generation)	20–40 mg/kg IV, SC q8–12h	More effective against gram-negative but less effective against gram-positive organisms than cephalexin. Variable activity against anaerobes
Cefovecin (third generation)	8 mg/kg SC q14 days	More effective against gram-negative but less effective against gram-positive organisms than cephalexin. Possibly better activity against anaerobes than cefotaxime
Cefuroxime (second generation)	10–15 mg/kg IV q8–12 h	More effective against gram negative but less effective against gram positive organisms than cephalexin, but not as effective as 3rd generation cephalosporins
Chloramphenicol	15–25 mg/kg PO, SC, IM, slow IV q12h	Good efficacy against gram-positive organisms and anaerobes. Moderate activity against gram-negative organisms. Not used routinely as cholestasis may increase risk of toxicity
Clindamycin	5.5–12 mg/kg PO q12h 10 mg/kg IV q12h	Effective against gram-positive organisms and anaerobes. Needs to be combined with drug effective against gram-negative organisms. Concentrated in the bile, but care with reduced liver function as excretion is via hepatic metabolism
Marbofloxacin	2 mg/kg PO, IV q24h	Good efficacy against gram-negative and some gram-positive organisms, but not effective against anaerobes. Preferred to enrofloxacin as decreased risk of retinal damage
Metronidazole	8–10 mg PO, IV q12h	Narrow spectrum against anaerobes. May cause nausea, vomiting, and neurologic signs. Intravenous infusions given over 20–30 minutes
Pradofloxacin	3 mg/kg PO q24h	Better efficacy against anaerobic organisms than marbofloxacin
Options pending culture results: Amoxicillin-clavulanate Cephalosporin + metronidazole Fluoroquinolone + clindamycin or metronidazole		

IM, intramuscular; IV, intravenous; PO, by mouth (*per os*); SC, subcutaneous.

enzymes return to normal. In some patients antibacterial therapy may need to be continued for 2–3 months, and repeat culture of bile may be warranted to assess response to therapy.

Surgery may be required to manage biliary obstruction, if identified. The above treatments should be initiated first to stabilize the patient as biliary surgery is complex and may require prolonged general anesthesia. Surgical procedures such as stenting of the bile duct, cholecystectomy, cholecystotomy or biliary bypass (cholecystoduodenostomy, cholecystojejunostomy) may be required.

Nutritional support is very important as, if hepatic lipidosis is not already present, these anorectic patients are at risk of developing it. Placement of a feeding tube is recommended. A nasoesophageal tube may be placed in the first instance, especially if prolonged clotting times are identified, but an esophagostomy tube is preferred. The wider bore of these tubes increases the range of diets that may be administered as well as enabling some medications to be given via this route. In addition, the chance of removal is reduced, and owners often can manage these tubes at home. Gastrostomy tubes may be placed at time of surgical intervention if required.

"Critical care" diets are generally appropriate as they are highly digestible, can be administered via feeding tubes and are supplemented with arginine, taurine, and antioxidants. Hepatic encephalopthy (HE) is usually a contraindication to feeding a high-protein diet but in this population of cats, signs of HE are generally attributable to arginine deficiency from anorexia and will correct with feeding protein. An exception to this is if HE is present due to development of acquired portosystemic shunts subsequent to severe fibrosis, although significant hepatic fibrosis is uncommon in cats. Longer term dietary management should consider the presence of concurrent diseases and be chosen accordingly. A diet for inflammatory bowel disease may be more appropriate than a "hepatic" diet, for example.

Table 63.2 Supportive therapies used in the management of feline hepatobiliary disease

Medication	Dose	Comments
Analgesia		
Buprenorphine	0.01–0.02 mg/kg SC, IV, IM q8h 0.02 mg/kg TM q8h	Partial mu agonist – may affect use of full mu agonist perioperatively. Can cause dysphoria
Fentanyl	2.5–10 µg/kg/h CRI 25 µg/h transdermal patch (>3 kg) 12.5 µg/h transdermal patch (<3 kg)	Full mu agonist. May be indicated with marked pain (e.g., bile duct obstruction or peritonitis)
Methadone	0.1–0.5 mg/kg IM or slow IV q4h 0.1 mg/kg/h CRI	Full mu agonist. May be indicated with marked pain (e.g., bile duct obstruction or peritonitis)
Morphine	0.1–0.4 mg/kg IM or slow IV q4h 0.1 mg/kg/h CRI	Full mu agonist. May be indicated with marked pain (e.g., bile duct obstruction or peritonitis)
Vitamins		
Cobalamin (vitamin B12)	0.125–0.25 mg/cat SC q7–14 days	Liver cobalamin stores may be depleted in the face of normal serum cobalamin; may help stimulate appetite
Vitamin K1	0.5–1.0 mg/kg SC, PO q12h for 3 doses	Given by SC injection using a 25 ga needle
Vitamin E	10 IU/kg PO q24h	Antioxidant often depleted with anorexia or malabsorption
Management of vomiting		
Cimetidine	2.5–5.0 mg/kg PO q12h	H2 receptor antagonist with weak antacid effects
Famotidine	0.5–1.0 mg/kg PO q12–24h	More potent H2 receptor blocker. Prokinetic effect unknown
Ranitidine	2 mg/kg PO, SC, slow IV q8–12h	Prokinetic effect may be beneficial in addition to H2 receptor blockade
Omeprazole	1 mg/kg PO, IV q12–24h	Antacid of choice; more potent thanthe H2 receptor blockers by causing complete blockade of the proton pump
Maropitant	0.5–1.0 mg/kg SC q24h	Antiemetic acting on NK1 receptors. May also provide some visceral analgesia
Metoclopramide	1 mg/kg/24h CRI	Central antiemetic effect in cats questionable due to lack of dopaminergic receptors, but peripheral prokinetic effects
Sucralfate	250 mg/cat PO q8–12h	Protects against esophageal, gastric, and duodenal ulceration
Hepatoprotection		
S-adenosyl-L-methionine (SAM-e)	20–40 mg/kg PO q24h 90 mg/cat/day	Nucleotide essential for major hepatic biochemical pathways with antioxidant and hepatoprotective properties. A higher dose is required if enteric-coated tablets are crushed for administration via feeding tube
Ursodeoxycholic acid (UDCA)	10–15 mg/kg PO q24h	Synthetic hydrophilic bile acids that aid bile flow. It has antiinflammatory, immunomodulatory, and antifibrotic activities, and is cytoprotective to hepatocytes
Milk thistle (common name for *Silybum marianum*)	20–50 mg/kg per day Optimal dosage unknown	Contains silibinin (sylibin/silymarin); may be useful for treatment of chronic and acute liver disease, and may modulate cirrhosis. Evidence base is limited
Immunomodulation		
Chlorambucil	2 mg/cat PO q48h (>4 kg) 2 mg/cat q72h (<4 kg)	Immunosuppressive effect is not well documented
Prednisolone	1–2 mg/kg PO q12h (LC) tapering to 0.5 mg/kg q24h 0.5 mg/kg PO q12–24h (NC)	Immunosuppressive doses used for LC; antiinflammatory doses used for NC

CRI, constant rate infusion; IM, intramuscular; IU, international units; IV, intravenous; LC, lymphocytic cholangitis; NC, neutrophilic cholangitis; PO, by mouth (*per os*); SC, subcutaneous; TM, transmucosal.

Vitamin supplementation is usually beneficial in anorectic cats. B vitamins become rapidly depleted and thiamine deficiency can contribute to neurologic signs, while cobalamin deficiency can exacerbate anorexia. Vitamin E is an antioxidant that also has antiinflammatory properties. Vitamin K supplementation may be required to correct coagulopathies (Table 63.2).

Symptomatic therapy can include antiemetics (e.g., metoclopramide or maropitant) and gastroprotectants (e.g., H2 blockers, proton pump inhibitors, sucralfate). Control of vomiting is important for patient comfort and to reduce the risk of feeding tubes becoming dislodged. Gastroprotectants may be beneficial due to the presence of concurrent inflammatory bowel disease and to address gastritis induced by persistent vomiting (see Table 63.2).

S-adenosyl-L-methionine (SAM-e) has a number of hepatoprotectant effects: it is a glutathione precursor (hence antioxidant properties), it stabilizes cell membranes, and it modulates inflammatory cytokines. As low glutathione levels are present in a high percentage of cats with hepatobiliary disease, administration of SAM-e should be beneficial, although no published data exist to support this claim (see Table 63.2).

Ursodeoxycholic acid (UDCA) is a hydrophilic bile acid that has a number of benefits: choloresis, that is, making the bile more liquid and promoting bile flow; replacement of more toxic, hydrophobic bile acids; antiapoptosis; antioxidant; and immunomodulation (see Table 63.2). It has been used as the sole therapy for treatment of primary sclerosing cholangitis in people, but its use as sole therapy for treatment of LC in cats did not compare favorably to prednisolone.

Immunosuppression is considered important for the management of LC, but should only be commenced once NC has been ruled out. Prednisolone is typically employed, starting at higher, immunosuppressive doses and tapering to as low a dose as possible once in remission (see Table 63.2). Some authors have also advocated the use of methotrexate or chlorambucil.

Development of fibrosis is seen with progression of the disease. While the use of colchicine to reduce fibrosis has previously been advocated in dogs, there are no studies to demonstrate benefit. Moreover, its use can be associated with significant side-effects. Current medical advice suggests that it not be recommended, although silymarin and UDCA may have potential antifibrotic effects.

Our poor understanding of the etiopathogenesis of the cholangitis-cholangiohepatitis complex, and lack of controlled clinical trials, combined with an inability on occasions to obtain diagnostic samples before antibacterial therapy, can often result in initiation of therapy with an antibacterial along with other supportive therapies as indicated. If a diagnosis of NC has been made, and improvement has plateaued, prednisolone at antiinflammatory doses could be introduced as this may be beneficial in attenuating the inflammatory response.

Prognosis

Prognosis will depend on the severity of the disease. Obstruction of the bile duct, necessitating surgical intervention, has a guarded prognosis, particularly where biliary diversion surgery is required. Cats with ascites similarly have a guarded prognosis as this is likely to represent the presence of significant fibrosis. However, cats that survive the initial acute phase of NC or that are diagnosed with LC often go on to live for several years. Relapses are possible, especially if there is a concurrent condition such as pancreatitis that may be difficult to control.

Lymphocytic cholangitis is likely a progressive disease, and dilation of the bile ducts may be irreversible. This has been proposed to increase the risk of these cats developing ascending infections and potentially cholecystitis, therefore although recurrence is not inevitable, periodic monitoring of liver parameters +/- ultrasonographic evaluation of the biliary system may be warranted.

Further Reading

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64

Canine Inflammatory Liver Disease

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The most frequently identified inflammatory liver diseases in dogs are nonspecific reactive hepatitis, acute hepatitis (AH), and chronic hepatitis (CH) and their histologic appearance has been standardized by the World Small Animal Veterinary Association's (WSAVA) Liver Standardization Group. Nonspecific reactive hepatitis represents a nonspecific response to a variety of extrahepatic disease processes, especially febrile illnesses and inflammation somewhere in the splanchnic bed. Histologically, it is characterized by an inflammatory infiltrate in portal areas, and sometimes in the parenchyma, without evidence of hepatocellular necrosis or apoptosis. It results from a disease occurring outside the liver, so will not be discussed further. AH is characterized by a combination of inflammation and hepatocellular apoptosis and necrosis, with the specific features varying according to the cause. The majority of AH cases occur as a result of toxin or drug ingestion, and are discussed further in Chapter 62.

Acute hepatitis can sometimes be caused by infection with certain bacteria or viruses, and these are detailed below. CH is defined histologically by the presence of hepatocellular apoptosis or necrosis, a variable mononuclear or mixed inflammatory cell infiltrate, regeneration, and fibrosis. It is the most frequently identified canine inflammatory liver disease and so will be the focus of most of this chapter.

Chronic Hepatitis

Etiology/Pathophysiology

The development of fibrosis is the key pathologic change that leads to the development of CH. The hepatic stellate cell, also known as the Ito cell or lipocyte, is central in the development of fibrosis in humans and rats, and evidence also suggests its involvement in the pathogenesis of hepatic fibrosis in dogs. Hepatic stellate cells reside in the space of Disse, between the sinusoidal endothelial cells and the hepatocytes. In the healthy liver, they are the major storage site of vitamin A, but in chronic liver injury they are stimulated to transform into collagen-secreting, activated cells that express smooth muscle-specific alpha-actin and secrete high-density matrix and collagen into the space of Disse. The secretion of collagen and formation of fibrous tissue from activated stellate cells are believed to be indirect via the release of cytokines from inflammatory cells, although some inflammatory mediators act on them directly. Fibrous tissue within the liver leads to the development of intrahepatic portal hypertension by altering sinusoidal tone and blood flow. The development of portal hypertension results in many of the complications of chronic liver disease such as ascites and gastrointestinal (GI) ulceration. The known or postulated causes of CH are listed below, although the majority of cases have no identifiable cause and thus are termed idiopathic.

Infectious Causes

Canine Acidophil Cell Hepatitis Virus

A potential viral cause of AH and CH was identified in 1985 and named "canine acidophil cell hepatitis virus" although no specific agent was isolated. Histopathologic examination revealed an inflammatory infiltrate with areas of hepatocyte necrosis and scattered numbers of large cells with acidophilic cytoplasm, termed "acidophil cells." When liver homogenate and serum from affected dogs were injected into naive animals, this resulted in the development of clinical and pathologic changes of AH that in some dogs progressed to CH. However, no further work to identify the potential transmissible hepatitis-causing agent was performed, nor have further reports emerged.

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Canine Adenovirus-1

Adenoviruses are medium-sized viruses, two of which are known to infect dogs: canine adenovirus type 1 (CAV-1) and canine adenovirus type 2 (CAV-2). CAV-1 is well known as a cause of AH in nonimmune dogs, but CH has also been experimentally reproduced in partially immunized dogs challenged with CAV-1. However, several studies have failed to identify CAV-1 in liver tissue from large numbers of clinical cases of CH.

Canine Hepacivirus

A novel virus, canine hepacivirus (CHV), was recently identified in outbreaks of respiratory illness in dogs from animal shelters in the USA. CHV was also identified at low levels in hepatocytes dogs that died of "unexplained GI illness" although the results of liver histology were not reported. Despite CHV being identified in canine liver tissue, it is unclear if this virus is hepatotrophic or if it causes disease. However, in two recent studies, there was no evidence of exposure to, or a carrier state of, CHV in large cohorts of dogs with CH, suggesting that the virus is probably not associated with canine CH.

Hepatitis Viruses A, B, C, E, and GBV-C

Although hepatitis B (HBV) and C viruses (HCV) are by far the most frequent causes of human chronic viral hepatitis, several other viruses are implicated. The more frequently described include hepatitis A (HAV) and E viruses (HEV), and GB virus-C (GBV-C), although these are generally associated with the development of AH. However, previous attempts using polymerase chain reaction (PCR)-based approaches have failed to identify HAV, HBV, HCV, HEV, and GBV-C in liver tissue from large numbers of dogs with CH.

Bacteria

Infection with leptospires is a well-known cause of AH, as detailed later in this chapter. Infection with leptospires can also cause CH, with histologic changes consisting mainly of lymphoplasmacytic, portal and intralobular inflammation, hepatocyte necrosis, and biliary stasis. The organisms are relatively sparse and difficult to find with conventional staining techniques, so it is possible that CH associated with leptospirosis is underrecognized. Using nested PCR, a recent study failed to detect *Leptospira* spp. DNA in 98 dogs with CH.

Infection with other bacteria is a relatively uncommon cause of CH. Bacillus piliformis, Helicobacter canis, Ehrlichia canis and Bartonella spp have also been identified in dogs with CH, but causality has not been clearly established. Dogs do develop cholangitis or cholangiohepatitis, and this is covered in further detail in Chapter 67. Additionally, granulomatous hepatitis is an unusual presentation, in which the predominant cell type present is the macrophage. Lesions are usually multifocal and have been associated with numerous bacteria, including *Nocardia*, *Mycobacterium*, *Rhodococcus*, *Bartonella*, and *Borrelia*. Chronic hepatic leptospirosis is a particular concern in these cases and should be ruled out with fluorescent in situ hybridization (FISH). In addition, several fungi have been associated with this specific histologic diagnosis.

Autoimmunity

An immune-mediated aetiology to human liver disease is well recognised, and the criteria for its diagnosis are well established. Diagnosis is based on increased serum alanine aminotransferase (ALT) activity, presence of positive serum autoantibody titres, increased serum IgG concentration, characteristic histopathology findings, and exclusion of other aetiologies. However, there is only anecdotal evidence for an immune-mediated cause to canine CH. Circulating autoantibodies were present in the serum of dogs with a variety of liver diseases, and antiliver membrane protein antibodies have been identified in serum of dogs with CH. However, the question that remains from all these studies is whether these autoantibodies are the primary cause of the disease, i.e. suggestive of an autoimmune aetiology, or whether they are a secondary phenomenon. Peripheral blood mononuclear cell proliferation in response to liver membrane protein was also significantly higher in dogs with CH compared to control dogs. Moreover, high numbers of CD3+ lymphocytes are found in the liver of dogs with CH, again suggesting the involvement of the immune system in the etiology of the disease. An immune-mediated aetiology to CH in some dogs is also suggested by the fact that there is a female gender predilection, along with clearly defined breed predispositions. In addition, the association of certain susceptibility and resistance MHC class II haplotypes with CH indicates a role of the immune system in disease development, although this does not necessarily point to an autoimmune aetiology.

Copper

The accumulation of copper in liver tissue has been described in several breeds of dog. Excessive accumulation includes that seen in copper-associated hepatitis, sometimes known as true "copper storage" disease, where the primary initiating event is a defect in copper excretion leading to secondary hepatocyte damage, and the copper accumulation which occurs secondary to an underlying inflammatory liver disease. Copper-associated hepatitis was first described in the Bedlington terrier over three decades ago. Since then, many studies have detailed its clinical course and pathologic features,

including the progressive accumulation of copper in hepatocytes starting in zone 3 and leading to the development of CH. Copper-associated hepatopathies have been reported in several breeds of dog including the Dalmatian, Labrador retriever, Skye terrier, West Highland white terrier, and Doberman pinscher. These may not be true copper storage diseases as copper does not build up throughout life, and the amount of copper stored is often not correlated with the severity of the underlying disease. Although uncommon in the United Kingdom, copper-associated hepatopathy is increasingly seen in other countries, especially The Netherlands. Disorders associated with excess copper accumulation are covered in more detail in Chapter 62.

Epidemiology

Historically, the term *canine CH* was poorly defined and used to describe a variety of inflammatory liver diseases. The terms *chronic active hepatitis* and *chronic lobar hepatitis* were used early in the description of the disease, although these names have now largely been abandoned in favor of CH. Improvements in the classification of canine CH were brought about by the WSAVA Liver Standardization Group which established standardized histologic criteria for diagnosis. Since the publication of these criteria, one study has demonstrated a postmortem prevalence of 12% in a first opinion practice setting in the UK. Data to assess the prevalence of the disease in other countries are not available, although anecdotally CH appears to be the most frequently identified inflammatory liver disease in dogs worldwide.

Signalment

Chronic hepatitis typically affects middle-aged to older dogs, with the median age for all breeds in a recent study being 8 years (range, 7 months to 16 years). Females appear to be predisposed, with a female to male ratio of 1.5:1.0 in one study. Several reports detail breed predispositions to CH. The first of these was performed on a Swedish population of dogs, and demonstrated that the American and English cocker spaniel, West Highland white terrier, Labrador retriever, Doberman pinscher, and Scottish terrier had an increased risk for CH. In this study, the disease was reported to occur more commonly in middle-aged to older animals and there was a gender predisposition in male English and American cocker spaniels and female Labrador retrievers. A recent study performed in the UK assessed the breed distribution by comparing the signalment of 551 cases with a histologic diagnosis of CH to that of a large control population. From a total of 61 breeds, the American cocker spaniel, cairn terrier, Dalmatian, Doberman pinscher, English cocker spaniel, English springer spaniel, Great Dane, Labrador retriever, and Samoyed were found to be at increased risk for developing CH (Table 64.1).

Table 64.1 Age and gender data for breeds with an increased risk for developing canine chronic hepatitis

Breed	Median age at diagnosis (range)	Gender
American cocker spaniel	5 years 6 months (2 years to 11 years 3 months)	1F, 5M
Cairn terrier	10 years 2 months (7 years to 13 years 5 months)	4F, 5M
Dalmatian	4 years 7 months (3 years to 12 years)	9F, 1M
Doberman pinscher	5 years 4 months (2 years 6 months to 10 years)	16F, 8M
English cocker spaniel	8 years 9 months (1 year 3 months to 14 years)	34F, 19M
English springer spaniel	5 years (1 year 2 months to 11 years)	60F, 20M
Great Dane	6 years 2 months (1 year 2 months to 7 years 11 months)	3F, 3M
Labrador retriever	8 years 3 months (2 year 8 month to 13 years)	63F, 32M
Samoyed	10 years (3 years 1 month to 11 years)	2F, 3M

F, female; M, male.

History and Clinical Signs

Clinical signs in dogs with CH vary, and are usually nonspecific and insidious in onset. Sometimes another disease, stress or therapy causes sudden decompensation. The liver has tremendous functional and structural reserve, and a significant loss of normal hepatic tissue can occur with minimal or no change in clinical signs. In addition, the liver has a remarkable capacity to regenerate following hepatic injury, providing the damage is not too severe or ongoing. Overt liver failure does not develop until at least 70–80% of functional capacity is lost, so the development of clinical signs implies marked impairment of liver function. In addition, some dogs with advanced CH or cirrhosis can be asymptomatic, or alternatively may present with signs of "acute" liver disease.

The clinician should pay particular attention to subtle waxing and waning GI signs, depression, lethargy, anorexia, weight loss, and polyuria and polydipsia. Additional signs that may be more suggestive of CH, although still not specific, include jaundice, ascites, coagulopathy, and neurologic signs caused by hepatic encephalopathy.

Clinical signs of hepatic encephalopathy, which are often intermittent, include behavioral changes, hypersialism, head pressing, circling, ataxia, temporary blindness, seizures, and coma. In one study of 101 dogs with both AH and CH, the most commonly identified clinical signs were lethargy (56/101), anorexia (56/101), vomiting (48/101), polyuria and polydipsia (47/101), and weight loss (28/101).

Physical examination findings are generally relatively unremarkable. Poor body condition is often seen in animals with CH. With progressive disease and the further development of fibrosis, liver size reduces in dogs with CH. Ascites and icterus may also be seen with chronic disease.

Diagnosis

Clinical Pathology

Clinical pathology is usually the next step in the investigation of a dog with suspected CH. Sometimes, results of clinical pathology performed for another reason, for example as a preanesthetic blood screen, may fortuitously reveal the presence of CH. Clinical pathology findings include elevations of liver enzymes, especially hepatocellular enzymes released as a result of liver cell damage, namely ALT and aspartate aminotransferase (AST). Increased ALT activity is the primary clinical laboratory finding in dogs with CH, and is raised in over 90% of cases. In addition, the markers of cholestasis, alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT), are invariably elevated. It is important to remember that liver enzyme activity is not a test of liver function, and very occasionally a dog with advanced CH may have liver enzymes within the reference interval. In addition, elevations in liver enzymes are not an uncommon reaction to many other diseases and these elevations can sometimes be marked.

While liver enzymes do not give any indication of liver function, there are other tests on the biochemistry panel which provide some information about liver function. Due to the development of fibrosis, liver function in dogs with CH is progressively compromised, and so these markers are particularly useful in diagnosis. With progressive liver dysfunction, levels of albumin, urea, glucose and coagulation factors decrease, while the concentration of bile acids, ammonia, and bilirubin increases. Hypoalbuminemia occurs in about 40% of cases, although with advanced disease (cirrhosis), this increases to 75%. None of these tests are completely specific for liver disease, so they should always be interpreted in the light of other clinical and clinicopathologic findings.

Both qualitative and quantitative abnormalities in erythrocytes may also be present in dogs with CH, in combination with alterations in white cell and platelet numbers. The more frequently encountered abnormalities in dogs with CH include mild nonregenerative anemia of chronic disease, which is normocytic and normochromic. Sometimes abnormal red cells including acanthocytes (irregular large surface projections) and/or target cells (codocytes), which are dense-centered cells surrounded by a clear area, can be identified on a blood smear. Dogs with CH may have a neutrophilic leukocytosis, although this is a nonspecific change. Thrombocytopenia may develop due to platelet sequestration or increased destruction, and alterations in platelet function (thrombocytopathies) may also occur.

Abnormalities may be present in the urine of dogs with CH, including a low specific gravity (<1.030), bilirubinuria, increased urobilinogen, urate crystals, and occasionally urate calculi. Approximately 10% and 60% of dogs have prolonged prothrombin time (PT) and partial thromboplastin time (PTT) respectively.

Diagnostic Imaging

Diagnostic imaging is usually the next step after clinical pathology in the assessment of the dog with suspected CH. Abdominal radiography can be used to assess liver size, as dogs with CH may have a reduced liver size. However, the liver may appear normal on routine radiographic evaluation, even when severely diseased. Ultrasonography is the preferred imaging modality for the investigation of liver disease. In one study of 67 dogs with CH, only 15 had no identifiable ultrasonographic abnormalities. Hepatic size was assessed as normal in 26, enlarged in eight and small in 26. Hepatic structure was found to be normal in 27, irregular in 31, and 11 had increased echogenicity. Nodular processes were observed in 16 dogs and ascites was present in 18. The reader is referred to Chapter 61 for further details on diagnostic imaging in the investigation of liver disease.

Liver Biopsy

It is not possible to make a definitive diagnosis of CH from the results of clinical pathology or diagnostic imaging. In some cases, a tentative diagnosis can be made but definitive diagnosis ultimately relies on histologic examination of liver tissue. Moreover, descriptors of severity of inflammation and the amount of fibrosis are provided, and these can be used prognostically and therapeutically. Liver histology will give vital information to help establish the most appropriate therapy. Without a biopsy, therapy of CH will be at best nonspecific and at worst counterproductive. Many methods are available for collection of liver tissue, and the method used will depend on clinician preference, availability of equipment, technical skill, type of lesion present, location, and clinical stability of the patient. Further details about the methods for collection of liver tissue are detailed in Chapter 60. The recently published ACVIM Consensus statement on the diagnosis and treatment of chronic hepatitis in dogs, recommends a wedge

biopsy taken at laparoscopy or laparotomy because trucut biopsies produce misleading results 50% of the time and also carry an increased risk of haemorrhage. Needle aspiration cytology is not reliable for the diagnosis of CH and is therefore not recommended.

The only real absolute contraindication for liver biopsy is severe coagulopathy. Prior to biopsy, coagulation status should be checked, by way of platelet count, measurement of PT, PTT, and ideally thromboelastography. In humans, thromboelastography can predict bleeding tendencies in cirrhotic patients, but data does not exist in dogs to determine how reliable this is as an assessment of bleeding tendencies. However, assessment of coagulation status should not be a substitute for proper technique and adequate postoperative care. If coagulation times are prolonged, vitamin K can be given by injection 24 hours prior to biopsy and then coagulation times retested. An alternative approach, if available, is the use of fresh-frozen plasma to assist in replenishing deficient coagulation factors. All animals should be hospitalised and monitored carefully for signs of hemorrhage for at least 12 hours after biopsy.

As detailed previously, standardized criteria for the histologic diagnosis of CH exist. The standard histochemical stain used in the assessment of liver tissue is hematoxylin and eosin, but consideration should be given to the use of additional stains for specific features such as reticulin (connective tissue), Perls' Prussian blue (ferritin), Fouchet's (bile pigments) and periodic acid–Schiff (polysaccharides). In addition, specific histochemical stains for copper, such as rubeanic acid or rhodanine, should be consider in at-risk breeds (see earlier) (Figure 64.1).

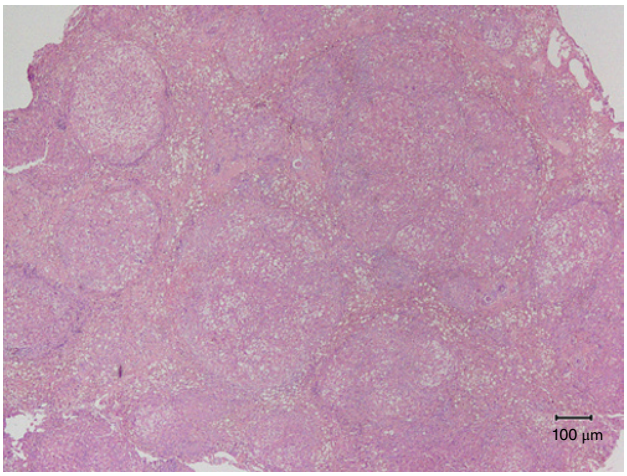


Figure 64.1 Low-power photomicrograph of liver tissue from an English springer spaniel demonstrating disruption to the normal architecture by a marked and generalized infiltrate of inflammatory cells and also bundles of fibrous tissue. Hematoxylin and eosin. Original magnification ×40.

Therapy

Therapy for CH is aimed at the underlying cause, if known. However, as the etiology of most cases is currently not understood, specific therapies are usually not possible. Hepatocytes have a remarkable capacity for regeneration, which means that early diagnosis and therapy have the potential to reverse disease mechanisms. It is also important to initiate therapy as early as possible in an attempt to inhibit fibrosis, which will ultimately lead to functional impairment. Therapy aimed at addressing clinical signs of liver disease, including ascites, GI ulceration leading to melena, and hepatic encephalopathy, is also an important part of therapy of the dog with CH. Copper chelators are important in dogs with copper-associated hepatitis. Careful dietary management to support the liver is essential too. Unfortunately, in veterinary medicine there is a lack of controlled studies on clinical efficacy and pharmacokinetics of the drugs commonly used in canine CH. As a result, many of our current therapeutic protocols are either derived from human hepatology or anecdotal reports or originate from low-quality veterinary clinical studies. The following refers to the recommended therapy of a dog with CH.

Corticosteroids

Corticosteroids have antiinflammatory, immune-modulating, and antifibrotic properties. They have a potent indirect antifibrotic action via reducing prostaglandin and leukotriene production from inflammatory cells, and a weak direct antifibrotic action by inhibiting mRNA and enzymes. Corticosteroids are indicated in the therapy of CH where there is biopsy evidence of ongoing inflammation, when there is mild to moderate fibrosis associated with an inflammatory infiltrate, and when infectious causes have been ruled out as far as possible. However, steroids are not without adverse effects, and these can be very severe and potentially life-threatening in some dogs with CH. Adverse effects include increased protein catabolism, fluid retention, GI ulceration, and risk of infections. Their use in humans with ascites, GI ulceration, and encephalopathy has been shown to decrease survival time, and the same is likely to be true in dogs. These are patients with portal hypertension. As advanced bridging fibrosis or cirrhosis is likely to be associated with portal hypertension, corticosteroids are therefore contraindicated if there is biopsy evidence of these changes. Dexamethasone tends to cause more adverse effects than prednisolone and should be avoided.

There have been limited numbers of studies evaluating the use of corticosteroids in dogs with CH. In an early study, prednisolone was used in 151 dogs at a dose of 2.2 mg/kg/day for 7–14 days, and resulted in increased

survival from a median of ten months to thirty months, and complete remission was reported in some dogs with no relapse. However, the diagnosis of CH was not made according to our current histologic criteria. In a more recent study of 36 dogs with idiopathic CH treated with prednisolone at 1 mg/kg/day for at least six weeks, at follow-up 11 dogs were in complete remission, eight dogs had recurrent clinical signs, and 17 had residual disease. In a prospective study of CH in English Springer spaniels, 14 dogs were treated with prednisolone at a mean dose of 1.2mg/kg/day. These dogs all demonstrated improved survival over a historical control group, and there was improvement in liver enzyme activity and bilirubin in all. Finally, a retrospective study demonstrated that when 13 Cocker spaniels were treated with prednisolone 0.5-1.25mg/kg/day, in combination with azathioprine, there was a longer survival than a historical control group. . In these reports, some dogs with CH demonstrate an improvement in clinical signs, laboratory data or histopathology, inferring an immunomodulatory or anti-inflammatory benefit. However, limited conclusions can be drawn from most of these studies, as the underlying cause of CH wasn't often known. In addition, variable doses of immunosuppressive drugs were used, and dogs usually received concurrent therapies. If there is strong evidence for an immune-mediated causes to CH (see earlier), the clinical should consider using an immunosuppressive dose of corticosteroids. However, if infectious causes have not been ruled out, and especially if hepatic histology is not typical for an immune-mediated aetiology, a lower dose should be used.

The duration of corticosteroid therapy, or method of dose reduction in dogs with CH is also not known. In human patients, corticosteroids are continued for at least six months beyond remission, and in some cases life-long. It is often difficult to assess remission in dogs, particularly as corticosteroids induce hepatic enzymes and so confuse attempts to follow the disease clinicopathologically. Repeat liver biopsy can be very useful, although sometimes results are nonrepresentative if the disease is patchy in distribution. The length of therapy therefore remains empiric and some animals remain on life-long therapy. In this situation the aim is to use a low alternate-day dose. Using an additional immunosuppressive alongside corticosteroids may enable a more rapid tapering of the corticosteroid.

Ciclosporin has also been used as an additional, or alternative, immune-modulating drug in canine CH. . In a retrospective study 48 dogs with suspected idiopathic CH were treated with 5.0mg/kg BID cyclosporine; 79% of dogs achieved biochemical remission, although no follow-up biopsies were taken to determine the effects of therapy on hepatic histology.

Antifibrotics

Progressive fibrosis in CH ultimately leads to reduced function and many of the clinical consequences of advanced liver disease. The most effective 'anti-fibrotic' in chronic liver disease is to remove the underlying cause. In addition to the antifibrotic action of corticosteroids, more specific antifibrotics exist. Colchicine, an alkaloid that binds tubulin, may be useful in some dogs with CH and moderate to marked fibrosis on biopsy, although it is not licensed for use in animals. Although it may improve survival in some human patients with advanced fibrosis, there are very limited reports of its use in dogs. If used, care should be exercised as adverse effects, including marrow suppression, anorexia and diarrhea, are seen relatively commonly. Again, it is very difficult to judge how long to treat for and a follow-up liver biopsy is necessary to assess response. The author does not use colchicine.

Cholerectics and Bile Acid Modifiers

Ursodeoxycholic acid (ursodiol, UDCA) is a hydrophilic bile acid that displaces toxic hydrophobic bile acids and also stimulates bile flow (it is a cholerectic). These two actions reduce cell damage and oxidative stress resulting from retention of bile acids in the liver. It has also been shown to have immunomodulatory actions by reducing immunoglobulin and interleukin production and expression of MHC-1 on hepatocytes. Recent studies show an additional antioxidant activity with a synergistic action with S-adenosyl-L-methionine (SAM-e) and vitamin E. No data on its use in canine CH are available, although because biliary stasis is invariably present, it is probably indicated in all cases. It also appears to be well tolerated with no significant adverse effects reported to date.

Antibiotics

The majority of dogs with CH do not appear to have an underlying bacterial etiology, and so do not require antibiotics. Having said that, due to compromised reticuloendothelial function, bacterial infections may be a secondary complication of many liver diseases, including CH, and so their use may be justified. Moreover, antibiotics should also be used if the patient has signs of hepatic encephalopathy. Because of their efficacy against enteric organisms and ability to concentrate in bile, suitable antibiotics include ampicillin, amoxicillin, cephalexin, fluoroquinolones, and metronidazole. Note that, because of its reliance of hepatic clearance, metronidazole should be used at half the routine dose in dogs with liver disease to avoid toxic adverse effects. The use of antibiotics in dogs with bacterial cholangitits/cholangiohepatitis is discussed in Chapter 67.

Antioxidants

These include vitamin E, zinc, silymarin (milk thistle), and SAM-e. Oxidant stress is likely to be increased due

to the effects of inflammation, reduced blood flow, and mitochondrial damage by refluxed bile acids. Oxidation is a significant mechanism of hepatic damage, therefore antioxidant therapy is reasonable. SAM-e increases hepatic and red blood cell levels of glutathione, a potent antioxidant, and is also a critical enzyme in transmethylation, transsulfuration, and aminopropylation pathways. As part of these pathways, SAM-e is essential to all cells and is particularly important in hepatocytes because of their central role in metabolism. It is widely available as a neutraceutical for dogs, sometimes in combination with silymarin. Although no experimental data exist, antioxidants are likely of benefit in CH. However, not all antioxidants are necessarily innocuous in liver disease; for example, ascorbate may increase liver damage by accumulating iron, so it is best to avoid supplementing vitamin C.

Copper Chelators

Copper chelators include 2,3,2-tetramine tetrahydrochloride (2,3,2-T), 2,2,2-tetramine tetrahydrochloride (2,2,2-T), penicillamine, and zinc. 2,3,2-T is the more potent chelator but is not widely available in a drug formulation. Penicillamine is an alternative copper chelator, but significant adverse effects can be associated with its use. Copper chelators should be reserved for dogs in which significant copper accumulation has been identified in liver tissues, primarily those animals with copper storage disease. Zinc is used as prophylaxis in dogs with copper storage disease, and commercially produced hepatic support diets often contain increased zinc for this reason. The use of copper chelators for the management of copper-associated hepatitis is discussed in Chapter 62.

Diuretics

Ascites in CH is usually due to portal hypertension, although in some animals hypoalbuminemia may contribute to the pathogenesis. If blood albumin is normal or near normal in the ascitic dog, portal hypertension is likely to exist. Portal hypertension leads to splanchnic pooling of blood with subsequent reduction in systemic arterial pressure and activation of the renin-angiotensin-aldosterone system (RAAS). RAAS activation then leads to further fluid retention and more ascites. Spironolactone, an aldosterone antagonist, is therefore the drug of choice in ascitic patients with portal hypertension, although it can take 2–3 days to work. For this reason, spironolactone combined with a thiazide diuretic or furosemide can be used in an attempt to increase its speed of action. Spironolactone also has the advantage that it does not induce hypokalemia, which can precipitate hepatic encephalopathy (HE) (hypokalemia allows ammonia to enter cells more easily).

Gastroprotectives

Portal hypertension is common in dogs with CH and leads to gut wall edema and potentially ulceration. This is one of the most common causes of death in dogs with chronic portal hypertension. Sudden GI bleeding can precipitate an acute encephalopathic crisis due to the high protein content of blood. An important way to reduce the incidence of GI tract ulceration is to ensure adequate enteral nutrition (see later), as anorexia predisposes to GI ulceration. H2 receptor antagonists, or proton pump inhibitors, are often used in the prevention and therapy of ulceration. However, there is some evidence that gastric pH is actually elevated in human CH, and, moreover, many ulcers are duodenal rather than gastric, so the rationale for these drugs is unclear. Traditionally, ranitidine is preferred as an H2 receptor antagonist in liver disease as it does not affect the cytochrome P450 system, and sucralfate should probably be used also.

Dietary Management

Appropriate dietary management is as important as drug therapy in the dog with CH. Each case is individual and the diet should be adjusted accordingly, so clinicians should resist the temptation to think that "one diet fits all." In particular, many dogs with CH are fed diets with inappropriate and excessive protein restriction, which may restrict hepatic regeneration and result in protein-calorie malnutrition. Specific recommendations include the following.

- Feed a palatable diet little and often (4–6 times a day) as many dogs with CH may be inappetent. Frequent feeding also reduces the development of HE.
- Feed highly digestible, high-quality protein in normal amounts whenever possible. Good-quality commercial diets are acceptable. Examples of high-quality proteins include soya and these can be supplemented if weight or blood albumin decreases. If signs of HE are suspected, feeding a normal amount of high quality digestible protein little and often is recommended. Excessive protein restriction may result in protein-calorie malnutrition and the breakdown of highly ammoniagenic endogenous proteins.
- Dogs with CH may have impaired carbohydrate metabolism, so a diet containing highly digestible, complex carbohydrates should be fed.
- Normal amounts of fat should be fed, although fat can be restricted if steatorrhea develops.
- Fermentable fiber is helpful in dogs with HE as it acidifies the colon and traps ammonia. It also increases nitrogen incorporation into bacteria and reduces bacterial ammonia production. Nonfermentable fiber is helpful in preventing constipation, a predisposing factor for hepatic encephalopathy.

- Zinc deficiency is common in human CH and is thought to also occur in dogs with CH. Supplementation reduces HE and decreases copper absorption from the GI tract and copper availability in the liver. Zinc may also have antiinflammatory, antifibrotic, and antioxidant effects.
- In dogs with excessive hepatic copper accumulation, primarily those with a primary copper storage disease, copper intake should be restricted. This includes not providing water from copper pipes in soft water areas.
- Fat-soluble vitamins include A, D, E, and K. Vitamin E is an antioxidant and can be supplemented in dogs with CH. Vitamin K supplementation may occasionally be necessary if clotting times are prolonged, especially preceding biopsy. Vitamins A and D should not be supplemented as vitamin A can cause hepatic damage and vitamin D can cause calcification in tissues.
- Vitamin B, a water-soluble vitamin, can also be supplemented, as there may be increased loss associated with polyuria.

The effectiveness of dietary therapy should be monitored by the assessment of clinical signs and making sure that the patient maintains body weight and blood protein levels. Consideration should also be given to the use of enteral feeding methods in the anorexic dog with CH.

Prognosis

The prognosis for CH is variable, and likely dependent on multiple factors, especially the underlying etiology and stage of disease. The presence of advanced fibrosis and cirrhosis is strongly associated with a reduced survival time in humans with CH, and the same appears to be true in dogs. In one study, the median survival time of a variety of breeds of dogs with CH was 18.3 months. Other studies have demonstrated mean survival times of approximately 18 months and 16 months, again in a variety of breeds of dog with CH. In Labrador retrievers with CH, the median survival was 374 days (range, 1–2645 days), whereas in English springer spaniels it was 189 days (range, 1–1211 days).

One of the most important individual prognostic indictors in CH appears to be the presence of ascites; the time from onset of clinical signs to death was two months for dogs with ascites, compared to 33 months for those without. Total serum bilirubin has also been shown to be significantly negatively correlated with a reduced survival time in dogs with CH. Other parameters associated with a shorter survival time in dogs with CH include anorexia, prolonged prothrombin time, prolonged partial thromboplastin time, thrombocytopenia, hypoalbuminemia, and hyperglobulinemia. Caution should, however, be employed when interpreting these data in the individual dog with CH, as prognosis is likely dependent on multiple variables.

Acute Hepatitis

Etiology/Pathophysiology

The majority of cases of AH are idiopathic. Of the known causes, toxin or drug ingestion is thought to be most common, and is discussed further in Chapter 62. Other causes of AH are discussed here.

As detailed previously, a potential viral cause of AH and CH was identified some 30 years ago and named "canine acidophil cell hepatitis virus." However, no specific agent was isolated, nor have further reports emerged. CAV-1 is probably the best known infectious cause of AH, particularly in non-Immune dogs, but it can occasionally cause disease in partially immune dogs. However, the use of widespread vaccination against this disease has significantly reduced its incidence, so cases of clinical disease are now uncommon.

Probably the most frequently implicated infectious cause of AH is due to *Leptospira* spp. The characteristic hepatic lesions in acutely infected dogs include edema and sinusoidal congestion, perivascular inflammation, hepatocyte necrosis, and cholestasis. Some animals also present with signs of renal dysfunction. Widespread vaccination has significantly reduced the incidence of disease although, at least in the UK, the majority of dogs are only vaccinated against two serovars. Clinical cases of leptospirosis due to infection with other serovars occur, so the use of vaccines providing protection against these additional serovars is recommended. Infection with other bacteria is a relatively uncommon cause of canine AH, although dogs do develop cholangitis or cholangiohepatitis.

Defects in copper metabolism leading to the development of AH have also been described in several breeds of dog. In one study of 21 dogs with AH, five had histologic evidence of increased copper accumulation and were diagnosed with copper-associated hepatopathy.

Epidemiology

Few data exist to determine the prevalence of AH in dogs. In part, this likely represents the failure to achieve a histologic diagnosis in many animals. In one study of 101 cases of primary hepatitis, AH was diagnosed in 21 dogs and CH in 67. Improvements in histologic classification of canine liver diseases, including that of AH, may therefore result in future prevalence studies.

Signalment

Acute hepatitis, like CH, typically affects middle-aged to older dogs, and females appear to be predisposed. In a study of 21 dogs diagnosed with AH, the mean age of

affected dogs was 7.8 +/– 4.1 years, with a range of 2.4–14.5 years. No comprehensive study has been performed to determine the breed predispositions to AH, although in this same study, Jack Russell terriers may have been at increased risk.

History and Clinical Signs

Clinical signs in dogs with AH are usually nonspecific and similar to those described for CH. Interestingly, in one study of dogs with AH, clinical signs had been present for 10.0 weeks (range, 0.5–52 weeks) before diagnosis. Again, the clinician should pay particular attention to subtle waxing and waning GI signs, depression, lethargy, anorexia, weight loss, and polyuria and polydipsia. Clinical signs of HE may also occur in the patient with AH. Physical examination findings are generally unremarkable, although the liver is occasionally palpably enlarged in the dog with AH. Dogs with an infectious etiology may also be pyrexic and show other signs of systemic disease.

Diagnosis

As discussed earlier, clinical pathology is usually the next step in the investigation of a dog with suspected AH. Clinical pathology findings include elevations of liver enzymes, including ALT, AST, ALP, and GGT. In one study, there was no significant difference in any routine biochemical or hematologic variable between dogs with AH and CH. However, if liver function is assessed, it is more likely to be within the reference range in dogs with AH.

Diagnostic imaging is often performed after clinical pathology in the assessment of the dog with suspected AH. Abdominal radiography can be used to assess liver size, although as detailed earlier, ultrasonography is the preferred imaging modality for the investigation of liver disease. In one study of 21 dogs with a histologic diagnosis of AH, all apart from two had abnormalities detected on ultrasonographic examination of the liver. Hepatic size was assessed as normal in seven dogs, enlarged in eight, and small in six. The hepatic parenchyma was found to be normal in seven dogs, irregular in 11, and to have increased echogenicity in three. Interestingly, three dogs with AH had evidence of ascites on ultrasonographic examination.

It is not possible to make a definitive diagnosis of AH based on results of clinical pathology or diagnostic imaging. Definitive diagnosis ultimately relies on histologic examination of liver tissue. However, as animals with AH may be systemically unwell, liver biopsy is often not performed in the acute setting, with patient treatment based on a tentative diagnosis. Fine needle aspiration cytology is not reliable for the diagnosis of AH, and is not recommended.

Therapy

Therapy for AH is aimed at the underlying cause, if known. However, as the etiology of most cases is currently not understood, treatment is generally symptomatic and supportive. In one retrospective study, dogs with AH were treated with antibiotics (5/16), hepatic support diet and ursodeoxycholic acid (7/16), and 5/16 dogs were not treated. Due to the potential for an underlying infectious cause, corticosteroids are usually avoided in dogs with AH . The use of antiviral drugs in dogs with CAV-1 infection has not been studied. Fluid therapy is required if the dog is anorexic, and short-term nutritional support by methods of assisted enteral nutrition is sometimes also required.

Prognosis

The prognosis for AH is variable, and likely dependent on multiple factors, such as the etiology, severity of disease, and how early treatment is instigated. In a previous study, the median survival time of dogs with AH was 34.9 months. It is also possible that AH progresses to CH in some dogs. For instance, in a study of 12 dogs with AH that had a repeat liver biopsy performed after approximately six weeks, histopathology revealed complete remission of inflammatory and degenerative changes in six dogs, no changes in one dog, and progression from AH to CH in five dogs.

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65

Cirrhosis and its Consequences

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Etiology/Pathophysiology

Cirrhosis

Development of hepatic fibrosis and subsequent cirrhosis is a common complication of chronic hepatitis (CH). Cirrhosis is defined histologically by the presence of diffuse bridging fibrosis and regenerative hepatic nodules. CH can be caused by a variety of different initial insults that include toxins or drugs, breed-associated metabolic errors, including disorders of copper metabolism, and infections, although the majority of cases are idiopathic. Regardless of the underlying cause, fibrosis may develop when CH is severe and/or is present for an extended period of time.

Fibrosis develops when hepatic myofibroblast-like cells become activated secondary to hepatic injury. These cells produce factors including transforming growth factor-beta (TGF-beta), which upregulate hepatic extracellular matrix components such as collagen and glycoaminoglycans. TGF-beta also upregulates inhibitors of metalloproteinases, resulting in decreased extracellular matrix breakdown. In CH, these changes result in progressive accumulation of extracellular matrix in the liver. Cirrhosis develops with the diffuse accumulation of fibrous tissue in the liver, resulting in conversion of normal hepatic architecture into structurally abnormal hepatic nodules (Figure 65.1). With the development of cirrhosis, a variety of adverse consequences develop, and these are predominantly related to the development of portal hypertension and progression of hepatic dysfunction.

Portal Hypertension

Portal hypertension (PH) is an increase in blood pressure within the portal vasculature, the vessels responsible for providing venous drainage to the intestines and spleen. The hypertension can be caused by any disease that results in obstruction of venous return of portal blood. PH can be classified according to location of the increase in blood pressure, including prehepatic, intrahepatic, or posthepatic causes. The type of portal hypertension caused by cirrhosis is an intrahepatic form of PH, as opposed to prehepatic PH that occurs in disorders of the portal vein itself, or posthepatic PH that occurs with right-sided heart failure or caudal vena cava disorders. With cirrhosis, hepatic sinusoidal endothelial cells have lost normal fenestrae and acquired a collagenous basement membrane in their place. This change, as well as other remodeling changes in the liver such as regenerative nodules and microthrombi, results in distortion of sinusoids and increases intrahepatic venous resistance, with resultant PH.

Ascites

Once PH is present, ascites may also develop as, according to Starling's law, the increased venous resistance and increase in portal venous hydrostatic pressure drive fluid out of the vasculature and into the interstitial space. Lymphatic drainage of the interstitial space may be able to deal with this extra fluid for some time, but when the regional lymphatics become overwhelmed and unable to control this increase in interstitial fluid, ascites will develop.

Additionally, ascites may develop as a result of hypoalbuminemia secondary to severe liver disease. Albumin is a plasma protein normally produced by the liver, and significant hepatic dysfunction may result in a clinically important decrease in albumin concentration. Albumin is the most important blood protein responsible for maintenance of normal plasma colloid oncotic pressure. If serum albumin levels decrease to less than approximately 1.6 g/dL, plasma colloid oncotic pressure will become too low to maintain intravascular volume and fluid will enter the interstitial space. Animals with cirrhosis will often develop both portal hypertension and

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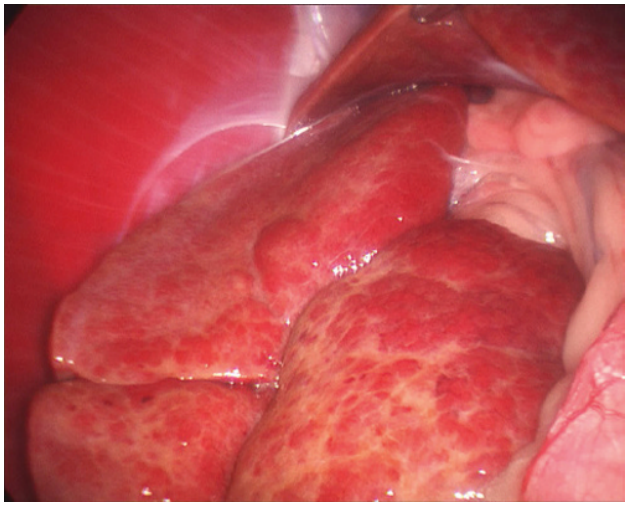


Figure 65.1 Laparoscopic view of a cirrhotic liver secondary to toxin insult from cycad ingestion. Note the pale and undulating appearance of the hepatic tissue.

hypoalbuminemia concurrently, further increasing the risk of development of ascites.

Acquired Portosystemic Shunts

Portosystemic shunts are anomalous venous vessels that join the portal blood with the systemic vasculature, while bypassing the liver. They can be congenital in origin or acquired secondary to cirrhosis/fibrosis or other causes of PH. If PH develops and does not resolve quickly, the development of multiple acquired portosystemic shunts (aPSS) may occur. Acquired shunts are thought to develop in an attempt to decrease PH. Experimentally, it takes 5–14 weeks of PH before acquired shunts develop. This continued increase in hepatic venous portal pressure results in the opening of embryonic vessels that arise between the portal vasculature and the cranial and caudal vena cava, resulting in the formation of multiple aPSS. These shunts vary in anatomic location, but are most commonly visualized as a plexus of small vessels found caudodorsal to the left kidney. They connect the portal vasculature with the vena cava, allowing for venous blood to bypass the liver. This blood remains unfiltered and enters the systemic circulation.

Hepatic Encephalopathy

One of the most important consequences in the development of aPSS is hepatic encephalopathy (HE). In the presence of aPSS, toxins normally filtered by the liver are transported from the gastrointestinal (GI) tract to the rest of the systemic circulation, including the central nervous system (CNS). While many toxins are involved in this process, ammonia is thought to be one of the most important and the only currently measurable encephalotoxin. Ammonia is a breakdown product of ingested proteins, and is normally absorbed by the GI tract, transported to the liver, and metabolized into urea. If aPSS are present, ammonia remains intact and is transported across the blood–brain barrier, resulting in neuronal dysfunction and alterations in neurotransmission. HE may result in increased activation of neuronal gamma-aminobutyric acid (GABA)/benzodiazepine receptors, which are responsible for neuronal suppression.

Gastrointestinal Ulceration

Gastrointestinal ulceration is another possible complication of severe hepatic disease or cirrhosis. In humans, GI ulceration is thought to be related to impaired gastric mucosal defense secondary to alterations in GI motility and circulation, and bile acid secretion. While this condition has been described in people, the etiology has not been evaluated in dogs and cats. Portal hypertension also likely contributes to the development of GI ulceration. Regardless of cause, GI ulceration is a recognized complication of liver disease in animals. If GI bleeding occurs as a result of ulceration, this can acutely increase the risk of HE. Blood is a highly ammoniagenic protein, and may result in a rapid increase of serum ammonia levels when absorbed following the digestion of blood. This rapid increase in ammonia may cause a sudden onset of signs related to HE.

Coagulation Disturbances

The liver is responsible for the production of coagulation factors, recycling and activation of vitamin K-dependent factors and protein C, production of thrombopoietin, and removal of clotting factors from the circulation. In a liver which is severely diseased from cirrhosis, coagulation abnormalities are likely to be present to some degree. Studies have shown that anywhere from 57–93% of dogs, and 82–98% of cats with liver disease have at least one alteration in coagulation parameters. Decreased factor production appears to play the most significant role in secondary hemostatic abnormalities, but consumption of factors due to disseminated intravascular coagulation (DIC) may also occur.

Thrombocytopenia may also occur secondary to liver disease in dogs, but is uncommon in cats. Thrombocytopenia is usually mild, and may occur secondary to decreased thrombopoietin production by the liver, increased sequestration in the spleen as a result of splenic congestion secondary to liver disease, increased consumption from low-grade DIC, and increased destruction due to autoantibodies.

Signalment

Signalment of an animal with cirrhosis largely depends on the underlying cause of liver disease, but cirrhosis is much more common in dogs than in cats. This may be due to a slower accumulation of fibrosis in cats, or development of more severe complications of hepatic failure before advanced fibrosis occurs. Males and females are likely to be equally affected, and dogs with breed-related risk of CH are more likely to be affected. For further details of dog breed predilections to CH, the reader if referred to Chapter 62. Dogs with idiopathic CH and copper-associated CH are often middle-aged to older, while dogs with lobar-dissecting hepatitis are usually young, around 2 years of age. Dogs or cats with a history of hepatotoxicity secondary to environmental toxins or drugs may be of any age.

History and Clinical Signs

The presenting clinical signs in chronic liver disease are often vague in nature, and include a history of inappetence, lethargy, vomiting, polyuria/polydipsia, weight loss, and/or diarrhea. Melena may be observed if GI ulceration is present. Ascites and icterus are more specific clinical signs that may be noted. Neurologic abnormalities such as depressed mentation, circling, ptyalism in cats, star-gazing, seizures, stupor or coma may also occur secondary to HE. These neurologic changes may be intermittent in nature, and frequently occur shortly following ingestion of a meal containing protein. Signs have usually been present for weeks to months, and are often progressive in nature.

Physical examination findings are also often nonspecific, and may only include weight loss or muscle wasting. If ascites is present, abdominal distension and a palpable fluid wave may be apparent. Splenomegaly may also occur in the presence of PH and pooling of blood in the spleen. Icterus may be visualized on the skin, sclera, or mucous membranes as a result of accumulation of bilirubin. Less commonly, petechiae or ecchymosis may be observed on the skin or mucous membranes secondary to thrombocytopenia or thrombocytopathy. Melena may be observed on rectal examination. If HE is present, neurologic examination abnormalities localizing to the forebrain may be present.

Diagnosis

Laboratory Testing

The most common laboratory abnormalities in patients with cirrhosis are alterations of liver-related enzymes. Patients with cirrhosis will often have a known history of elevated liver enzymes, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT). However, in occasional cases of severe hepatocellular loss, liver enzymes may be within normal limits simply due to the low number of remaining hepatocytes. Liver pseudofunction tests may also be abnormal, and suggest some degree of liver dysfunction. It is estimated that a reduction of approximately 70–80% of overall hepatic function must be present before these alterations occur. Pseudofunction tests include decreased albumin, BUN, cholesterol, and/or glucose, and an increase in bilirubin. All of these pseudofunction compounds are produced or metabolized normally by the liver, and will be altered in states of liver dysfunction.

On a complete blood count, microcytosis may be noted in patients with acquired or congenital PSS, secondary to a deficiency in mobilization of iron stores. Anemia may occur from GI ulceration and blood loss or bleeding secondary to coagulopathy. Mild thrombocytopenia may be present due to decrease in hepatic synthesis of thrombopoietin. Leukocytosis is nonspecific, but may occur secondary to stress, inflammation, or infection.

Urinalysis is often normal in patients with cirrhosis, but may demonstrate dilute urine as a result of decreased BUN concentration. Urea is a major component of the renal medullary concentration gradient, and, when decreased, may lead to the development of dilute urine. Bilirubinuria may be observed, and is always significant in the cat, and if 2+ or greater is also significant in the dog. Urate crystals may be observed in as many as 40–70% of dogs with canine PSS, and secondary urinary tract infections are possible as a result of dilute urine.

Coagulation testing should be undertaken if hepatic biopsy is to be performed, or if any clinical signs of bleeding are observed. Prothrombin time (PT) and partial thromboplastin time (PTT) may be increased, and antithrombin, fibrinogen, and protein C levels are decreased in dogs and cats with cirrhosis due to poor production of coagulation factors and/or decreased recycling of vitamin K. Vitamin K deficiency may be especially important in cats with severe liver disease. Evaluation of platelet function testing via buccal mucosal bleeding time may also be abnormal secondary to a thrombocytopathy.

Hepatic function testing can be performed by measuring pre- and postprandial bile acid concentrations or blood ammonia levels. Both tests may be elevated in the face of significant liver dysfunction or aPSS secondary to cirrhosis. Postprandial bile acids are considered to be more sensitive for detection of PSS but elevated ammonia may be more specific. Additionally, ammonia is currently the only measureable HE toxin, so the finding of hyperammonemia may also suggest a higher risk of clinical signs related to HE. However, ammonia sam-

ples are labile, and must be placed on ice and analyzed within 30 minutes to ensure accurate results. Hepatic function tests are commonly altered in dogs with cirrhosis, but as cats uncommonly develop significant fibrosis, function can remain normal in this species.

For further details of laboratory testing in patients with liver disease, the reader is referred to Chapter 60.

Imaging

Imaging modalities most commonly utilized for further evaluation of cirrhosis and its complications include abdominal radiographs and abdominal ultrasound. Abdominal radiographs are the most commonly available imaging modality, but are relatively nonspecific for hepatic disease. Cirrhosis may result in microhepatica, which can be visualized on abdominal radiographs. However, this is a change that may be seen in other hepatic diseases such as congenital PSS. Ascites secondary to PH or hypoalbuminemia may be visible radiographically as loss of abdominal serosal detail.

Abdominal ultrasound is a very useful noninvasive imaging modality that can be utilized to further diagnose liver disease and its complications (Figure 65.2). Ultrasound can evaluate hepatic parenchymal echogenicity and uniformity, overall hepatic size, biliary structures, hepatic and portal vessels, and identify very small volumes of ascites that might not be visible radiographically. It can also be utilized to identify multiple aPSS. Ultrasound is also useful in guiding safe collection of samples of ascites or bile for fluid analysis, or ultrasound-guided "Tru-Cut" biopsies.

Unfortunately, while ultrasound is a very useful noninvasive test, it does not identify changes pathognomonic for a specific liver disease, and should never be used to rule out the possibility of liver disease. Many dogs and possibly cats without sonographic abnormalities may still have important liver abnormalities on histopathology. Ultrasound is also not a reliable method to diagnose cirrhosis. In a study evaluating ultrasound findings with histopathologic diagnoses, there were no sonographic features significantly associated with cirrhosis, and it was concluded that ultrasound could not reliably be used to detect the presence, absence, or severity of fibrosis. In fact some animals with cirrhosis had ultrasonographically normal appearing livers. But sonographic findings may still be useful in suggesting the possibility of cirrhosis and its consequences. Findings that would be most suggestive of cirrhosis and subsequent PH include identification of multiple aPSS, a small liver with irregular margins, presence of ascites, and a hyperechoic echotexture. But ultimately, biopsy and histopathology are required to obtain a definitive diagnosis of cirrhosis.



Figure 65.2 Ultrasonographic image of a cirrhotic liver. Note the presence of large-volume ascites, a small liver with irregular hepatic margination, and mottled echogenicity.

Other imaging modalities may also be useful in diagnosing the cause or complications of cirrhosis. Computed tomography (CT) and magnetic resonance imaging (MRI) may provide a more complete evaluation of hepatic vasculature than abdominal ultrasound. When utilized with contrast, CT and MRI may also provide further evaluation regarding location of neoplasia and possible metastasis. Rectal or transsplenic nuclear scintigraphy can be useful in the diagnosis of PSS, when ultrasound is inconclusive, although scintigraphy may not be able to distinguish congenital versus aPSS. Further details of diagnostic imaging in the investigation of cirrhosis and its complications can be found in Chapter 61.

Cytology and Fluid Analysis

Fine needle aspiration cytology is an inadequate method to diagnose cirrhosis. While cytology may help identify the underlying cause of cirrhosis, it cannot confirm the presence or absence of fibrous tissue

Cytology of ascitic fluid may be utilized when attempting to identify whether the ascites is caused by PH, infectious disease, or neoplastic disease. Typically, ascites secondary to PH is a modified transudate (also refereed to as a protein-rich transudate), or possibly a pure transudate. PH ascites is nonneoplastic, and noninflammatory in origin. Cytology and culture of bile may also be important in diagnosing the underlying cause of cirrhosis. Biliary cultures have been shown to yield a significantly higher rate of positive growth than hepatic tissue cultures.

Histopathology

The gold standard diagnosis of cirrhosis is liver biopsy with histopathology that identifies the presence and extent of fibrosis. Not only is it important to document

the presence and severity of cirrhosis, but it is crucial to attempt to identify the underlying disease that has resulted in the development of fibrosis/cirrhosis. This will allow for specific treatment to be directed at the underlying cause.

Due to the risk of coagulopathy in dogs with hepatic disease, coagulation testing including PT, PTT, platelet count, and possibly buccal mucosal bleeding time (BMBT) should always be performed prior to liver biopsy. Interestingly, results of these parameters do not consistently predict risk of bleeding after liver biopsy in human patients with chronic liver disease. Fibrinogen concentration should also be evaluated if possible, as it may be decreased in cirrhosis. In humans, thromboelastography (TEG) analysis can predict bleeding tendencies in cirrhotic patients, but the value of TEG in predicting bleeding in our canine and feline patients with liver disease is unknown. In cases of hypofibrinogenemia or other coagulopathy, transfusion with cryoprecipitate or fresh frozen plasma should be performed prior to biopsy. Vitamin K1 therapy (1–1.5 mg/kg q12–24h for three doses) prior to biopsy may also be necessary, especially in cats.Assessment of coagulation status should, however, not be a substitute for proper technique and adequate post-operative care.

Biopsy may be obtained through ultrasound-guided "Tru-Cut" needles, laparoscopically, or via exploratory laparotomy. Each method has practical advantages and disadvantages when it comes to cost, time involved, invasiveness, and availability. But collection of a wedge biopsy via laparoscopy or exploratory laparotomy is generally considered to be a superior method of sample collection. It has been shown that morphologic diagnosis of needle biopsy specimens and wedge biopsies (considered the gold standard) only agreed in 40% of animals with liver disease. If the "Tru-Cut" biopsy method is utilized, two or more samples should be collected to minimize sampling error. Further details on the methods to collect liver tissue can be found in Chapter 60.

Treatment

Cirrhosis is considered irreversible. Therefore, the most important aspect of treatment is addressing the underlying cause of liver disease as early as possible to prevent further development of fibrosis/cirrhosis, and to minimize the risk of cirrhosis-associated complications. Corticosteroids have been shown to have positive long-term effects in the treatment of idiopathic chronic hepatitis, and may have minor antifibrotic properties (see Chapter 62). Copper-chelating medications such as D-penicillamine or trientine should be utilized in cases where primary copper-associated chronic hepatitis is diagnosed. In cases of previous toxic hepatopathy or idiopathic disease, specific treatment may not be possible. In all cases of cirrhosis, treatment must also include management of any important complications of cirrhosis.

Colchicine (0.03 mg/kg/day) is the only specific drug in veterinary medicine currently used to stop the formation of fibrosis. It is thought to stimulate collagenase activity, increasing the breakdown and decreasing the formation of collagen. Colchicine is reported to have important and common side-effects, including vomiting, diarrhea, and neurologic signs. Additionally, there are no large studies that have shown positive benefit from this medication, it has not been evaluated in cats, and it is currently cost-prohibitive for many pet owners. As a result of these problems, most clinicians do not currently recommend its use, even in documented cases of hepatic cirrhosis.

Glucocorticoids may be beneficial in some cases of cirrhosis. Steroids interact with TGF-beta signaling pathways and may reduce fibrotic progression, although this effect may be relatively weak. More importantly, prednisone/prednisolone (1 mg/kg/day) may be useful in inhibiting hepatic inflammation, if present. This decrease in inflammation will result in decreased activity of hepatic stellate cells, responsible for formation of further fibrosis. Glucocorticoids may be most beneficial for treatment of dogs and cats with active hepatic inflammation that have not yet developed fibrosis/cirrhosis. Evidence supporting use of glucocorticoids in the absence of hepatic inflammation is lacking, so their use may or may not provide additional benefit in treatment of cirrhosis alone. Moreover, the adverse effects of steroids in animals with advanced fibrosis can be very significant. Due to their ability to cause gastric ulceration, they should be used with extreme caution in animals with , as these animals already have a compromised GI tract blood flow. Steroids cause muscle breakdown so may also potentiate HE.Further details on the use of corticosteroids in dogs with chronic liver disease can be found in Chapter 62.

Losartan is another medication that shows promise for fibrosis/cirrhosis but has not yet been evaluated for this purpose in small animals. Losartan is an angiotensin II receptor antagonist that has been shown in rodent models to inhibit hepatic stellate cell activation and attenuate hepatic fibrosis. It is currently utilized in veterinary medicine for its effects on proteinuria. No studies have shown if losartan may be an effective therapy in preventing fibrosis development in dogs or cats.

Ascites

Ascites may spontaneously improve with specific treatment of the underlying liver disease. Reducing hepatic inflammation, when present, may decrease PH

and therefore decrease the volume of ascites. If this is ineffective, treatment with diuretics is indicated. Spironolactone is the drug of choice in these cases due to its sodium-wasting but potassium-sparing effects, with a starting dose of 1–2 mg/kg/day. Aldactazide, a combination of spironolactone and hydrochlorothiazide, may also be administered. Low-dose furosemide (1-2 mg/kg PO q12h) can also be utilized, but carries a risk of worsening HE due to its acidifying effects. Therefore, it should only be added to therapy when other diuretics fail to fully control the ascites. Dietary sodium restriction may also be beneficial to help decrease volume of ascites. Diets with <0.05 g/100 kcal of sodium have been recommended. It is important to monitor electrolytes and renal values while on these medications, and taper to lowest effective dose to control clinical signs of ascites.

Abdominocentesis may be performed when necessary for severe abdominal distension resulting in patient discomfort or respiratory difficulties. Removing large volumes of ascites may result in cardiovascular collapse and poor perfusion, in addition to lowering body protein levels, so it is recommended to only remove 20–50% of the total volume of effusion in one procedure.

Hepatic Encephalopathy

In treating HE, efforts are classically focused on lowering the amount of encephalopathic toxins in the colon. This can be performed by both dietary changes and administration of lactulose and/or antibiotic therapy. Because ammonia is derived from protein sources, historically a protein-restricted diet with reduction in aromatic amino acids has been recommended in dogs with HE secondary to cirrhosis. However, protein restriction is controversial, and evidence from human medicine actually suggests that patients with cirrhosis require additional, not reduced, amounts of protein. What is probably more important is to ensure that the protein content of the diet is highly digestible and is fed little and often. Dairy and soy proteins have been found to promote less HE compared to meat protein. Commercial hepatic diets are available for dogs, although in some dogs the protein level may be too low, and muscle catabolism may occur. In these dogs, supplementation with highly digestible, high-quality protein in limited amounts may be necessary.

Lactulose is a nonabsorbable disaccharide that acidifies the colonic lumen, converting ammonia (NH_3) into ammonium (NH_{4+}). The positively charged ammonium is membrane impermeable, compared to the neutral charge of ammonia. Lactulose is also a cathartic, decreasing GI transit time for production and absorption of ammonia. Lactulose dosing starts at 0.25 mL/kg PO q8–12h, with adjustments in dose as needed to achieve a goal of 2–3 soft, but formed stools daily.

Antibiotics have also been used for HE in an effort to decrease the volume of colonic urease-producing bacteria responsible for production of ammonia. The two most commonly utilized antibiotics are neomycin (22 mg/kg q8h) and metronidazole (7.5 mg/kg q12h). Neomycin is an oral aminoglycoside. Aminoglycosides are very poorly absorbed by the GI tract, so it is thought that the effects will usually remain within the GI tract. However, neomycin carries a risk of nephrotoxicity and ototoxicity, even when given orally, so acute kidney injury can occur. Metronidazole may result in vomiting, diarrhea, or neurotoxicity, especially when administered at high doses or chronically. Alternatively, amoxicillin/clavulanic acid can be used at standard doses to decrease in the patient with HE.

Emerging evidence also suggests that inflammatory cytokines are synergistic with ammonia in precipitating HE. Treating concurrent inflammatory and infectious disease in other organs is therefore an important part of managing the patient with HE.

Emergency treatment of HE is warranted if a patient presents with seizures or coma, or otherwise is severely neurologic and unable to safely receive oral medications. A warm water cleansing enema (10–15 mL/kg water) should be given to remove fecal material and allow for a retention enema with lactulose. Lactulose (5–10 mL/kg) should then be infused at a 30% dilution and allowed to remain in the colon for 10–15 minutes. Flumazenil is an antagonist for benzodiazepine receptors and is used as a reversal agent for benzodiazepines. Because HE may cause stimulation of GABA/benzodiazepine receptors, flumazenil (0.01–0.02 mg/kg IV) may also provide acute improvement in neurologic depression in cases of HE.

If seizures are present, diazepam or other benzodiazepine medications should not be administered as these may increase the stimulation of GABA/benzodiazepine receptors and risk worsening neurologic depression. Instead, levetiracetam (20 mg/kg) may be given IV for acute seizure control. Phenobarbital may also be utilized. If prolonged seizure activity has been present or there are clinical signs of cerebral edema, mannitol infusion may also be necessary.

Gastrointestinal Ulceration

Gastrointestinal ulceration and bleeding can increase the risk of HE due to digestion of blood proteins and absorption of ammonia. Therefore, aggressive treatment is warranted in cases of GI ulceration. Proton pump inhibitors such as omeprazole (1 mg/kg q12–24h) have

been proven to have superior acid-blocking effects compared to H2 blockers in dogs and should be utilized in these cases. Sucralfate may also be of benefit in rapid healing and prevention of continued bleeding.

Coagulation Disturbances

Disturbances in coagulation will usually only need to be treated in the face of active bleeding, or if a biopsy is to be pursued. Vitamin K1 therapy may also be beneficial either for acute hemorrhage or prior to biopsy, especially in cats. For active bleeding, cryoprecipitate (1 unit/10 kg) should be administered for hypofibrinogenemia, as it provides the most concentrated source of fibrinogen. Fresh-frozen plasma (10–20 mL/kg) may also be utilized for fibrinogen and other factor replacement.

Hepatoprotectants

The evidence regarding hepatoprotectant therapy in veterinary medicine is generally lacking. It is unclear when and which hepatoprotectant might be most beneficial for specific hepatic diseases in dogs and cats. Therefore, it is difficult to make recommendations regarding their use in animals with cirrhosis. However, the use of ursodeoxycholic acid, S-adenosyl-L-methionine (SAM-e), silymarin, N-acteylcysteine, and vitamin E have all been anecdotally or experimentally recommended as potentially beneficial in the treatment of severe liver disease.

One of the more promising hepatoprotectant medications is ursodeoxycholic acid (ursodiol, UDCA). Ursodeoxycholic acid is a synthetic hydrophilic bile acid that is thought to provide a cholerhetic effect, decreasing levels of more "toxic" hydrophobic bile acids. It is also thought to have immunomodulatory and antioxidant effects. It has been advocated for use in CH and gallbladder mucoceles. Its utility in the treatment of cirrhosis is unknown.

S-adenosyl-L-methionine has also been advocated for use in cases of hepatic disease. It is thought to increase available levels of glutathione, an important antioxidant of the liver, by increasing levels of the glutathione precursor methionine. Glutathione production may become inadequate in cases of chronic inflammation and continuous oxidative stress. SAM-e was reported to be effective in veterinary medicine in a case of acetaminophen toxicity, and may provide protection against steroid hepatopathy. It is unknown if it provides benefit in cases of cirrhosis.

Silymarin, silybinin, or milk thistle, is another antioxidant and free radical scavenger that increases levels of superoxide dismutase (SOD). It has proven efficacy in veterinary medicine against hepatic toxicity from *Amanita* mushroom and acetaminophen toxicity. It was also shown to decrease CCNU-induced hepatotoxicity when used in combination with SAM-e. Again, its use for treatment of cirrhosis has not been evaluated.Further details on the use of hepatoprotectants in dogs with chronic liver disease can be found in Chapter 62.

Monitoring

The frequency of monitoring depends on the severity of illness and the underlying disease. Rechecking electrolytes and renal parameters is of the utmost importance when utilizing and adjusting doses of diuretic therapy. Liver enzymes, most importantly ALT, should be evaluated every 2–4 weeks in animals being treated with glucocorticoids for inflammatory liver disease. If HE is present, monitoring fasting ammonia levels may provide useful information regarding response to HE treatment.

Prognosis

Prognosis for cirrhosis is generally guarded, as cirrhosis is an irreversible condition. Prognosis may also vary widely based on whether or not the underlying hepatic disease is treatable, and the severity of cirrhotic complications such as HE and PH. One study evaluated dogs diagnosed with CH with and without cirrhosis, and found that noncirrhotic dogs with CH had a median survival time (MST) of 33 months, compared to cirrhotic dogs MST of only 1.3 months. Ascites has been reported to be a negative prognostic indicator in dogs with CH, with survival time from onset of clinical signs to death of only two months, when compared to dogs with CH and no ascites.

Conclusion

Cirrhosis is a severe, irreversible condition that occurs as a consequence of underlying liver disease. It often leads to additional complications including portal hypertension, ascites, multiple aPSS , HE, gastric ulcers, and coagulopathy. Early recognition and diagnosis of liver disease followed by specific treatment are always warranted to prevent the development of cirrhosis. Once cirrhosis and its complications are present, supportive care is the only treatment option and prognosis is guarded to poor.

Further Reading

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66

Portosystemic Shunts and Microvascular Dysplasia

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Etiology

Portosystemic shunting refers to a condition where blood bypasses the liver and travels from the hepatic portal circulation to the systemic circulation through one or more connections that can occur at a microvascular or macrovascular level.

Congenital portosystemic shunts (CPSS) occur as a result of an error in embryonic development where primordial vessels either develop abnormal connections or fail to undergo atresia. This has been shown to have a genetic basis in some breeds, including the Maltese, Irish wolfhound, and Cairn terrier. Inheritance, as assessed by pedigree analysis and test-mating, appears to be complex – either digenic or polygenic with variable expression.

Rarely, intrahepatic shunts may result from failure of the ductus venosus to close. This is most commonly reported in Irish wolfhounds (considered to be digenic in this breed). Left-divisional shunts may be encountered in any breed, but it is unclear how often these represent failure of the ductus venosus to close, versus other vascular malformations.

Acquired shunts develop as a result of increased vascular resistance within the portal system, the hepatic sinusoids or the hepatic veins (in the face of normal central venous pressure). The most common cause is hepatic fibrosis/cirrhosis, although other conditions such as portal vein thrombosis, periportal neoplasia, hepatic arteriovenous fistula, and dynamic hepatic vascular occlusion are sometimes encountered.

Microvascular dysplasia (MVD, which has more recently been termed portal vein hypoplasia (PVH) without portal hypertension, refers to abnormal development or absence of the portal microvasculature within the liver. As different authors use different terminology, this spectrum of conditions will be referred to henceforth as PVH-MVD. PVH-MVD may occur with or without CPSS. Dogs and cats with primary PVH-MVD (but no CPSS) may develop acquired shunts within the first few years of life due to chronic portal hypertension, in which case they fall into a category termed "noncirrhotic portal hypertension."

Classification and Anatomy

Portosystemic shunts are classified according to three criteria:

- congenital versus acquired
- single versus multiple
- macroscopic versus microscopic.

Congential portosystemic shunts are further classified according to their point of origin as either extrahepatic (originating from the hepatic portal vein or one of its source vessels) or intrahepatic (originating from one of the hepatic branches of the portal vein). Extrahepatic shunts are described by their origin and insertion (e.g., portocaval, splenoazygous). A subset of extrahepatic shunts that insert into the phrenic or hepatic vein has recently been characterized in various countries. Intrahepatic shunts are typically described according to the division of the portal vein from which they arise (left, central, and right-divisional).

A subset of dogs with CPSS have portal aplasia and no demonstrable portal circulation to their liver. In these cases, the shunt represents the only outlet from the portal circulation, inserting directly into the systemic venous circulation. Unfortunately, there is no surgical option for these patients. This anatomic variant may be associated with other malformations such as interruption of the caudal vena cava with azygous continuation, abdominal situs inversus, and segmentation of the spleen.

Acquired shunts are usually multiple and generally extrahepatic. Multiple intrahepatic shunts have been identified in patients following thrombogenic coil occlusion of intrahepatic shunts but it is not yet known

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whether they represent preexisting or acquired vascular communications.

Traditional acquired shunts may occur between any branch of the portal and systemic vasculature, but they are typically small and tortuous and cluster around the cranial and caudal aspects of the kidneys, especially the left kidney. Communications with the remnant ovarian veins may occur in spayed females; these single vessels may become particularly large and noticeable, especially in cats.

In PVH-MVD , shunts are considered to be microscopic, occurring between the hepatic portal and hepatic venous systems, thereby bypassing the sinusoids.

Pathophysiology

Dogs and cats with portosystemic shunting usually have low functional hepatic mass. The liver either fails to grow normally as it is deprived of its normal blood supply, trophic factors (such as insulin and hepatic growth factor) and nutrients, or liver function is impaired as a result of a primary hepatopathy (in cases with acquired portosystemic shunts).

The major clinical signs associated with portosystemic shunting result from failure of the liver to metabolize substances being absorbed from the gastrointestinal tract, receive pancreatic hormones, and metabolize other circulating hormones. There is deranged nitrogen metabolism and the capacity of the liver to produce urea is diminished, leading to elevated levels of circulating ammonia and low blood urea nitrogen (BUN) levels. Serum bile acids, which normally undergo almost complete enterohepatic circulation, are also elevated in systemic samples. Abnormal filtering or metabolism of a variety of other substances absorbed into the portal venous blood (branched chain and aromatic amino acids, bacteria and bacterial toxins) is responsible for the cardinal clinical signs of portosystemic shunting (Table 66.1).

Neurologic perturbations caused by the liver dysfunction resulting from portosystemic shunting leading to neurologic abnormalities are termed hepatic encephalopathy (HE) (see description later).

It is becoming increasingly recognized that infection and inflammation also play a role in development of encephalopathy in laboratory animals and humans. Circulating blood levels of C-reactive protein (a marker of inflammation) have relatively recently been shown to be elevated in dogs with HE, suggesting that this is also likely to be an important mechanism in dogs. HE may be complicated by hypoglycemia in patients that are inappetent or being fasted, as a result of low hepatic glycogen reserves in the hypoplastic or damaged liver.

Circulating levels of these substances will fluctuate according to whether the animal has eaten, the diet, and other factors affecting gastrointestinal transit time, bacterial flora or the production of ammonia within the gut. Gastrointestinal hemorrhage is a known risk factor for development of HE, and can be a particular problem in patients with end-stage liver disease and portal hypertension, or dogs with CPSS that develop gastrointestinal ulceration (see later).

Deranged nitrogen metabolism causes a tendency for urinary ammonium biurate crystalluria and calculus formation, which may lead to irritation of the renal pelvis with hematuria, ureteral obstruction or (more commonly) urethral obstruction.

Polyuria and polydipsia are common in patients with portosystemic shunts. The mechanism is not completely understood but is probably multifactorial. Contributing factors include low plasma BUN and poor renal concentrating ability, and increased thirst resulting from systemic inflammation and fever.

Abnormal blood flow within the hepatic sinusoids results in impairment of delivery of vital substances to

Table 66.1 Clinical and diagnostic features of different conditions causing biochemical evidence of hepatopathy

	Age	HE	Ascites	Jaundice	Diarrhea	Elevated shunt fraction
CPS	Younger	Yes	Rare*	No	Rare	Yes
PVH-MVD	Any age	No	No	No	No	No
Noncirrhotic PH	Young to middle-aged	Yes#	Yes	No	Yes	Yes#
Cirrhotic PH	Older	Yes#	Yes	Yes	Yes	Yes#

* Possible in patients with very low serum albumin.
# Once acquired shunts have developed.
CPS, congenital portosystemic shunts; HE, hepatic encephalopathy; MVD, microvascular dysplasia; PH, portal hypertension; PVH, portal venous hypoplasia.

the hepatocytes, eventually resulting in cell damage and death. Cell damage is followed by accumulation of lipid within the hepatocytes, cell death and phagocytosis by macrophages, which then coalesce to form lipogranulomas. Interstitial fibrosis eventually leading to cirrhosis has been observed in some patients with CPSS, but is far more likely to be seen in patients with acquired portosystemic shunts resulting from end-stage hepatopathy of another etiology.

Pathophysiology of Portal Hypertension

Portal hypertension (leading to acquired portosystemic shunts) is by definition an increase in portal venous pressure above the expected normal of 8–12 mmHg (note that patients with CPSS will usually have portal pressures comparable or slightly higher than central venous pressure (typically 4–8 mmHg). Portal hypertension occurs when the resistance to vascular flow within the hepatic portal vein or sinusoids increases, causing sequestration of blood within the viscera. Reduction in the arterial to venous pressure gradient across the capillary beds of the gut causes reduced blood flow and hence reduced oxygen delivery to tissues. Alteration of hydrostatic pressure, often accompanied by reduced plasma oncotic pressure resulting from the patient's underlying liver disease, allows fluid to leak from the capillaries into both the intestinal lumen and the peritoneal cavity, resulting in ascites and diarrhea. In acute, severe portal hypertension, frank blood may leak into the lumen of the bowel, resulting in hematemesis and hematochezia. Edema and swelling of the intraabdominal organs causes stretching of the capsules and peritoneum, and hence this condition can be quite painful.

Reduction in blood flow through the hepatic sinusoids results in lower venous return to the right atrium, with a resultant fall in cardiac output and the compensatory changes of tachycardia and reduced stroke volume. Hypovolemic shock will eventuate if the compensatory mechanisms are not sufficient to assure adequate tissue oxygen delivery, or if ongoing fluid losses into the bowel and peritoneal cavity cannot be replaced.

In patients that are able to compensate for mild to moderate portal hypertension, small veno-venous communications open within a few days. These take the path of least resistance from the portal circulation into a nearby branch of the systemic venous system, and therefore tend to occur where the vascular systems are in closest proximity to one another (root of the mesentery, esophageal hiatus, perianal region). These vessels are thin-walled and tortuous and usually cluster in plexi.

Although congestive heart failure or caudal vena caval obstruction causes hepatic venous distension, this does not result in acquired portosystemic shunting because the hydrostatic pressure is increased within the caudal vena cava as well as the hepatic sinusoids and there is hence no hydrostatic drive for the portosystemic shunts to occur.

Ascites resulting from increased hydrostatic pressure within the caudal vena cava (caval tumors, right-sided congestive heart failure) tends to be a modified transudate due to leakage of protein-rich hepatic lymph, whereas ascites resulting from mild to moderate portal hypertension tends to be a transudate. Ascites occurring in fulminant portal hypertension may also be sanguinous if the capillaries or splenic capsule rupture. Portal hypertension is likely to result in splenomegaly, with a normal to small-sized liver, unless the obstruction occurs at the level of the hepatic venules or hepatic veins (Budd–Chiari syndrome).

Epidemiology

Signalment

Acquired shunts may be seen in any species or breed of patient in which diseases causing hepatic fibrosis or cirrhosis occur. A good example of such a disease in dogs is chronic hepatitis. A subset of patients with acquired shunts resulting from portal hypertension caused by congenital PVH-MVD will present before the age of 3 years and may be indistinguishable from patients with CPSS (see further discussion in Diagnosis section).

Congenital shunts are seen most commonly in purebreed dogs, or cross-bred dogs with parents of breeds that are overrepresented amongst the shunt population. Many breeds have been reported as predisposed around the world, the most notable being a number of terriers (Yorkshire, cairn, Maltese, Jack Russell), Chihuahuas, miniature schnauzers, pugs, toy poodles, Australian cattle dogs, Labrador and golden retrievers, and Irish wolfhounds.

In general, extrahepatic shunts are more common in terriers and other small-breed dogs, whereas intrahepatic shunts are more common in medium- to large-breed dogs. However, exceptions occur (e.g., toy and miniature poodles) and some form of shunt imaging is recommended prior to surgical exploration. Patients from breeds that are not known to be predisposed to CPSS are more likely to "break the rules" and should be evaluated especially carefully.

PVH-MVD tends to occur in similar breeds to those affected with CPSS, and has been best characterized in the terrier-type breeds such as Maltese, Yorkshire and cairn terriers.

History and Clinical Signs

Patients with portal vascular abnormalities may be clinically asymptomatic (abnormality detected after routine wellness screening, or preanesthetic blood testing), display vague and self-limiting clinical signs, or present with severe neurologic abnormalities associated with HE.

Common clinical signs include a picky appetite or pica, failure to thrive, hypersialism (most evident in cats), sporadic vomiting, polyuria and polydipsia, urinary irritation and obstruction caused by ammonium biurate calculi, episodes of abnormal mentation accompanied by ataxia, and amauratic (apparent) blindness. Cats with CPSS may have copper-colored irises, although this is not always the case, and it is not pathognomonic .

Dogs with CPSS sometimes present with a history of generalized motor seizures, although in a subset of cases the seizures are caused by a co-morbidity such as idiopathic epilepsy or granulomatous meningoencephalitis (more recently referred to as meningoencephalitis of unknown etiology), rather than the shunt itself (see Prognosis section). Behavior changes including aggression may occasionally prompt presentation. Dogs with CPSS may have other intermittent problems that seem to result from systemic debility, such as coughing, ocular discharge, and urinary tract infection.

Ascites is very uncommonly seen in dogs with CPSS unless they have been on a restricted protein diet for an extended period of time. Ascites is more common in cases of portal hypertension accompanying end-stage liver disease or portal venous hypertension/dysplasia.

Diagnosis

There are a number of diagnostic methods, including demonstration of liver dysfunction, confirmation of portosystemic shunting, imaging of the shunt, and histologic evaluation of the liver.

Clinical Pathology

Biochemical abnormalities typically include low to low-normal BUN, cholesterol, albumin, glucose and protein C, andelevatedliverenzymes(alanineaminotransferase[ALT], alkaline phosphatase[ALP]). Serum bile acid activity is measured before (resting) and after eating (post prandial), to gauge the degree to which bile acids leak into the systemic circulation from the portal vein, rather than being extracted by enterohepatic circulation. Serum bile acid activity should be elevated in animals with portosystemic shunts, and the post prandial sample is more frequently abnormal than the resting sample. Plasma ammonia levels can also be measured before and after administration of an ammonium chloride solution per rectum (ammonia tolerance test). Ammonia is labile in serum, and the ammonia tolerance test is somewhat more invasive and can be very dangerous, and thus serum bile acids are preferred over ammonia as a clinical screening test. Hematologic abnormalities include anemia with microcytosis and often a mature neutrophilia.

Confirmation of Portosystemic Shunting

This is most easily done using nuclear scintigraphy; imaging the patient following rectal or transsplenic administration of technetium pertechnetate. Contrast portography, following injection of radiographic contrast agent through a catheter placed in the jejunal vein or percutaneously by means of splenic injection (splenoportography), provides another mechanism for confirmation that portal blood is passing directly into the caudal vena cava and bypassing the liver. Contrast portography also provides a mechanism for determining the anatomy of the portosystemic shunt, if a good-quality study is achieved. Chapter 61 provides further details on the methods to image the animal with a portosystemic shunt.

Imaging of the Portal Vasculature

Abdominal sonography is the least expensive and invasive modality, but confidently finding a portosystemic shunt can be difficult in very small dogs, dogs with intestinal gas or ingesta, or with shunts that are in unusual locations. Even in the hands of an experienced sonographer, shunts may not be located in up to 25% of patients. Even when the vessel is not identified, circumstantial evidence for CPSS may include turbulence within the prehepatic caudal vena cava, renomegaly, microhepatica, and urinary calculi.

Three-dimensional imaging using computed tomography (CT) or magnetic resonance imaging (MRI) is becoming the “gold standard” of diagnosis. Dual-phase CT angiography (DPCTA) allows confirmation of portosystemic shunting, clarification of the exact shunt anatomy, identification of other congenital abnormalities, calculation of liver volume, assessment of hepatic perfusion in both the arterial and venous phase, and identification of urinary calculi. DPCTA is essential for planning transvenous coil embolization.

Differentiating CPS from PVH-MVD

Dogs with these two conditions may present in exactly the same way, although dogs with PVH-MVD are less likely to demonstrate overt signs of HE. Confirmation by nuclear scintigraphy, or advanced imaging, that there is no macroscopic shunt, and identification of the histologic

features on liver biopsy in the absence of another hepatopathy that could explain the biochemical perturbations are required for definitive diagnosis of PVH-MVD.

Therapy

Medical Therapy

Medical therapy is aimed at ameliorating the signs of HE by reducing the amount of ammonia (and other substances) produced in the gut, and the degree to which they are absorbed. Medical management is often employed in those animals that show few clinical signs on presentations, are older, in which financial or owner-lead reasons limit surgery, or which have a shunt that is not amenable to ligation. The main aims of therapy are to decrease the formation of gut derived encephalotoxins, especially ammonia. Therefore the mainstays of current therapy are a combination of dietary alterations, oral antibiotics to suppress bacterial populations that produce encephalopathic toxins and local acting agents to reduce gastrointestinal uptake of ammonia (e.g. lactulose). Controlled trials have not been performed in animals to determine the optimal treatment for HE and so current recommendations are based on anecdotal evidence.

Feeding a high-quality digestible diet is the mainstay of management of the stable patient. Protein restriction is controversial, and generally not recommended, as some authorities report that dogs with CPSS actually have normal to increased requirements. If protein restriction is required, a commercial restricted protein diet is the easiest to prescribe. For clients who wish to formulate their own diet, protein sources should be easily digestible and metabolizable. Vegetable and dairy proteins tend to be better tolerated than meat-based ones, with cottage cheese being a palatable option for many patients. Cats have more stringent dietary requirements than dogs, and this should be taken into account when choosing a diet. Patients with reduced hepatic mass will have poor glycogen reserves and a tendency toward hypoglycemia, so meals should be given frequently.

Lactulose is prescribed for symptomatic patients, with the goal of reducing intestinal pH and thereby trapping ammonia within the gut, and by virtue of its action as an osmotic cathartic, hastening intestinal transit time and reducing the time available for absorption of ammonia. In patients that are actively encephalopathic and unable to tolerate oral medication, lactulose may be administered rectally.

Antibiotics may also be prescribed, with a view to reducing the intestinal bacterial population and thus reducing ammonia production. Further details about medical management of the patient with liver disease can be found in Chapter 65.

There is evidence that patients with liver disease are at increased risk for gastrointestinal ulceration, and anecdotal reports of this being a particular problem in dogs with intrahepatic shunts. Therefore, many clinicians include some type of antacid medication (H2 receptor antagonist or protein pump inhibitor such as famotidine or omeprazole) as part of the standard medical management protocol. Finally, emerging evidence also suggests that inflammatory cytokines are synergistic with ammonia in precipitating HE and that controlling inflammation in other organs is an important part of managing the patient with HE.

Surgical Therapy

Surgical therapy is indicated for patients with CPSS, or hepatic arteriovenous fistulae, where the primary problem can be resolved. Patients with acquired shunts secondary to end-stage liver disease or PVH are unlikely to benefit from surgical attenuation of their shunts as the shunts are providing a mechanism for decompressing the portal system and reducing portal hypertension. Dogs with PVH-MVD, and those with portal vein aplasia, are also not candidates for surgical intervention. However, the results of liver biopsy may inform medical management in patients with acquired liver disease, and this often provides justification for surgical exploration.

Surgical therapy for CPSS is aimed at identifying the shunt and attenuating it. As most patients have poorly developed hepatic portal circulation and relatively high portal vascular resistance, total immediate occlusion of the shunt is highly likely to result in life-threatening portal hypertension. Therefore, surgical methods aim either to provide partial occlusion (which may be increased in stages by subsequent procedures) or application of a device to promote slow occlusion. The goal of slow or staged occlusion is to allow the intrahepatic portal circulation time to regenerate, with reduction in vascular resistance, at the same time as the shunt is being slowly or incrementally occluded.

The main techniques used for slow occlusion of extrahepatic shunts are cellophane bands and ameroid constrictors. Cellophane bands promote occlusion by stimulating a foreign body reaction and fibrosis between the band and the shunt wall. Ameroid constrictors produce some mechanical occlusion as the ameroid clay takes up fluid, but also cause local inflammation with fibrosis and thrombosis of the shunt vessel. More recent reports have described the use of a variety of other clear films for shunt occlusion in dogs and cats, including polypropylene and polyethylene. These seem to be as effective as cellophane, probably due to the chemicals incorporated during the manufacturing process.

Intrahepatic shunts were historically addressed by surgical attenuation using either extravascular dissection or a transvenous approach under partial venous inflow occlusion. In recent years, minimally invasive procedures have become more common, with an expanding body of international experience in interventional techniques such as percutaneous thrombogenic coil embolization (PTCE). This technique results in much less morbidity. The downsides are the need for advanced equipment (including fluoroscopy) and expertise, and the likelihood that repeated procedures will be required for complete shunt occlusion (see Prognosis section).

Surgical Attenuation

Surgical exploration is performed through a ventral midline celiotomy, which may be extended cranially by transdiaphragmatic incision or median sternotomy. Combination of a paracostal incision with a ventral midline celiotomy is also an effective way of exposing the craniodorsal abdomen, but is rarely required for shunt surgery. A standard exploration should be performed to evaluate the portal vasculature and identify the portosystemic shunt. If present, acquired shunts will usually be visible around the cranial aspect of the left kidney.

Perioperative Monitoring and Treatment

Serum glucose concentration should be monitored regularly due to the tendency for hypoglycemia. Albumin levels may drop markedly when intravenous crystalloid is administered at surgical rates, and plasma transfusion is sometimes required. However, serum albumin increases relatively little following plasma transfusion, and therefore human albumin solutions are an alternatively way to increase serum albumin. Hemodynamic parameters should be measured regularly during and following surgery to gauge trends and allow early detection of developing portal hypertension. Patients can be severely polyuric prior to surgery and may require increased fluid rates to avoid dehydration postoperatively. Potassium supplementation may be required.

Complications of Surgery

A large range of complications have been reported following surgery for CPSS. Anesthetic-related complications include hypotension (mainly in cats), hypothermia due to small body size and poor body condition, and hypoglycemia for reasons previously described. Intraoperative hemorrhage is not usually a major issue unless tearing of the vessels occurs during dissection. This is more likely during treatment of intrahepatic shunts, but unlikely if careful technique is used when dissecting extrahepatic vessels. Although some perturbations in coagulation parameters have been reported in dogs with CPSS, most patients do not experience clinically significant problems with coagulation. This is much more likely to be a problem in patients with end-stage liver disease.

The major life-threatening complications that occur perioperatively are portal hypertension and postligation neurologic dysfunction. The incidence of portal hypertension has been greatly reduced by adoption of the slow occlusion techniques, and publication of guidelines for safe shunt attenuation. Mild to moderate portal hypertension may not cause life-threatening problems; affected patients may have inappetence or diarrhea for a short period of time, or develop ascites. Assuming they are able to compensate hemodynamically for the reduced central venous return, and the bowel does not become critically hypoxic, they will eventually develop acquired shunts and a consequent return of portal pressure towards normal. Early published reports suggested that up to 20% of patients can be expected to develop acquired shunts but more recent studies, in which patients underwent postoperative evaluation using DPCTA, showed that the incidence is probably less than 10%, with an additional 10% of patients experiencing ongoing shunting as a result of misplacement or failure of the attenuating device to promote complete occlusion.

Postoperative neurologic sequelae range from blindness or muscle twitching, through disorientation, to generalized motor seizures and status epilepticus. Hypoglycemia and HE may also produce signs that can be difficult to distinguish from true postligation neurologic dysfunction . In addition, patients experiencing seizures preoperatively may continue to have seizures postoperatively if the seizures were caused by something other than their CPS.

Hypoglycemia, HE, and the seizures of idiopathic epilepsy should be manageable by evaluating the patient and relevant bloodwork, and treating accordingly. Postligation neurologic dysfunction seizures and status epilepticus constitute a much more serious problem with a guarded prognosis. The cause of these seizures is still not well understood, but may include factors such as imbalance of neurotransmitters, cerebral edema, and derangements in cerebral blood flow. Historically, seizures were considered to occur acutely, with patients found when they were already in status epilepticus. Closer observation of patients following surgery has shown that in many cases, the condition is progressive. Patients start behaving abnormally, vocalizing and showing signs of disorientation and inappropriate mentation. They do not interact appropriately when being handled. They are ataxic and often display compulsive movements. Left untreated, they will develop facial twitches that progress to generalized motor seizures and status epilepticus. Several studies have shown an incidence of seizures in up to 5% of dogs following surgery for CPSS.

Anecdotal experiences suggest that older dogs and pugs may be at greater risk for seizures, but this has not been definitively proven. Cats seem at greater risk for neurologic sequelae, including blindness and twitching, in addition to seizures. Preoperative treatment with phenobarbitol and levetiracetam (Keppra®) has been shown to significantly reduce the incidence of seizures, although published reports and anecdotal experience suggest that the risk is not completely abolished.

Therapeutic Decision Making

In light of the fact that many patients have mild clinical signs, and surgical shunt attenuation has a significant morbidity/mortality rate, owners are sometimes faced with a difficult choice between long-term medical management and surgical correction. Some dogs live apparently normal lives with no management at all, whereas others develop severe clinical signs within the first few months of life. On risk–benefit analysis, a young puppy with obvious HE is more clearly a candidate for surgery than an 8-year-old dog in which CPSS is detected on a routine wellness check. An exception would be the older male dog in which CPSS is diagnosed following urethral obstruction with ammonium urate calculi. Medical management in these patients may not control stone formation, and as urethral obstruction is, in itself, potentially life-threatening, many owners will opt for surgical correction of the CPSS. Likewise, patients with severe polyuria/polydipsia may be generally happy but present unacceptable management issues, making surgery an attractive option.

Many dogs with severe clinical signs will become near-normal on medical management, prompting the owners to question the necessity for surgery. The choice then is between lifelong dietary management and other therapies, weighed against a high probability for return of liver function to normal following CPSS attenuation.

Ongoing Evaluation

There are two main factors that should be considered when determining a patient's progress, either with medical or surgical management: liver function and the presence and degree of portosystemic shunting.

Biochemical Evaluation

Liver function is usually monitored indirectly by measuring blood levels of the products of hepatic metabolism including albumin, cholesterol and BUN . Return of cholesterol and BUN to reference levels is a good indicator that liver function is returning to normal. Serum bile acid levels are a sensitive indicator of macroscopic or microscopic portosystemic shunting. Postoperatively, patients may have normal serum biochemistry and a normal technetium scan in the face of continuing mild elevations in serum bile acids. The significance of these mild elevations to long-term prognosis is not yet known. Protein C has been proposed as a useful monitoring tool but the assay is not offered widely, and results from different laboratories may differ, making interpretation of single results difficult.

Nuclear Scintigraphy

Per rectal scintigraphy provides an estimate of shunt fraction and is helpful in determining the degree of shunt closure following surgery. It does have some interobserver variation, and we reported some dogs with normal technetium scans following surgery that had persistent shunting through small tributary vessels. Therefore, the results of scintigraphy should be interpreted in the context of other measures such as serum biochemistry and imaging. Percutaneous transsplenic scintigraphy is more accurate and may provide information about shunt anatomy in the hands of an experienced operator, but is more invasive and not yet performed routinely.

Abdominal Sonography

Assuming that the shunt was sonographically visible before surgery, postoperative sonography is a mechanism for confirming closure of the shunt, increase in liver volume, and decrease in kidney size. It is also useful for identifying or monitoring development of urinary calculi.

Computed Tomography

Dual-phase CT angiography is emerging as the most reliable way to evaluate patients postoperatively, allowing calculation of liver volume and perfusion, and evaluation of shunt anatomy, presence of persistent shunting through the original shunt or acquired vessels.

Interpretation of Surgical Outcomes

Historically, patients have undergone minimal objective follow-up after surgical attenuation, making interpretation of published outcomes difficult. Patients with persistently abnormal blood values may have persistent shunting, acquired shunts, PVH-MVD, or some other hepatopathy. Persistently abnormal technetium scans are now recognized to occur in a variety of scenarios, including failure of the occlusion device to promote complete occlusion, malpositioning of the occlusion device, and development of acquired shunting. Clearly, neither of these techniques is able to identify the etiology for the abnormal result, and thus inform the most appropriate management plan.

Imaging using sonography may be helpful if the abnormal vessel(s) are visible. The ideal strategy for evaluation would include serial serum biochemistry including

serum bile acids and protein C, nuclear scintigraphy, and DPCTA. This battery of tests should be used as the gold standard for future research studies attempting to evaluate surgical outcomes, but is not realistic for clinical patients, many of whom have shown resolution of their clinical signs and for whom the risk of anesthesia and contrast imaging is not warranted. Advanced imaging should, however, be considered for patients displaying persistent biochemical or scintigraphic abnormalities six months following surgery.

Prognosis

While medical management can be successful for a prolonged period in many patients, the published literature suggests that outcomes following surgery are better, as long as the surgery is performed before severe secondary changes in liver function occur. A more recent study has shown that those undergoing surgical ligation of the shunting vessel have a longer median survival time, and a lower frequency of ongoing clinical signs. The mortality rate following correction of CPSS (including PTCE) is less than 5%. Up to 80% of patients receiving slow occlusion devices for extrahepatic CPS can be expected to regain normal liver function, with a median survival of 152 months. The mortality and morbidity rates are higher for surgical correction of intrahepatic shunts, and for cats with CPSS of any anatomic type, and the chance of return to liver function is lower than for dogs with extrahepatic CPSS.

The prognosis for patients undergoing PTCE has not yet been established definitively. However, early reports suggest that the mortality and morbidity rates are low, and patients are highly likely to show substantial clinical improvement, although complete closure of the shunt is unlikely.

Regardless of the technique used, the clinical impact of residual flow through the original shunt has yet to be determined. Intuitively, a reduction in shunt fraction should improve hepatic function, but the actual shunt fraction at which a patient might resume a normal diet and not show clinical signs is not known.

Approximately 10% of patients will never return to normal liver function even following complete shunt occlusion and will likely require lifetime medical management, although interestingly, they are often less severely affected clinically once acquired shunts have developed than they were with a single shunt.

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67

Diseases of the Gallbladder and Extrahepatic Biliary Ducts

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The gallbladder is a bladder-like organ possessing a thin, mucosa-lined wall with a muscular layer and an outer serosal layer. Its function is to store, modify, and secrete bile, which is synthesized in the hepatocytes and reaches the gallbladder via bile canaliculi, lobar bile ducts, and eventually the cystic bile duct. During its time stored in the gallbladder, bile becomes concentrated (up to 10 times) and mildly acidified. Gallbladder contraction propels bile into the common bile duct (CBD) and then via the sphincter of Oddi into the proximal duodenum at the major duodenal papilla. Gallbladder contraction is stimulated by cholecystokinin, gastrin, and motilin, which in turn are released in response to fatty acids, peptides, and amino acids in the stomach and duodenum.

In cats, the CBD joins the pancreatic duct, sharing a common opening into the duodenum at the duodenal papilla. In dogs, the pancreatic and CBD meet only at the papilla; in many dogs, an additional separate pancreatic duct enters the duodenum more distal to the papilla.

Etiology/Pathophysiology

Disorders of the canine and feline biliary tract are more frequently acquired than congenital, although congenital biliary cysts, malformations, and biliary atresia have been reported. The flow of bile from the gallbladder to the duodenal papilla, as well as the chemical character of bile and the mucosal immunity (secretory IgA and mucosal mononuclear cells), serves to reduce the risk of biliary bacterial infection. *In vivo* studies and molecular techniques have detected transitory bacteria in bile of normal dogs. Interruption or obstruction to flow may allow these transitory bacteria to colonize the tract, causing bacterial cholangitis.

Trematode infections (*Platynosomum fastosum* and other *Platynosomum* spp.) of the biliary tract are found occasionally in cats in the southern USA, in South America and Asia, with clinical disease ranging from asymptomatic to severe obstructive cholangitis or subsequent neoplastic transformation to cholangiocarcinoma.

Mucosal resistance to the extreme chemical nature of bile is afforded by secretion of mucin from mucous glands within the biliary tract. Hypersecretion, possibly as a result of inflammatory stimuli or transporter defects (ABCB4 phosphatidylcholine translocator mutation in Shetland sheepdogs), may result in accumulation of mucin within the gallbladder in dogs, leading to the formation of a biliary mucocele (Figure 67.1). Untreated biliary mucoceles may rupture, as the gallbladder wall becomes necrotic under pressure from the accumulating concretion of mucus. Bile is a highly irritating substance, so leakage into the abdomen results in a chemical peritonitis ("bile peritonitis"). Cholecystocentesis is contraindicated in biliary mucocele patients because of the risk of gallbladder rupture.

Biliary obstruction may be either intrinsic to the biliary tract or outside it. Blockage of biliary flow results in posthepatic jaundice. One of the more common causes of biliary obstruction is acute pancreatitis. This occurs due to the intimate association of the body of the pancreas with the CBD near the duodenal papilla – the point of entry of the CBD into the small intestine. Pancreatic carcinoma or biliary carcinoma similarly may result in complete bile duct obstruction. Inflammation or neoplastic infiltration of and around the duodenal papilla (e.g., duodenal lymphoma, carcinoma) is an occasional cause of jaundice.

Choleliths are uncommon in cats and dogs but may cause bile duct obstruction or rupture. Most canine and feline choleliths contain some bile pigments, rather than being pure cholesterol liths such as those commonly found in humans. A predisposition to cholelithiasis may occur due to gallbladder motility disorders, endocrine disease, cholestasis, cholangitis or supersaturation of the components of bile (cholesterol, pigments).

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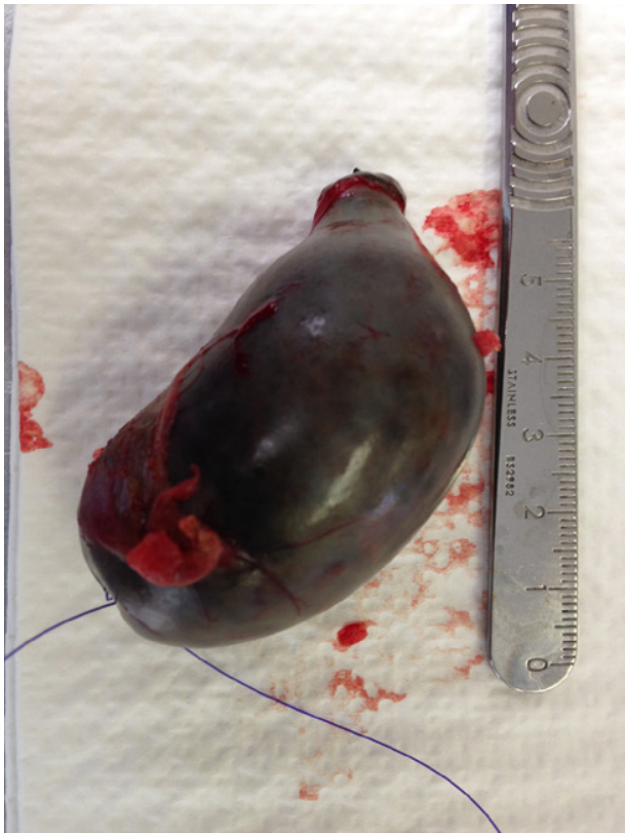


Figure 67.1 A distended gallbladder removed from a dog with a mucocele.

Primary biliary neoplasia ranges from benign choledochal cysts and biliary cystadenoma to biliary carcinoma, which may originate in the intrahepatic or extrahepatic biliary system. Biliary neoplasia occurs more commonly in cats. The gallbladder is susceptible to infarction if the cystic artery – the sole arterial blood supply to the organ – is compromised by trauma or thrombosis.

Bacterial cholangitis may occur due to ascending bacterial infection from the gastrointestinal tract, hematogenous spread or colonization by the aforementioned transitory bacteria.

Epidemiology

Arguably, the most common disorders predisposing to biliary tract disease are endocrine diseases such as hyperadrenocorticism, diabetes mellitus, and hypothyroidism. Of these, hyperadrenocorticism increases risk of gallbladder mucocele by up to 29 times; the association with hypothyroidism and diabetes mellitus is less concrete.

Inflammatory bowel disease (IBD) is a common comorbidity with cats with cholangitis, just as there is a strong association of IBD with primary sclerosing cholangitis in humans. Although such a strong association is not reported in dogs, inflammation around the duodenal papilla can alter bile flow and may encourage bacterial colonization of the biliary tract. Likewise, intestinal motility disorders or small intestinal bacterial overgrowth may augment infection risk by increasing numbers of potentially pathogenic bacteria that may ascend the biliary tract.

Biliary flukes are not prevalent in Europe, but are more commonly found in the southern USA, South America, and Asia. Infection requires ingestion of a secondary intermediate host such as a frog or lizard.

Signalment

Particular species and breed associations are found for certain biliary disorders. Neoplasia occurs more commonly in middle-aged to older cats and dogs, but benign and cystic disorders may be acquired even in individuals less than 2 years of age. Biliary flukes are reported in cats but are far less common in dogs. Mucocele formation is more common in Shetland sheepdogs, border terriers, miniature schnauzers and cocker spaniels and become increasingly common in dogs beyond middle age. Mutation of a phosphatidylcholine translocator (ABCB4) has been identified in affected Shetland sheepdogs. Choleliths are more commonly found in miniature schnauzers and miniature poodles, particularly in older females.

Pancreatic neoplasia does not have a strong breed predisposition, but pancreatitis is more commonly associated with cocker spaniels and miniature schnauzers. Of note is the often marked inflammatory swelling of the pancreas in cocker spaniels with pancreatitis, which may be erroneously described as a pancreatic tumor based on diagnostic imaging findings. Those breeds with predispositions towards endocrine disease (e.g., hypothyroidism, hyperadrenocorticism) may be more commonly affected by bile stasis, cholangitis, and biliary mucocele.

History and Clinical Signs

Nonobstructive biliary tract disease may be insidious in onset, with vague clinical signs such as lethargy, pyrexia, anorexia, and vomiting. Pyrexia is more likely to be present with florid inflammation, bile peritonitis or bacterial biliary infection but can also be seen with cholelithiasis, presumably due to secondary bacterial infection. Clinical signs may be mild and therefore present for weeks or months before veterinary attention is sought.

Vomiting may be a clinical sign associated with biliary disease itself or caused by an underlying associated problem such as pancreatitis. A history of dietary indiscretion or ingestion of fatty foods may be relevant in cases of acute pancreatitis. Abdominal pain may result from the obstruction or distension of the bile ducts or gallbladder or from inflammation of the biliary tract and surrounding area (e.g., local peritonitis). Patients with biliary mucocele may also exhibit abdominal pain and, if significantly obstructive, may become jaundiced. Jaundice (icterus) becomes clinically evident as yellow discoloration of the mucus membranes, skin, and sclera when the serum bilirubin exceeds around 2 mg/dL. The exact concentration at which icterus becomes clinically visible will depend upon the patient's own pigmentation and hemoglobin concentration (mucous membrane pallor makes icterus more evident). Total biliary obstruction prevents pigmentation of the feces, resulting in pale "acholic" feces.

Diagnosis

Clinical Examination

It should be apparent from clinical examination if the patient is jaundiced, but jaundice is only clinically evident when serum bilirubin levels exceed 2 mg/dL. As previously mentioned, how evident hyperbilirubinemia is will depend upon multiple factors. Examination of the sclera or internal aspect of the pinna (the latter particularly in cats) may display more obvious evidence of icterus.

Cranial abdominal pain may manifest as a hunched posture, "prayer posture" or via the patient's response to palpation. Once again, how evident this subjective finding is will depend upon patient factors and also concurrent problems such as pancreatitis. Pancreatic pain usually localizes to the right cranial abdominal quadrant, but may be more diffuse. In some patients, pancreatic pain does not manifest until pressure is placed directly upon the pancreas during ultrasonography. A very distended gallbladder might be palpable beyond the hepatic margin in some patients, but this is unusual. If rupture of the biliary tract has occurred then an abdominal effusion may be present, potentially resulting in a fluid wave on ballottement. Often, however, patients with bile peritonitis have tensed abdominal muscles, because of the associated pain, which limits clinical examination.

Blood Chemistry

Following centrifugation, the plasma or serum of a jaundiced patient's blood will appear deep yellow (icteric). This interferes with some colorimetric blood biochemistry tests.

Blood biochemistry in biliary tract disease varies depending upon the degree of biliary obstruction as well as the accompanying hepatic and pancreatic disease.

In an icteric patient, total bilirubin will be increased. If the patient has significant cholestasis, then bile acids will also be increased. If total bilirubin is increased then nothing additional may be inferred from measurement of bile acids or performing a bile acid stimulation test – the patient has either significant hepatic functional compromise or bile duct obstruction.

Increases of the concentration of biliary canalicular enzymes in the blood are expected (alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT]) with cholestasis or biliary tract inflammation. Bile acids are toxic to hepatocytes, so it is extremely common for animals with bile stasis to have elevation in hepatocellular enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST]). Patients with concurrent hepatic parenchymal disease may also have increased hepatocellular enzymes. If hepatic disease is advanced enough to impair hepatic function, then urea and albumin may be reduced due to poor hepatic synthesis and conversion. Similarly, coagulation factors may be depleted due to reduced recycling of the vitamin K-dependent factors (II, VII, IX, X), resulting in prolonged coagulation times (prothrombin time, activated partial thromboplastin time).

The inflammatory response may cause increased synthesis of globulins. Pancreatitis may be reflected by elevations of amylase and lipase, due to leakage from the pancreas, but these enzymes have poor specificity and may be spuriously elevated in hemoconcentrated patients and patients with other diseases. Amylase and lipase are even less sensitive and specific in cats than in dogs. Pancreatic species-specific lipase is a more sensitive and specific test, but it must be remembered that a positive result does not necessarily indicate that pancreatitis is the primary problem as gastrointestinal disease, peritonitis, or pancreatic neoplasia can also result in increased pancreatic specific lipase. Additonally, a normal value does not exclude pancreatitis as a possible differential diagnosis.

Hematology

The complete blood count can reflect the inflammatory disease by revealing increased numbers of neutrophils which, in marked inflammation or infection, may exhibit a left shift or toxic changes.

Urinalysis

Icteric patients are, by definition, hyperbilirubinemic, which results in bilirubinuria, imparting a deep yellow color to the urine. On microscopic examination of urine sediment, bilirubin crystals may be evident.

Diagnostic Imaging

Radiography

Radiography may give an overall impression of the size of the liver but usually does not give information regarding structure. It may identify the presence of radiodense choleliths within the biliary tree or gallbladder. Rarely, the gallbladder may be visible as a "porcelain gallbladder" with a fine mineral opacity delineating the gallbladder wall. This may be caused by dystrophic mineralization due to neoplasia of the gallbladder. If peritonitis has developed subsequent to biliary rupture, then effusion will cause loss of radiologic contrast in the cranial abdomen or a "ground glass" appearance.

Ultrasonography

Transcutaneous abdominal ultrasonography is the mainstay of imaging of the biliary tract. It affords assessment of the bile ducts within and outside the liver, ensuring that the ducts are patent and not distended. The gallbladder may be examined and measured, noting any material within the lumen as well as the wall thickness. The common bile duct should be followed from the gallbladder to the point of entry into the duodenum at the major duodenal papilla. Intestinal gas may impede this examination. The normal common duct may measure 3 mm diameter in dogs or up to 4 mm diameter in cats.

Choleliths appear as hyperechoic structures with distal acoustic shadowing. If a cholelith is causing complete obstruction then the bile duct may appear dilated proximally. Choleliths do not commonly cause obstruction, but may be associated with nonobstructive bile duct dilation. In humans and most likely in dogs, such nonobstructive dilation may be associated with bacterial infection of the bile duct. In this circumstance, it is difficult to determine whether the cholelithiasis is the cause or the consequence of cholangitis.

Complete bile duct obstruction does not necessarily result in gallbladder distension but often causes dilation of the major bile ducts, sometimes giving a very tortuous appearance on ultrasonography.

Echogenic sediment or "sludge" is a normal finding in many dogs and cats but should be dependent (i.e., affected by gravity) and not obscuring the lumen. "Sludge balls" are echogenic, roughly spherical accumulations of bile and mucus that move depending upon patient position. They may pose a risk for bile duct obstruction.

Gallbladder mucoceles classically have a hyperechoic stellate appearance on ultrasound, with strands of the echogenic material extending to the gallbladder wall. Early or incipient mucoceles may have a more subtle appearance, but the main feature is of immobile nondependent sludging occupying the majority of the gallbladder.

Advanced Imaging

Computed tomography and magnetic resonance imaging may yield more detailed information about the extrahepatic biliary ducts and gallbladder. They can be useful for detecting neoplasia, characterizing anatomic anomalies and detecting choleliths. The main advantage of advanced imaging above abdominal ultrasound is that regions of the abdomen are usually not missed on advanced imaging, though methodical radiologic review is essential and time-consuming. Whereas gastrointestinal gas may obscure the bile ducts by reflecting ultrasound, this is not a problem with advanced imaging. When assessing the abdomen for neoplasia on computed tomography, the thorax may also be scanned to assess for possible metastasis. Intravenous contrast may be used to assess the vascularity of a structure to assist in diagnosis. The requirement for sedation, anesthesia, and exposure to ionizing radiation must be considered.

Endoscopy

The duodenal papilla may be assessed during endoscopy, which affords the opportunity for gastrointestinal biopsies. Some small studies of endoscopic retrograde cholangiography and cholangiopancreatography in cats and dogs have documented that this procedure is feasible, but there is no tangible benefit over advanced imaging. Cholangiopancreatography has been used historically to induce pancreatitis for experimental purposes in dogs – this in itself casts doubt over its diagnostic utility and safety. Using a similar procedure employing a side-angled endoscope, it is feasible to cannulate and therefore stent the common bile duct in the case of functional obstruction (e.g., acute pancreatitis, pancreatic mass).

Cholecentesis

If inflammatory or bacterial cholangitis is suspected then bile sampling is indicated. This may be performed under ultrasound guidance or during a laparotomy or laparoscopy. While potential complications include bile leakage and subsequent peritonitis and vagal-induced arrhythmias, most samples taken in this way do not cause complications. The gallbladder should be emptied as much as possible during the procedure to reduce the pressure of the residual contents and the risk of leakage. Bile obtained should be examined cytologically and should also be submitted for gram staining and bacterial culture and sensitivity (the author prefers to submit two transport charcoal swabs of bile – one for aerobic and one for anaerobic culture conditions). Ideally, both aerobic and anaerobic culture should be performed. In a study of patients with hepatic inflammation, nearly one

quarter had positive bile culture whereas 6% had positive culture of liver tissue. In patients with confirmed cholecystitis, more than half had a positive bile culture.

Laparotomy and Laparoscopy

Direct examination of the extrahepatic biliary system and gallbladder affords an opportunity for biopsy, cytology, and potentially palliative and curative surgical intervention. Complete bile duct obstruction is an indication for surgical intervention. Bile ducts may be stented for short- or long-term management of obstruction, to allow resolution of the underlying disorder (e.g., acute pancreatitis causing complete extrahepatic bile duct obstruction).

Surgical exploration may be done via laparotomy or laparoscopy. Whichever technique is adopted, the opportunity should be taken for biopsy of the liver and pancreas, cholecentesis, and possibly intestinal biopsy. Surgery is required for assessment and potentially repair of the biliary tract in cases of bile peritonitis. Cholecystectomy is indicated in the case of gallbladder mucocele.

Cytology

Fine needle aspirates may be taken, under ultrasound guidance, from the liver, pancreas, and associated lymph nodes. Similarly, cholecentesis and abdominocentesis may be performed to investigate potential inflammatory or infectious processes. As previously mentioned, cholecentesis is contraindicated if biliary mucocele is suspected – diagnosis may be confirmed at surgery.

Therapy

Surgery

The patient should be stabilized first as biliary surgery is complex and may require prolonged general anesthesia. As detailed above, dogs with gallbladder mucoceles are treated surgically by way of cholecystectomy with or without biliary bypass (cholecystoduodenostomy, cholecystojejunostomy). Surgery is often required for animals with extrahepatic bile duct obstruction, especially if this is complete or persistent. Rupture of the biliary tract, resulting in bile peritonitis, is another indication for surgical intervention.

Antibiotics

Antibiotic choice for biliary infections should be ideally based upon results of culture and sensitivity. A 4–6-week course is advisable in the absence of a nidus for infection (e.g., cholelith). One large retrospective study of bile and liver culture in dogs and cats with hepatobiliary disease found that *Escherichia coli*, *Enterococcus* spp., *Bacteroides* spp., *Streptococcus* spp., and *Clostridium* spp. were the most common isolates. This study suggests that empirical antibiotic choice for hepatobiliary infection could include a fluoroquinolone for gram-negative cover alongside a penicillin or metronidazole for gram-positive and anaerobic organisms. It cannot be stressed enough, however, that responsible antibiotic usage demands culture and sensitivity testing, particularly before employing antibiotics such as fluoroquinolones. Repeating bile culture to monitor response to treatment should be considered, as significant antibiotic resistance can develop during the course of treatment.

Cholerectics

Sludging and stasis of bile promote biliary inflammation and infection. Additionally, hydrophobic bile acids are cytotoxic and damage cell membranes. Ursodeoxycholic acid (ursodiol, UDCA) is a hydrophilic bile acid, which exerts cytoprotective and antioxidant effects and induces choleresis (increased bile flow). The recommended dose is 10–15 mg/kg once daily. In addition to using this drug in cholangitis, it may have some efficacy in treating early mucoid bile accumulation (early gallbladder mucocele). Ursodeoxycholic acid is contraindicated in complete bile duct obstruction and is not an alternative to surgery for gallbladder mucocele.

Antioxidants

In addition to the antioxidant effects of ursodeoxycholic acid, other antioxidant drugs are commonly used in hepatobiliary disease. S-adenosyl-L-methionine (SAM-e) increases glutathione production in cat and dog livers, assisting conjugation and acting as an antioxidant. SAM-e has been shown to reduce hepatotoxicity following acetaminophen administration. Milk thistle-derived silymarin has strong antioxidant properties and has been shown to exert hepatoprotective effects when administered alongside some chemotherapy drugs. Those formulations which complex silymarin with phosphatidylcholine have much improved bioavailability. Vitamin E is a widely available antioxidant that also reduces transcription of proinflammatory cytokines.

Parasiticides

Praziquantel or fenbendazole may be used as flukicidal therapy.

Prognosis

Biliary neoplasia bears a grave prognosis as resection is rarely achieved and metastasis is common. Stenting of the bile duct may be of palliative use and can be performed at endoscopy, laparotomy or as a laparoscopy-assisted procedure. Bacterial cholecystitis and cholangitis bear a favorable prognosis if the infection is identified and treated. Gallbladder mucocele has an excellent prognosis following successful surgery, but the perioperative period carries risks such as bile peritonitis and inducing pancreatitis. Rupture of the biliary tract of any cause bears a guarded prognosis, particularly if bacterial infection is present. There is a broad spectrum of prognoses with pancreatitis with extrahepatic bile duct obstruction, depending upon the severity and complications. Acute pancreatitis carries a guarded prognosis, but may reach a successful outcome in a good proportion of cases with intensive management.

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Section 8

Neurologic Disease

68

The Neurologic Examination

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Anatomic Diagnosis

What is the most important first step in evaluating a patient presented for a neurologic disorder? It is making the anatomic diagnosis based on the results of your neurologic examination. Did you ever think about who first made these correlations between the neurologic signs exhibited by a patient and the location of the lesions responsible for these clinical signs? Based on textbook publications that were available to me, you have to credit the keen observations of two veterinary pathologists for this: Jack McGrath at the University of Pennsylvania School of Veterinary Medicine and Anthony Palmer at the Cambridge University School of Veterinary Medicine. These two astute veterinarians both published a textbook in 1956 and 1965 respectively that recorded their observations of the location and character of nervous system lesions with the clinical observations supplied to them by the clinicians that examined the patient prior to its death. Thus began the concept of an anatomic diagnosis.

I was a veterinary student at the College of Veterinary Medicine at Cornell University from 1954 to 1958. The majority of my clinical neurology education took place in a course in Applied Anatomy in my third year of college. This course taught the clinical signs associated with cranial nerve abnormalities and the effects of specific nerve dysfunction on the gait of the animal. I joined the faculty of the Department of Anatomy at this college in 1963 and was given the responsibility of teaching the new course in neuroanatomy to first-year veterinary students in their second semester. As a rule, veterinary students have a need to understand the reason why they must study a subject. When a course in clinical neurology does not exist or is a brief exposure in the third year, most students will find it difficult to concentrate on neuroanatomy in their first year. If you agree with this, then you will understand that combining the teaching of neuroanatomy and clinical neurology in one course is the solution and the foundation for making an appropriate anatomic diagnosis. The first-year student is readily able to handle this. Now, in the 21st century, when the need for teaching time is so critical, it should be recognized that the most effective teaching of neuroanatomy and clinical neurology is as a vertically integrated course taught by a board-certified veterinary neurologist ideally in the first year of the curriculum. Most veterinary neuroanatomy courses are taught by nonveterinarians and as a result there is no correlation to clinical disorders.

As an example of how far we have come, consider this. Prior to the mid-1960s, there was no understanding of the pathogenesis of what was known as coonhound paralysis then and is now known as polyradiculoneuritis. There had been a few case studies published that suggested that these dogs became paralyzed following the trauma to their cervical spinal cord caused by their continual jumping up on the trees where they had followed a raccoon. Now, you should recognize the fallacy of this observation because you understand that a cervical spinal cord lesion cannot cause the diffuse lower motor neuron disorder that is present in these paralyzed dogs. Hopefully, your education has taught you how to distinguish tetraplegia caused by a lower motor neuron disorder from one caused by an upper motor neuron disorder.

Fifty years ago, we were just learning the importance of making an anatomic diagnosis and how to do it. Now, we are faced with how to select the most useful diagnostic procedure to support our most presumptive clinical diagnosis from a plethora of diagnostic instruments. Issues of expense and patient safety are most prevalent. However, all of these ancillary procedures are meaningless without an accurate anatomic diagnosis.

I was asked to write about the approach to a neurologic patient. This must be a compassionate hands-on approach that requires your utmost patience as well as that of your patient so that a thorough physical neurologic examination can be performed. An accurate anatomic diagnosis will be dependent on this cooperation between you and

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your patient. It is perfectly appropriate to make a fool of yourself as you attempt to gain the cooperation needed from your patient. When you think about this, you are asking this patient to perform movements never asked of it before. It is really remarkable how well most of them cooperate. The reward will be as accurate an anatomic diagnosis as possible.

Examination of a patient with signs of a neurologic disorder should include a review of the history, a complete physical examination, a neurologic examination, and appropriate ancillary procedures. The purpose of the neurologic examination is to determine the neurologic abnormalities and, based on that, the location of the lesion or lesions in the nervous system responsible for causing these abnormalities. The location is the anatomic diagnosis. The continual use of a routine systematic procedure will provide you with the experience and confidence to make an accurate anatomic diagnosis.

The differential diagnosis must be based on the anatomic diagnosis, and the order of significance of these disorders will depend on your evaluation of the signalment and history. Be sure to consider all five major kinds of lesions in your differential diagnosis or a list of these with which you are comfortable. My list includes malformation, injury, inflammation, neoplasia, and degeneration (MIIND). Your experience with the anatomic diagnosis together with the signalment and history will often lead to a presumptive clinical diagnosis. Further examination of the patient with ancillary procedures must depend on your differential diagnosis and what you consider to be the most likely clinical diagnosis. Many factors will be considered in this selection, including the cost to the owner.

Be sure to record carefully all your observations from the neurologic examination, and never rely on your memory. Many forms are available for recording your observations. Some of these forms list in detail every possible response that is present or absent, with numbers to estimate the level of response. The considerable variation between individual patients of the same species makes the recording of the degree of a response less reliable and often misleading. I prefer a less time-consuming form that is easier to follow and adaptable to all species. An example of this follows.

NEUROLOGIC EXAMINATION

PATIENT IDENTIFICATION: _____
SIGNALMENT:_____
HISTORY:_____
MENTAL STATUS:_____
GAIT AND POSTURE:_____

CRANIAL NERVES:
II and VII: Menace: OS OD
II and III: Pupil Size: OS OD
Light in OS: OS OD
Light in OD: OS OD
III: Strabismus
V: Atrophy of temporal/masseter muscles
VI, III and IV: Strabismus
VII and V: Palpebral reflex
VIII: Nystagmus
IX, X: Swallowing
XI: Atrophy of trapezius muscle
XII: Tongue movement/atrophy

SPINAL NERVE REFLEXES:

POSTURAL REACTIONS:
Patellar: L R
Hopping: LF RF LH RH
Flexor: LF RF LH RH
PAW REPLACEMENT: LF RF LH RH
PERINEAL:
NOCICEPTION:
OTHER:

ANATOMIC DIAGNOSIS:

DIFFERENTIAL DIAGNOSIS:

Examination

The neurologic examination can be divided into five parts.

1) Sensorium – mental attitude
2) Gait and posture
3) Postural reactions
4) Muscle tone, size, and spinal nerve reflexes
5) Cranial nerves

The order in which these parts are performed is usually determined by the degree of patient cooperation and your preference. We usually perform the examination in the order listed. However, if the patient is resting comfortably in its cage, performing the cranial nerve examination first may be preferable. If the patient is excited or apprehensive, performing the cranial nerve examination may be more convenient after the patient has been handled for the examination of its gait, postural reactions, and spinal nerve reflexes.

Sensorium – Mental Attitude

An assessment should be made and recorded of the patient's sensorium, its mental attitude and response to the immediate environment, and attitude to being handled by you. The owner is the best judge of subtle changes in the patient's behavior in its normal environment. Be sure to explore this issue when you obtain the history. Considerable patient variation exists in how alert and responsive the patient may be in the examination room of a veterinary hospital. Do not mistake a very laidback behavior for depression. Descriptive terms for this portion of your examination include alert and responsive, depressed, lethargic, obtunded, semicoma (stupor), and coma. Other descriptions include acting vague, disoriented, hyperactive, propulsive, and aggressive.

As a rule, alterations in the patient's normal sensorium reflect disturbances in the ascending reticular activating system (ARAS) and limbic system components of the cerebrum or rostral brainstem. Be sure to evaluate the sensorium of a recumbent patient thoroughly. Recumbency from diffuse neuromuscular disease or focal cervical spinal cord disease will not alter the patient's sensorium. A dog that is recumbent with polyradiculoneuritis may appear to be severely depressed or lethargic because it has no voluntary movement to show a response. The quality of the tetraparesis or tetraplegia with a cervical spinal cord lesion is the same as that caused by a mid- to caudal brainstem lesion, but the latter circumstance will often alter the patient's level of response to its environment.

Gait and Posture

Examination of the gait should be performed in a place where the patient can be walked with a leash and where the surface is not slippery. Most hospital floors have a very slippery surface, which facilitates cleaning but is poor for evaluating a gait disorder and can be dangerous if the patient slips and falls. A washable carpet is very useful for small animals and can be rolled up between examinations. If you are constructing a small animal hospital, you should consider having a covered area with a specialized surface used in playgrounds that is relatively soft, provides excellent traction for the patient, and is easily cleaned. The material is called Vitriturf® and is available from Hanover Specialties, Inc., Hauppauge, New York.

Observe the patient while it is standing for a head tilt, lowered position of the neck, trembling, degree of tarsal extension, and tail position. You should evaluate the gait both as you lead the patient and as an assistant leads the patient. Most deficits are best seen during a slow walk and as it turns. Walk the animal back and forth in a straight line and in circles in each direction. Observe the patient from all directions. In our opinion, most abnormalities are best seen from a side view. Be aware of breed characteristics that influence the posture and gait. The overflexed tarsus in German shepherd dogs is an example.

Is your patient unwilling or unable to move normally? When you see a gait disorder, this question is the first one that you need to answer. This circumstance is especially true when the patient is short strided or does not support weight well on one or more limbs. A loss of support from a femoral or radial nerve disorder will mimic a severe painful disorder causing a reluctance to bear weight.

Pattern recognition is critical in evaluating gait disorders. With experience, clinicians recognize specific patterns in abnormal gaits that suggest an anatomic diagnosis. These patterns can be described but observing them on videos is the best way to learn them. See www.neurovideos.vet.cornell.edu. These patterns have five components, consisting of two qualities of paresis and three qualities of ataxia.

Paresis is defined as "weakness" in the dictionary, but in clinical neurology, it is defined as "a deficiency in the generation of the gait or the ability to support weight." This definition includes the two qualities of paresis, which are lower motor neuron (neuromuscular) and upper motor neuron. Lower motor neuron (LMN) paresis reflects degrees of difficulty in supporting weight and varies from a short stride that is easily mistaken for a musculoskeletal lameness to complete inability to support weight, causing collapse of the limb whenever

weight is placed on it. Animals with LMN disorders affecting both pelvic limbs will occasionally use them simultaneously. This action is described as *bunny hopping*. Be aware that bunny hopping can also be seen in orthopedic disorders, as well as spinal cord dysplasias. Upper motor neuron (UMN) paresis causes a delay in the onset of protraction, which is the swing phase of the gait. The stride will usually be longer than normal. Stiffness and spasticity may be apparent in the stride. Most of the UMN pathways necessary for gait generation are anatomically adjacent to the pathways of the general proprioceptive (GP) sensory system, and lesions usually affect both simultaneously. Therefore, the gait that reflects UMN paresis also reflects ataxia caused by dysfunction in the GP system. It is unnecessary to recognize the separate clinical signs of dysfunction of these two systems. Therefore, we recognize a pattern that reflects the combined dysfunction of UMN paresis and GP ataxia. As you observe the gait of a dog with UMN paresis and GP ataxia, you have the sense that the patient does not know where its limbs are located. This is never a concern with LMN paresis.

Ataxia is a synonym for incoordination, and we recognize three qualities of ataxia: (1) GP, (2) vestibular (special proprioception [SP]), and (3) cerebellar. GP ataxia reflects the lack of information reaching the central nervous system (CNS) that informs the CNS of where the neck, trunk, and limbs are in space and the state of muscle contraction at any time. Without this GP information, the onset of protraction of a limb may be delayed, and the stride may be lengthened. During protraction, the limb may swing to the side (abduct) or swing under the body (adduct), overextend during protraction, scuff or drag one or more digits, and in the support phase, stand on the dorsal aspect of the digits. Remember that these clinical signs overlap with those caused by dysfunction of the UMN. The gait pattern of a patient with a focal cervical spinal cord lesion between the C1 and C5 segments reflects dysfunction of the UMN and GP systems and is observed as spastic tetraparesis and ataxia. This cervical spinal cord pattern is often recognized by the overextension of the thoracic limbs creating an overreaching or floating action. This clinical sign can be augmented by holding the head and neck extended as the patient is led. This unique form of hypermetria must not be confused with cerebellar ataxia in which the limb is overflexed on protraction. At no time do we try to differentiate between conscious (cerebral) and unconscious (cerebellar) GP pathways! No examination will clearly differentiate these two pathways from each other or from the UMN pathways. No pure conscious proprioceptive deficit exists. This term should be dropped from the clinician's vocabulary.

Vestibular ataxia reflects the loss of orientation of the head with the eyes, neck, trunk, and limbs, which results in a loss of balance. Lesions limited to this system cause the patient to lean, drift, or fall to one side. However, the patient's strength and awareness of where its limbs are in space are normal with lesions confined to this system. This ataxia is usually accompanied by a head tilt and sometimes abnormal nystagmus. We will occasionally blindfold our patients with bandage material which will exacerbate the vestibular ataxia.

Cerebellar ataxia most commonly causes hypermetric ataxia characterized by sudden bursts of motor activity with a marked overflexion of the limbs on protraction. Vestibular system components exist in the cerebellum that, if dysfunctional, may cause loss of balance, head tilt, and abnormal nystagmus. As a rule, hypertonia accompanies cerebellar ataxia.

Postural Reactions

Remember that spinal nerve reflexes require only the specific nerves that innervate the area being tested and the spinal cord segments with which they connect. Postural reactions depend on the same components as the spinal nerve reflexes plus the cranial projecting pathways in the spinal cord white matter to the brainstem, cerebellum, and frontoparietal portion of the cerebral hemisphere and the caudal-projecting UMN pathways that return from the cerebrum and brainstem and comprise tracts in the white matter of the spinal cord that terminate in the cervical and lumbosacral intumescences. These postural reactions test the integrity of nearly the entire peripheral and central nervous systems. By themselves, the postural reactions are relatively less reliable for lesion location.

The degree of functional limb deficit will determine the need for postural reaction testing. In a patient that is recumbent with tetraplegia or is paraplegic, you need not perform postural reactions in the affected limbs. However, in the paraplegic patient, you must test the thoracic limb postural reactions so as to avoid overlooking a focal cranial thoracic lesion or a multifocal disorder.

In small animals, we evaluate muscle size and tone just before our evaluation of the postural reactions. Be sure to talk to your patient continually, and use its name to gain its cooperation. Stand over the patient with both of you facing in the same direction. Simultaneously palpate the muscles of the neck and both thoracic limbs from proximal to distal for any evidence of atrophy. Flex and extend each limb for range of motion and to determine the degree of muscle tone. A short stride or stiffness in the gait may be caused by a joint disorder, limiting the range of motion. When you place the limb back on the ground surface, turn the paw over so that its dorsal surface bears the weight of the limb to determine how

rapidly the paw is replaced. Most normal small animals immediately return the paw to its normal position. This response is known as the paw replacement reaction that requires many peripheral and central components to be normal. This test is not just for conscious perception of GP and should not be called the CP test. This term is a misnomer that we are well aware will be difficult to eliminate from the clinical language of veterinarians, even boarded veterinary neurologists.

Moving on, palpate the thoracolumbar epaxial muscles and then the muscles of both pelvic limbs followed by flexing and extending those limbs for tone and range of motion and checking for paw replacement. Check for the degree of tail tone, and while extending the tail, evaluate the anal tone.

Hopping responses, in our opinion, are the most reliable of the postural reactions that we test. While still straddling the patient, move back to the thoracic limbs and elevate the abdomen with one hand so that the pelvic limbs are not bearing any weight. With your other hand, pick up the thoracic limb on that side. With all the weight supported on that thoracic limb, hop the patient laterally. Go as far as you can without moving your pelvic limbs. Then, switch hands and hop the patient back on the other thoracic limb. Repeat this test many times until you are sure the thoracic limbs are normal or abnormal. Only evaluate hopping in the lateral direction. As you stand over your patient and look down the lateral aspect of the limb that is being hopped, the limb should move as soon as you move the shoulder region laterally over the paw. Any delay in this response is abnormal. The hopping movements should be smooth and fairly rapid and not irregular or excessive. The paw should never drag or land on its dorsal surface. Carefully compare one thoracic limb with the other.

To test the hopping responses in the pelvic limbs, stand beside the patient, and place your forelimb that is closest to the patient's head between its thoracic limbs with your hand on its sternum. Lift up on the thorax just enough to take the weight off the thoracic limbs. With the other hand, pick up the pelvic limb on the side where you are standing and push the patient toward the pelvic limb that is bearing the weight. This action will force the patient to hop laterally on that pelvic limb in a direction away from you. After a few hops, switch sides, and hop the patient back on the other pelvic limb. Keep repeating this test until you have determined that the response is normal or abnormal. The responses should be brisk and smooth but will not be quite as rapid as in the thoracic limbs. While you are hopping the patient, you will also be aware of the degree of tone in the limb that is bearing all the weight.

In large dogs that are too heavy to lift for this testing, the same observations can be made while the patient is walked on one side (hemiwalking). Hemiwalking is performed by standing on one side of the patient. Grasp each limb on that side and lift the limbs off the ground and push the patient toward its opposite side. The patient will hop with both limbs on that side. Switch sides and repeat the hemiwalking performance on the opposite limbs. Be sure to compare one thoracic limb with the other and one pelvic limb with the opposite pelvic limb.

In small animals in which the hopping responses are equivocal or difficult to interpret, testing the placing responses may be useful. Pick up the patient and bring its thoracic limbs to the edge of a shelf, table, or chair so that the dorsal surface of the paw contacts the front surface of the object. The normal patient will immediately place its paws on the horizontal surface of the object. Test both thoracic limbs while holding the patient from both sides. For some unknown reason, occasionally the normal patient will not respond on the side on which it is being held. Blocking the vision of the patient while conducting this test may also be useful. Do this by extending its head and neck so that it cannot see the protruding surface of the shelf, table, or chair. Whether the lack of vision or the position of the head and neck helps exacerbate the placing deficits is unclear.

In cooperative patients in which you are not sure of the thoracic limb function, you can wheelbarrow the patient while holding its head and neck in extension. With one of your forelimbs, elevate the abdomen of your patient, and with the other hand, hold the head and neck in extension and force the patient to walk forward. With this posture, vision is compromised, and the need for GP is increased.

Remember that patients with LMN disease that still have some voluntary movements will hop or circle rapidly if their weight is supported because their GP is unaffected. This observation may help distinguish between subtle UMN and LMN paresis. When we are presented with a patient that we suspect has LMN paresis, we will hop the patient with and without supporting all the weight on the affected limb or limbs. As already stated, the patient with LMN paresis should know exactly where the limb is located during these postural reactions.

When presented with a recumbent patient, you should pick it up and hold it in a standing position. Get help if the patient is too large for you to handle alone. By holding it in this position and lifting it up and down, you can readily determine the quality of the muscle tone, whether they are hypotonic-flaccid from LMN disease, or hypertonic from spasticity of UMN disease. You can determine whether any voluntary movements are present in the limbs, and while supporting the patient, you can determine the presence and quality of the hopping responses.

One might conclude that these postural reactions are relatively nonspecific. This conclusion is absolutely

correct. Why then are they useful? First, testing postural reactions acts as a screen for detecting abnormalities in the nervous system. Abnormal responses will be the first clinical sign of any progressive lesion in any part of the central or peripheral nervous system that is involved in limb movement. One or more of these postural reactions may be abnormal before any detectable abnormality in the gait is observed. Second, their importance in localizing lesions is dependent on the results of the rest of the neurologic examination. If the gait is normal in the environment of your examination and one or more of the postural reactions are abnormal in the limbs on one side of the body, a contralateral prosencephalic lesion is strongly suggested. This test is the most useful of the three clinical tests that we use for prosencephalic disorders. If you have a patient with clinical signs of a unilateral vestibular system disorder with a normal gait but the postural reactions are abnormal, then the lesion is in the central components of the vestibular system.

Remember to use terminology that all clinicians can understand. Lesions that affect the UMN pathways also affect the GP pathways; thus when you describe a gait abnormality as paraparesis, also include pelvic limb ataxia. Use tetraparesis and ataxia for C1–C5 spinal cord lesions and hemiparesis and ataxia for unilateral C1–C5 spinal cord lesions that affect the gait. If the gait is normal and the postural reactions are abnormal on one side, describe it that way, and do not refer to this abnormality as hemiparesis. Be sure your reader can clearly understand what you have observed.

Muscle Tone and Size, and Spinal Reflexes

In small animals, examination of these features is performed in the recumbent patient that is gently restrained by an assistant. You can conduct this test unassisted in a cooperative patient by gently kneeling on the patient's neck to hold it in lateral recumbency. For cats, toy breeds, and puppies, you might want to sit on the floor with your back against a wall and your knees held together and flexed. Place the patient with its back resting against your thighs. This position is also useful for the cranial nerve examination.

Flex and extend the limbs on the nonrecumbent side to assess muscle tone, and palpate the muscles again for any indication of atrophy. For the patellar reflex, hold the pelvic limb in partial flexion, and, with the limb as relaxed as possible, lightly strike the patellar ligament with a human pediatric patellar hammer or any blunt instrument. The response is a brisk extension of the stifle. This response can be graded as 2 for normal, 1 for depressed, and 0 for absent; grade 3 is hyperactive, and grade 4 is clonic. A clonic reflex is one in which, after the response to a single stimulus, the stifle repeatedly rapidly relaxes and extends for a brief period, creating a tremor. Grades 2, 3, and 4 occur with UMN lesions. This is the most reliable tendon reflex and determines the integrity of the femoral nerve and the L4, L5, and L6 spinal cord segments. Always check the patellar reflexes in both limbs while in both recumbencies because, in normal dogs, it will occasionally be absent in one position and not the other. We have no explanation for this phenomenon. Also recall that, in dogs 10 years of age or older, one or both patellar reflexes may be absent with no other neurologic signs present. The presence of normal tone and the lack of any atrophy suggest that the basis for this sign is on the sensory side of the reflex arc, which may involve an age-related sensory neuropathy. However, this suggestion has not been proven. The patellar reflex is the most reliable tendon reflex in our examination of a patient.

Other tendon or muscle reflexes elicited by striking the tendon (gastrocnemius muscle – tibial nerve) or muscle (cranial tibial muscle – fibular nerve) are of limited use because they are not present in all normal small animals and some occur in denervated muscle. I do not consistently perform these reflexes. Be sure to test the patellar reflexes before the withdrawal reflexes because the latter require a noxious stimulus that may upset your patient.

The withdrawal-flexor reflex is evaluated in both pelvic limbs. This reflex requires an adequate noxious stimulus that differs between individual patients. A pin may be adequate in many cats but not in many dogs. I prefer using tissue forceps because the degree of compression can be adjusted to the individual patient. Compress the skin at the base of the third phalanx of a digit with enough pressure to elicit the reflex and usually a slight conscious response in a normal patient. By increasing the compression of the digit, the stimulus becomes sufficiently noxious to elicit nociception. Your digital pressure is sometimes sufficient, but a pair of tissue forceps is usually more reliable. Remember that this noxious stimulus tests both the spinal nerve reflex and the pathways in the CNS for nociception. You can have a reflex loss without loss of nociception; therefore you must use care in the amount of pressure you apply to avoid excessive discomfort to the patient and injury to you by the patient.

This withdrawal reflex is a more complex reflex. The sensory neurons tested depend on the digit being tested or the autonomous or cutaneous zone that you select for this noxious stimulus. Compression of the first digit stimulates receptors innervated by the saphenous nerve (femoral nerve, spinal cord segments L4–L6). Compression of digits 2–5 stimulates receptors innervated by the sciatic nerve (tibial nerve on the plantar surface and fibular nerve on the dorsal surface). The motor response involves primarily the sciatic nerve in the pelvic limb, with caudal thigh muscular branches responsible for

stifle flexion, the fibular nerve branch for tarsal flexion, and the tibial nerve branch for digital flexion. Be aware that the flexion of the hip is the responsibility of motor neurons in the femoral nerve and the ventral branches of all the lumbar spinal nerves that innervate the psoas major muscle. An animal with a complete dysfunction of its sciatic nerve can still flex the hip when the medial side of the crus or metatarsus is stimulated. The latter receives sensory innervation from the saphenous nerve branch of the femoral nerve. The spinal cord segments associated with the sciatic nerve are L6, L7, and S1. As you increase the forceps compression, nociceptors will be stimulated and voluntary effort will be added to the reflex you are testing if the pathway is normal. Remember that these reflexes will still be intact with a transverse lesion cranial to the L4 spinal cord segment, but nociception will be lost in the pelvic limbs.

Lesions of nerves cause both reflex loss and hypalgesia or analgesia. Lesions of the spinal cord tracts cause hypalgesia or analgesia but will spare the reflexes in the limbs caudal to the lesion. As you perform this reflex and observe flexion of the limb that is stimulated, watch the opposite pelvic limb. In some animals with severe UMN dysfunction, you may observe extension of the opposite limb. This reaction is called *cross-extension* and is a clinical sign of release from inhibition and is an abnormal response. In the dog with severe diffuse LMN paralysis caused by polyradiculoneuritis, the only evidence of nociception will be movements of the jaw as the dog attempts to vocalize and movements of the eyes.

In the thoracic limb, only the withdrawal reflex is reliable. The biceps (musculocutaneous nerve) and triceps (radial nerve) tendon reflexes are not consistently elicited in normal animals. For the biceps reflex, place your finger on the distal portion of the muscle at the elbow, and lightly strike your finger with the hammer and feel the muscle contract or observe a brief elbow flexion. Striking the triceps tendon may elicit a brief elbow extension. Striking the extensor carpi radialis muscle (radial nerve) may elicit a brief carpal extension. Because of the numerous muscles and nerves involved with the withdrawal response from a noxious stimulus of a thoracic limb digit, this evaluation method is a crude test for the entire brachial plexus and the cervical intumescence. The sensory nerve or nerves tested depend on the autonomous or cutaneous zones selected. In small animals, compression of the digits 1–5 stimulates the sensory components of the radial nerve dorsally and the median and ulnar nerves on the palmar surface. The motor neurons involved are in the axillary nerve (shoulder flexion), musculocutaneous nerve (elbow flexion), and the median and ulnar nerves (carpal and digital flexion).

With your patient still being restrained in lateral recumbency, evaluate the tail and anal tone, and gently pinch the skin of the perineum and observe for a tightening of the anus. This response is the perineal reflex (pudendal nerve, sacral spinal nerves, and sacral spinal cord segments). This reflex is often accompanied by tail flexion (caudal nerves and segments).

When this testing is completed, return your patient to a standing position, and perform the cutaneous trunci reflex evaluation. Using your tissue forceps and starting at the level of the sacrum, pinch the skin on the dorsal midline or on either side of the trunk and look for truncal skin movement due to reflex contraction of the cutaneous trunci muscle. In normal animals, this response will usually be bilateral. Progress cranially with your midline stimulus until a response is elicited or until you determine that it is absent. Some variation exists on where you will first elicit a muscle contraction in normal animals. In most dogs, this contraction will occur by approximately the midlumbar level. Sometimes the contraction cannot be elicited in some normal dogs and cats. The forceps compression stimulates the sensory neurons in the dorsal branches of the spinal nerves that innervate the area of skin stimulated. Because of the short caudal distribution of these dorsal branches, each spinal nerve innervates the skin for a distance of approximately two vertebrae caudal to the intervertebral foramen where the spinal nerve emerges from the vertebral canal. The general somatic afferent (GSA) neurons that are stimulated synapse in the respective dorsal gray column on long interneurons, the axons of which enter the adjacent fasciculus proprius bilaterally with a predominance on the contralateral side. Here, these axons course cranially to the C8 and T1 spinal cord segments to terminate in the ventral gray columns by synapsing on the general somatic efferent (GSE) neurons that innervate the cutaneous trunci via the brachial plexus and the lateral thoracic nerve. This reflex is absent in injuries that cause an avulsion of the roots of the brachial plexus. In these patients, this reflex will be present only on the side opposite to the injury. This reflex may help locate a transverse thoracolumbar spinal cord lesion where it will be absent when the stimulus is applied caudal to a line that is approximately two vertebrae caudal to the lesion.

At this point in your neurologic examination, if any indication exists of a possible spinal cord dysfunction, carefully palpate the vertebral column for any location of discomfort.

Cranial Nerves

The cranial nerve examination should be performed when the patient is the most relaxed. In most cooperative patients, this examination is performed after the examination of the gait and spinal nerve reflexes. With very young animals, the examination is often performed

before you handle them at all. The less restraint you use, the better your examination will be. As soon as you try to restrain young small animals, the ensuing struggle will make the cranial nerve evaluation very difficult. Puppies and kittens may be wrapped in a towel and placed between your thighs when you sit on the floor with your back against the wall and your knees flexed. This same floor position can be used for toy breeds. For all other small animals, we examine the cranial nerves while standing over the standing patient facing the same way as the patient, similar to when we performed the postural reactions. The cranial nerve examination can be performed by the numbers I–XII or by regions. We prefer the latter method, starting with the eyes, where either part or all of cranial nerves II–VIII are evaluated.

Vision – Menace and Pupils

We always start with the menace response. Cover one eye with your hand. In small patients, use the hand that is holding the head to cover one eye and menace the opposite eye. This reaction is a learned response that may not be developed until 10–12 weeks in puppies and kittens. Before this age, you may be able to assess vision by determining their ability to follow objects moving in their environment. The menace response requires normally functioning eyes, the optic nerves (cranial nerve II), and the visual pathway to the visual cortex in the occipital lobe via the lateral geniculate nucleus. The efferent response involves association axons from the occipital cortex to the motor cortex and then an UMN pathway to the brainstem terminating in the contralateral facial nucleus in the medulla. This pathway may include a connection through the cerebellum via the pontine nuclei. The majority of this central visual pathway caudal to the optic chiasm is contralateral to the eye being menaced. Some normal patients need a mild stimulus to get a response. I usually tap their orbital or frontal bone region with my hand to arouse their attention and to observe for an intact palpebral reflex to be sure the facial nerve is functioning. In the normal menace response, the menacing gesture elicits closure of the palpebral fissure. This closure is dependent on normal facial nerve innervation of the orbicularis oculi. Be careful to avoid touching any part of the face, especially the hair of the eyelids or the long vibrissae (whiskers), and to avoid creating a sudden air movement that might stimulate the hair or skin of the face. This action creates a cranial nerve V–VII reflex.

If the menace response is absent, we immediately touch the eyelid to be sure the facial nerve innervation is intact to cause palpebral fissure closure. If facial paralysis is present, then we look for eyeball retraction and third eyelid elevation or head retraction movements to determine if vision is present. Setting up a maze of objects in the patient's environment is sometimes necessary to determine if the animal can see and avoid these objects when walking around them.

Immediately after the menace test, the pupil size and response to light should be evaluated. Most patients have a dark-colored iris, which makes seeing the border of the pupil difficult without some light assistance. Cats with a yellow iris are an exception. You need a bright source of light such as that from a Welch Allyn halogen pen light or an Energizer pen light.

Initially, hold the light on the midline over the nose just close enough so that you can see the margin of the pupils and determine their size and if any anisocoria is present. Then bring the light source as close as possible to one eye without touching the patient's face. If no response occurs, move the light so that it shines on all aspects of the ocular fundus. Quickly swing the light into the opposite eye and observe what happens to that pupil. Then quickly return the light source to the original eye. Keep repeating this swinging light action until you are comfortable with your findings, and record them accurately. To prevent confusion, record what happens in each eye when the light is directed into one eye, and perform this maneuver for both eyes. See how this pupillary light reflex is recorded on the neurologic examination form in this chapter. In the normal patient, the pupil will rapidly constrict when the light is directed into it (the direct response), and the opposite pupil will also constrict without moving the light (the indirect or consensual response). Because of the major axonal crossing that occurs at the optic chiasm and at the level of the pretectal nuclei, light directed into one eye will cause a stimulus that will reach both oculomotor nuclei. When you swing the light to the opposite eye, the pupil has already constricted from the light directed into the first eye, and it stays constricted. As you repeatedly swing the light back and forth between the eyes, the pupils remain constricted in the normal animal.

The process I have described here is the way in which I observe the direct and indirect (consensual) pupillary light responses, but avoid using these terms, which can be confusing to students and clinicians alike. I will sometimes evaluate pupil size in a darkened room to help determine the origin of anisocoria.

Test yourself on the anatomic diagnosis of the following examples of eye examinations. (OS is oculus sinister and refers to the left eye. OD is oculus dextra and refers to the right eye. OU is oculi uterque and refers to both eyes.)

- A patient has no menace response in OS with a normal palpebral reflex. No anisocoria is observed. Light directed into OS causes no response OU. Light directed into OD causes a normal response OU. As you swing

the light from OD where the pupil is constricted back to OS, the OS pupil that was constricted from stimulation of OD is now dilating back to its original size. This asymmetry is repeated as you swing the light back and forth between the two eyes. When you cover OD with your hand, the OS pupil fully dilates. *Anatomic diagnosis*: in OS or the left optic nerve. In most cases with this anatomic diagnosis, room light entering the normal eye is sufficient to keep the pupil in the affected eye constricted. Occasionally, the pupil on the affected side will be slightly larger than the pupil on the unaffected side in room light.

- A patient has normal menace responses. Anisocoria is present with the pupil in OD widely dilated. Light directed into OD causes the pupil to constrict only in OS. Light directed into OS causes only the OS pupil to constrict. *Anatomic diagnosis*: right oculomotor nerve general visceral efferent (GVE) component, ciliary ganglion, ciliary nerves. Be aware that this reaction may be the first clinical sign of an extraparenchymal mass lesion ventral to the diencephalon compressing the oculomotor nerve and causing a loss of function of the GVE preganglionic neurons, which may precede the loss of function in the GSE neurons. This disparity between the altered pupil size without ptosis or strabismus is useful in making an anatomic diagnosis of the different components of the oculomotor nerve.
- A patient has no menace response OD with a normal palpebral reflex. Anisocoria is present with the OD pupil widely dilated. Light directed into OD causes no response OU. Light directed into OS causes only the OS pupil to constrict. *Anatomic diagnosis*: right optic nerve and the GVE neurons of the right oculomotor nerve, ciliary ganglion, ciliary nerves. A retrobulbar neoplasm or abscess might produce this result.
- A patient acts blind and has no menace response OU with normal palpebral reflexes. In room light, the pupils are mildly dilated. Light directed into OS causes the pupils to constrict OU. Light directed into OD causes the pupils to constrict OU. This dog's sensorium is normal. *Anatomic diagnosis*: both eyeballs, optic nerves, optic chiasm, or optic tracts.

Patients with lesions in the retina (retinal degeneration, sudden acquired retinal degeneration) or optic nerves (optic neuritis) OU often lose their vision and are clinically blind but still have light-responsive pupils when a bright light is directed into the eyes. However, room light is insufficient to cause normal constriction, and the pupils will appear mildly dilated. This response can be explained by the disease process sparing the retinal neurons involved with these light responses or, more likely, with progressive loss of function of retinal neurons, the threshold for loss of vision is lower than that for pupillary constriction to light. In other words, the pupillary light reflex neurons are the last to lose function when lesions disrupt the retina or optic nerve.

The anisocoria of Horner syndrome has no effect on the menace response and both pupils will respond to light directed into either eye. The pupil asymmetry with Horner syndrome will be more obvious in a dark room where the absence of room light will further dilate the normal pupil.

Anisocoria may result from many intraocular disorders. Iris atrophy is fairly common in older dogs and creates dilated unresponsive pupils with no interference with vision. Be sure to evaluate the iris thoroughly with your bright light source. Neurologic causes of anisocoria include disturbances to cranial nerves II and III and the sympathetic ocular innervation. Examination of the patient in a darkened room may help determine the cause of anisocoria in your patient.

Palpebral Fissure and Third Eyelid

Observe the size of the palpebral fissures and their symmetry. In small animals, the fissure will be smaller with oculomotor nerve dysfunction (loss of function of the levator palpebrae superioris muscle causing ptosis), sympathetic innervation dysfunction (loss of the orbitalis smooth muscle function in the orbit), and secondary to atrophy of the muscles of mastication from dysfunction of the mandibular nerve from the trigeminal nerve or chronic myositis. An elevated third eyelid will be apparent with sympathetic denervation, as well as secondary to atrophy of the muscles of mastication. The third eyelid elevates in tetanus secondary to the tetanus of the extraocular muscles that results in retraction of the eyeball and in animals with a facial paralysis when they are menaced.

Strabismus

Strabismus is an abnormal position of the eyeball. While examining the eyes, you can appreciate whether they are normally positioned in the orbits. Normal ocular position is dependent on the innervation of the extraocular muscles by cranial nerves III, IV, and VI and the normal function of the vestibular system. Repeatedly move the head in a horizontal (dorsal) plane from one side to the other. Watch the excursions of the eyeballs. The degree of adduction (medial rectus, cranial nerve III) should be the same as the abduction (lateral rectus, cranial nerve VI). This is normal physiologic nystagmus and requires a normal vestibular system as well as normal oculomotor and abducent nerve function. In some cats, you will only see this response at the end of the head movement. A ventrolateral strabismus occurs with oculomotor nerve dysfunction, a medial strabismus with abducent nerve dysfunction, and an ocular extorsion with trochlear

nerve dysfunction. The last of these abnormalities causes the dorsal aspect of the pupil to rotate laterally in cats. In dogs, in which the pupil is round, a fundic examination will show a lateral deviation of the retinal vein that emerges from the superior edge of the optic disk and normally courses in a superior direction. A vestibular strabismus is usually ventrolateral and is present only in some positions of the head.

Nystagmus

Nystagmus is an involuntary oscillation of the eyeballs. In normal animals, a jerk nystagmus occurs when the head is moved rapidly. This normal physiologic nystagmus was observed when the eyes were examined for the function of cranial nerves III and VI. Abnormal nystagmus occurs with dysfunction of the vestibular system. In severe cases, it is continual and is observed when the head is resting in its normal posture, as well as in any change of the head position. This disorder is a resting or spontaneous nystagmus. In less severe and chronic disorders, the abnormal nystagmus may be seen only when the head is held in different positions. This disorder is called a positional nystagmus.

While you are holding the head in its normal resting position, look at the eyes for any resting nystagmus. To facilitate this, use one hand to pull the facial muscles caudally enough so that the retraction of the eyelids will expose the limbus of the eye to better observe it for any abnormal nystagmus. Move the head laterally to one side, hold it there, and observe for any development of a positional nystagmus. Repeat this maneuver on holding the head directed to the opposite side. Then hold the head and neck in extension and observe for any positional nystagmus. If you are suspicious of subtle vestibular system dysfunction and you have not observed any abnormal nystagmus with the head held in a laterally flexed or dorsally extended position, place the patient on its back in dorsal recumbency. Extend the patient's head and neck, and look for any positional nystagmus. Be sure to record the direction of the abnormal nystagmus, as well as the plane of rotation. The direction is defined as the direction of the quick phase of the jerk nystagmus. The plane of rotation may be horizontal, rotatory, or vertical. As a rule, a consistently vertical nystagmus with no rotatory component usually indicates involvement of the central components of the vestibular system. Look for possible change in this direction with different positions of the head. With peripheral vestibular system disorders, the jerk phase of the nystagmus is always directed away from the side of the lesion and is either in a horizontal plane or is rotatory. If the direction of the nystagmus changes with different head positions, then a disorder of the central components of the vestibular system is present.

When you have the head and neck in extension, look at the position of the eyeballs, without retracting the eyelids, to observe in small animals that both eyeballs have also elevated and are still centered in the palpebral fissure and no sclera is exposed dorsal to the limbus. Sclera that is exposed dorsally indicates inadequate elevation of the eyeball and either an oculomotor nerve dysfunction or a vestibular system dysfunction; the latter disorder is a vestibular strabismus. With vestibular strabismus, this eyeball deviation is present only in some head positions, and the eyeball adducts normally when physiologic nystagmus is examined.

On rare occasions, a rapid resting pendular nystagmus is present at all times and in all positions of the head. The eyeball excursions are rapid and to the same degree in both directions. This ocular tremor is congenital and associated with anomalies of the retina or the decussation of the optic axons at the optic chiasm. Vision is normal. This is most common in Siamese cats.

Facial and Trigeminal Neurons

Up to this point in your cranial nerve examination, all of your evaluations have been directed at the eyes and orbital structures. Some of these evaluations have involved part of the innervation that is dependent on normal facial and trigeminal nerve function. At this point, I reevaluate all of the facial and trigeminal nerve functions that are practical.

For the facial nerve, repeat the palpebral reflex (cranial nerves V and VII) by touching both corners of the eyelids for each eye. The sensory nerves are branches of both the ophthalmic and maxillary nerves from the trigeminal nerve and the closure of the fissure is a function of the palpebral branch of the facial nerve. Observe the symmetry of the face and the position of the ears. The erect ears of all cats, some breeds of dogs, and those dogs that have had ear crop surgery will not droop with facial paralysis because of the rigidity of the auricular cartilage. You will feel atonia when you palpate the ear, and the ear will not move when the skin of the ear canal is stimulated with your forceps or by blowing in the ear. You may be able to palpate the loss of tone in the lips, and, in many patients, you may observe a droop of the lips. Elevate the head and observe the lips at the angle of the mouth. More lip mucosa may be exposed on the denervated side (VII), and the animal may tend to drool on that side. Facial paralysis does not cause a deviation of the philtrum in dogs and cats. Be aware that a deviated philtrum in a dog is most likely the result of tetany of the facial muscles on the side to which the philtrum is directed. This hemifacial tetany can be confirmed by its disappearance with local or general anesthesia. In older literature, this observation is known as hemifacial spasm, which is a misnomer.

For the trigeminal nerve, palpate the muscles of mastication for any denervation atrophy caused by dysfunction of the mandibular nerve from the trigeminal nerve. The only evidence of unilateral loss of function of the mandibular nerve will be unilateral atrophy of the muscles of mastication. Be sure to palpate for this atrophy because you will not see it in breeds with a thick hair coat, such as an old English sheepdog. No clinical evidence of any loss of jaw function will be observed; they can still bite vigorously. A dropped jaw that the patient cannot move requires dysfunction of both mandibular nerves. The observation of a dropped jaw is sometimes aided by holding only the superior jaw and associated lips elevated and observing the gap created by the inability to elevate the inferior jaw to close the mouth. Place the blunt end of your tissue forceps against the nasal septum. The normal patient will immediately move its head away from the stimulus. This action tests two anatomic pathways. One is the integrity of the ipsilateral branch of the ophthalmic nerve from the trigeminal nerve that innervates the mucosa of the nasal septum. The other is the nociceptive pathway that projects predominantly to the opposite side of the rostral brainstem and the somesthetic cortex of the opposite cerebral hemisphere. This evaluation is one of the three clinical examinations that we routinely use for prosencephalic dysfunction. We do not routinely check the autonomous zones of the other two branches of the trigeminal nerve.

Cranial Nerves IX, X, and XII

Cranial nerves IX, X, and XII are examined together with the so-called gag reflex. This examination is performed rapidly because the patient usually objects to the manipulation that is necessary, especially cats.

Grasp the superior jaw with one hand and pull down on the inferior jaw with the other hand to open the mouth. The resistance felt is the result of the function of the masticatory muscles that close the mouth and are innervated by the mandibular nerves from the trigeminal nerves. Quickly look at the surface of the tongue for its size and any movement that is present. Push the tongue with your finger and observe for any movement. This maneuver evaluates the sensory branches of the trigeminal nerves (V) and the motor neurons in the hypoglossal nerves (XII). Then insert your finger through the oral cavity into the oropharynx and laryngopharynx. Feel for the muscle tone and evaluate the patient's sensory response to this maneuver. This response is the gag reflex. The sensory nerves stimulated include the trigeminal branches to the tongue surface and oropharyngeal surface of the soft palate and both the sensory and motor neurons in the glossopharyngeal (IX) and vagal (X) nerves. This assessment of the gag reflex is difficult to evaluate and is usually quite subjective. A more reliable indication of dysphagia usually comes in the form of a complaint by the owner as they watch their animal eating and drinking. These functions can also be assessed by watching the patient prehend and swallow food.

I do not routinely test for olfaction or hearing because they are difficult to evaluate objectively, especially when they are incomplete. The owner's observation of their animal's behavior is more reliable for disorders of these functions. Brainstem auditory-evoked potential (BAER) testing is the most reliable way to evaluate hearing function, especially with unilateral disorders. Tests for olfaction have been described.

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69

Central Nervous System Trauma

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Spinal Trauma

Traumatic spinal cord injury (SCI) is a devastating disease in human and veterinary medicine. The majority of SCIs result from vehicle-related accidents but other important causes include gunshots, dog fights, falls, accidental owner-induced injuries, and falling objects.

Pathophysiology of Spinal Cord Injury

The normal spinal cord is a stable structure throughout life, but it exhibits modest decrements in myelinated axon and neuron numbers with advancing age. Its complexity greatly exceeds that of other tissues, and its thin cellular processes can extend long distances, thereby increasing their vulnerability. It has unique vascular barriers and fluid compartments. Its cellular components and the tissues that they form are highly susceptible to injury. Together with the brain, this organ has the least ability to undergo self-repair. Increasing evidence indicates that the spinal cord also has distinct differences from the brain in its injury responses.

The pathophysiology of SCI can be divided into two phases: the initial primary injury and subsequent secondary injury.

- *Primary injury* refers to the initial traumatic insult to the spinal cord, which results in immediate severing of axons and death of spinal cord cells.
- *Secondary injury* invariably follows and leads to progressive tissue damage for weeks after the initial insult. It results from a complex series of related events on a number of physiologic levels. Hypotension and hypoxia are important preventable causes of secondary injury at a clinical level and must be recognized and either prevented or treated proactively. Numerous secondary injury mechanisms also occur on the cellular level, and although their delayed time course theoretically provides a window for therapeutic intervention, we are currently less capable of halting these processes, which include vasospasm and localized ischemia, delayed cell damage and apoptosis, ion-mediated cell damage and excitotoxicity, and neuroinflammation, as well as mitochondrial dysfunction and oxidative cell damage.

Clinical signs associated with spinal trauma are caused by injury to the spinal cord, the spinal nerves as they exit the vertebral canal, and the vertebral column itself. The different injuries resulting from trauma include vertebral fractures, subluxations and luxations, flexion/extension injuries, and traumatic disk herniations. Subluxation and luxation can occur in combination with a vertebral fracture or due to soft tissue disruption only, without evidence of vertebral injury. These injuries occur most frequently at the lumbosacral, thoracolumbar, and atlantoaxial junctions. Cats are more likely to suffer sacrocaudal fractures than dogs, and typically have a combination of fracture and luxation, whereas approximately 20% of dogs suffer a luxation only.

These events can cause spinal cord contusion and laceration, and can result in compression by bone, soft tissue or blood (hematomas). Ongoing instability can result in repeated contusive injuries, additional laceration of the cord, and increasing severity of compression. Compression of the spinal cord reduces perfusion, potentially causing neuronal and glial cell death by the secondary injury mechanisms described above. Demyelination is a common finding histopathologically, as a result of both direct damage to myelin and death of oligodendrocytes. Physical deformation of axons can cause failure of ion channels, changing membrane permeability and producing conduction block that rapidly reverses when decompressed. Ongoing spinal cord compression can also cause development of syringohydromyelia cranial to the compression site, potentially causing neuropathic pain in addition to further neurologic deterioration.

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Spinal Cord Instability

Instability of the vertebral column can have devastating consequences for the patient.

Sudden luxation of an unstable vertebral unit can cause spinal cord transection, contusion, and compression. Sometimes apparently stable fracture/luxations have just enough movement to cause repeated small spinal cord contusions, producing deterioration in neurologic status. Stability is produced by the interaction of the vertebrae with each other via intervertebral disks and synovial joints at the articular facets. The dorsal and ventral longitudinal ligaments, interarcuate ligaments, and spinal musculature provide further support.

While there are different methods of predicting instability, the most commonly used method divides the spine into three compartments (Figure 69.1). Compartment 1 contains the ventral three-quarters of the vertebral body and disk, and the ventral longitudinal ligament; the second consists of the dorsal one-quarter of the vertebral body, the disk and the dorsal longitudinal ligament; and the third compartment includes the articular facets, lateral pedicles, dorsal laminae, interarcuate ligaments, and dorsal spinous processes. Disruption of any two of the three compartments is suggestive of instability. Sometimes muscle spasm or impaction of fracture fragments into each other renders a potentially unstable injury stable for practical purposes. It is also important to remember that disruption of the soft tissues of the intervertebral disk, dorsal and ventral longitudinal ligaments, and synovium of the articular processes disrupts all the compartments and causes instability.

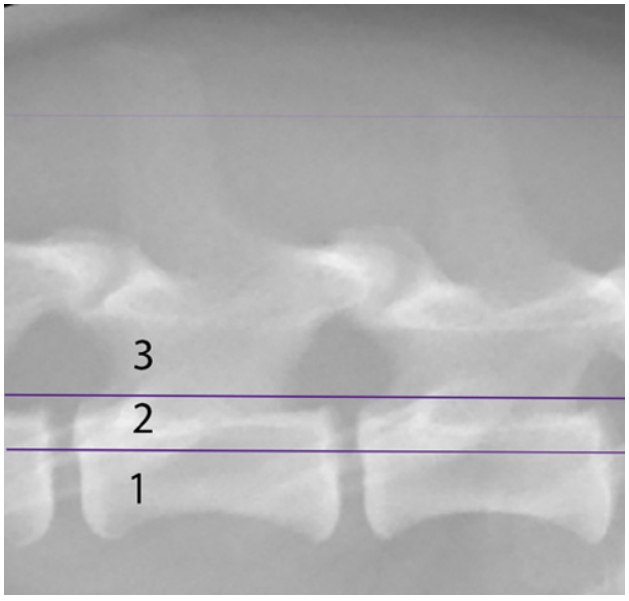


Figure 69.1 A lateral radiograph of the lumbar vertebrae illustrating the three compartments used to determine vertebral stability after a fracture.

Clinical Assessment of the Spinal Injury Patient

Once systemic assessment and stabilization has been completed, attention shifts to more directly assessing and treating the injured spinal cord. A detailed neurologic examination is imperative to establish baseline function and becomes the baseline against which subsequent examinations and clinical progression are judged. The neurologic examination should be aimed at localizing the lesion and determining its severity.

Special attention should be paid to determining the presence of voluntary motor function and nociception in each limb. In cases of suspected sacrocaudal fracture or luxation, nociception in the tail base and perineal region should be assessed. It is not unusual for there to be more than one site of injury and so neurologic signs can be multifocal and peripheral nerve injury such as brachial plexus avulsion can complicate the clinical assessment. A full neurologic assessment should be performed cautiously, as clinical deterioration is possible due to vertebral instability. Such a deterioration can be catastrophic, particularly in patients that have suffered an atlantoaxial injury.

Patients who have suffered trauma can have other soft tissue injuries. It is not uncommon for spinal trauma victims to have significant thoracic trauma causing pneumothorax, pulmonary contusions, and traumatic myocarditis with their attendant signs. In addition, cervical spinal cord injury may affect motor control of intercostal and diaphragmatic muscles. The ability to ventilate should therefore be assessed carefully. Abdominal trauma can result in a ruptured bladder, splenic and hepatic injury. Finally, neurologic signs can be masked by appendicular fractures, and complicated by head injury.

Thoracolumbar spinal cord injury severity is commonly graded as follows.

- 0 – Normal
- 1 – Painful
- 2 – Conscious proprioceptive deficits, ataxia and paraparesis
- 3 – Nonambulatory paraparesis
- 4 – Paraplegia with nociception intact
- 5 – Paraplegia with loss of nociception

Lack of nociception is not as relevant in tetraparesis, but special attention should be paid to the respiratory rate and pattern in any nonambulatory tetraparetic or tetraplegic patient with a view to detecting hypoventilation.

Imaging of the Spinal Cord Injury Patient

When SCI is present, imaging is used to confirm the injury and delineate the anatomy of the lesion.

Survey Radiography

Thoracic radiographs should be evaluated after a significant trauma, looking for pleural effusions, contusions, pneumomediastinum, and pneumothorax as well as the possibility of pericardial effusion and diaphragmatic herniation. If a vertebral injury is suspected, it is recommended that survey lateral radiographs are taken of the entire spine prior to additional manipulation of the animal (Figure 69.2). Sites particularly predisposed to fracture and luxation include the atlantoaxial junction, the thoracolumbar junction, and the lumbar and lumbosacral spine.

As some fractures can be subtle, good-quality and well-positioned radiographs from orthogonal planes are necessary. This may be accomplished with the animal awake and immobilized; analgesia may be required. Poor radiographic technique resulting in rotation of the spine (especially in the cervical area) can make assessment for unstable and malaligned vertebral segments difficult. Extreme care should be taken in positioning the animal for ventrodorsal views; horizontal beam radiographs can be obtained if the equipment is available.

Sedation may be necessary to achieve accurate positioning for radiography in some animals. This should not be performed if the examiner is unsure of the physical diagnosis, as sedation often influences the results of the neurologic examination. Additionally, sedation or anesthesia results in the loss of voluntary paraspinal muscle contraction, and unstable vertebral segments may be more likely to subluxate.

It is important to remember that radiographs provide a static record of the location of the vertebrae at the time of the study but they do not allow for assessment of how extensive the displacement of the vertebrae was at the time of the injury and prior to radiology. As a result of the strong paraspinal musculature, vertebrae can be significantly displaced acutely at the time of injury but then subsequently pulled back into a more normal position.

Advanced Imaging

Advanced imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) is needed to evaluate spinal cord compression and to ensure that additional lesions unidentifiable on survey radiographs are not present. CT is invaluable in identifying bone defects that may not be apparent on survey radiography (Figure 69.3). Three-dimensional reconstruction from CT images may provide additional anatomic information regarding bone contour for surgical planning (Figure 69.4).

Magnetic resonance imaging is optimal for delineating the soft tissues involved in the injury as well as identifying spinal cord compression, spinal cord swelling, disk herniations, and the presence of intraparenchymal

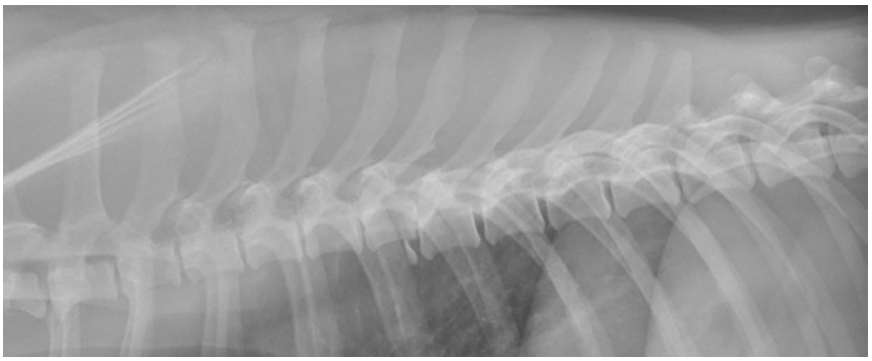


Figure 69.2 A lateral radiograph of the thoracic vertebrae confirms a fracture luxation affecting T6–T7.

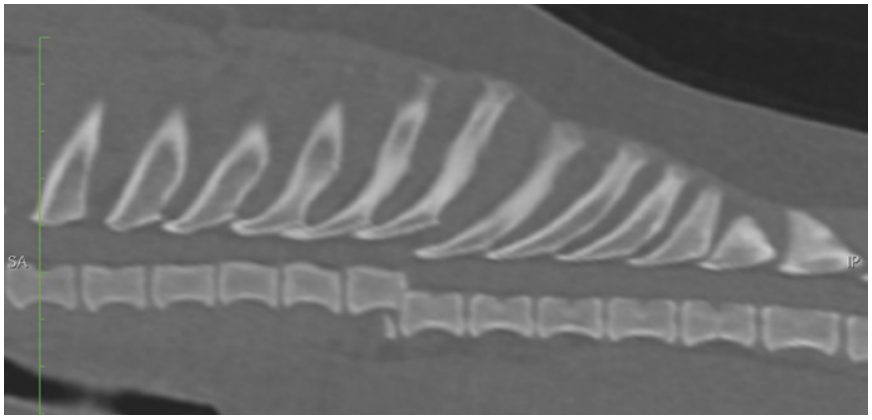


Figure 69.3 A sagittal reconstructed CT scan of the thoracic vertebrae of the case seen in Fig. 69.2. Although the spinal cord cannot be seen in detail, compression of the cord can be inferred from the stenosis of the canal seen with this image at the site of the luxation.

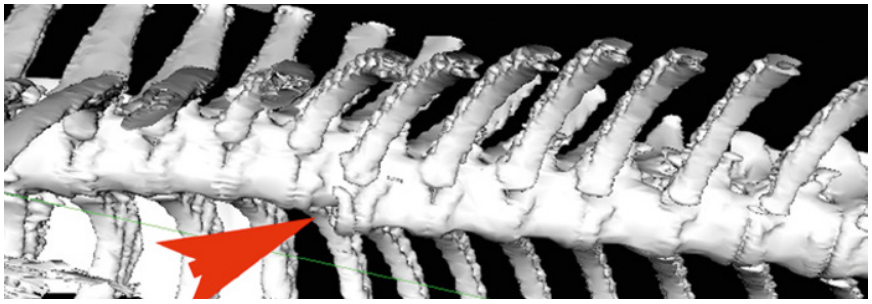
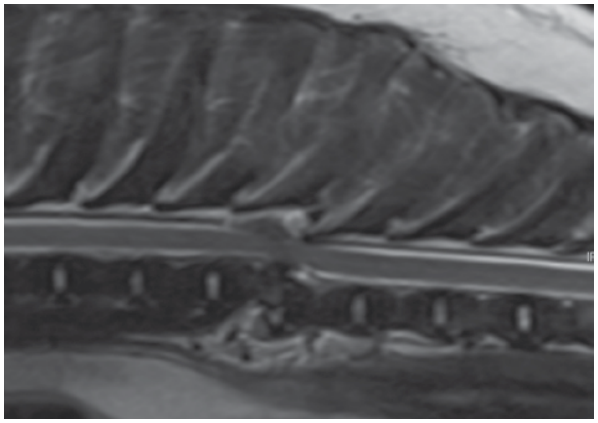


Figure 69.4 A 3D CT reconstruction of the thoracic vertebrae of the case seen in Fig. 69.2. This ventral view of the spinal column assists in the understanding of the vertebral fracture (*arrowhead*).

(a)



(b)

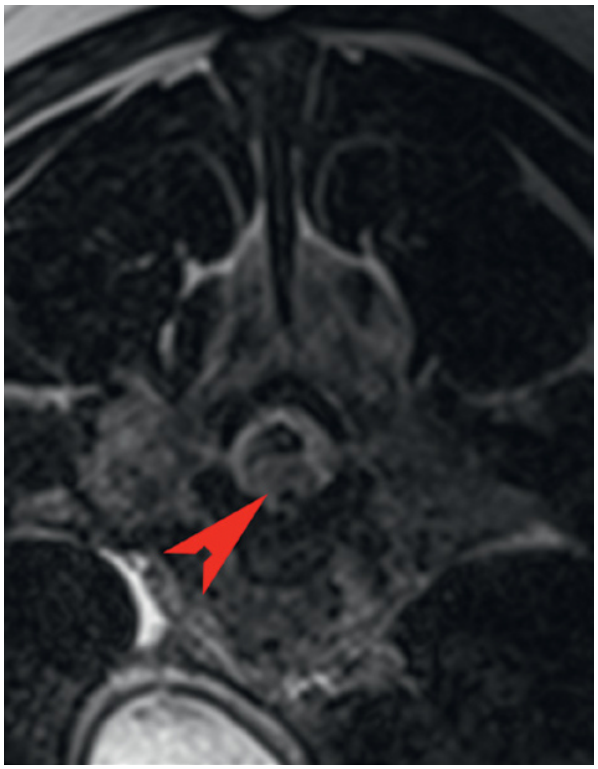


Figure 69.5 A sagittal (a) and transverse (b) T2-weighted MRI of the case seen in Fig. 69.2. The spinal cord can be seen in detail at the site of the injury with the cord compressed by hemorrhage within the canal (*arrowhead*).

hyperintensity and/or hemorrhage, which may assist in the prediction of adverse neurologic outcomes after SCI (Figure 69.5).

Both CT and MRI are useful to measure vertebral body size from the transverse views, essential when considering the maximum depth of surgical implants to be used.

Urinary Tract Assessment

In addition to blood urea and creatinine values and urine specific gravity levels, urethral catheterization may be required in patients that have undergone a severe concurrent abdominal or pelvic trauma in order that urine production may be assessed over the subsequent 72 hours. This will also be of value in those patients with systemic shock due to the traumatic event. Abdominal ultrasonography may be required to evaluate the bladder wall and kidneys, and to detect the presence of free abdominal fluid; contrast-enhanced imaging of the urinary tract may provide further information on the function and form of the individual structures.

Current Treatment Options for Spinal Cord Injury

The standard of care in veterinary medicine remains to stabilize the patient physically and medically and decompress the spinal cord, although the evidence for early decompression in dogs has not yet been clearly demonstrated in a prospective manner. However, there is evidence in humans that early decompressive surgery may reduce hospitalization time and, hence, complications, and improve the neurologic outcome in some. Spinal column surgery is a rapidly changing field but although operative nuances have seen dramatic change, the reality is that decompression, realignment, and stabilization remain the primary offerings of the spine surgeon for the acute SCI patient.

Initial Management

The top priority in managing acute SCI secondary to exogenous trauma is assessment and stabilization of vital signs, with strict adherence to a life support protocol.



Figure 69.6 Securing a dog or cat to a board in lateral recumbency can reduce vertebral movement prior to external or internal stabilization of a fracture luxation.

At the time of stabilization, patients with SCI should be immobilized by stabilizing *both* the body and head using a rigid spine board (Figure 69.6).

Airway

Although airway and spine protection share top priority, airway management takes precedence; risking iatrogenic SCI is justified in exceptional circumstance when required to secure or protect the airway.

Breathing

Respiratory insufficiency can be an important cause of early mortality after SCI. Cervical injuries can paralyze the diaphragm and cause respiratory arrest. Lower cervical injuries can affect the intercostal muscles, causing a paradoxical breathing pattern. Paralysis of the intercostal musculature is associated with a decrease in forced vital capacity and maximal inspiratory force because inspiration can cause chest wall collapse. Patients who compensate initially can fatigue rapidly, and indeed, many patients with cervical injuries can require intubation in the first 24 hours. It is thus useful to monitor vital capacity in such patients where possible; intubation should be considered in patients whose vital capacity is markedly reduced. Hypoxia is an important cause of secondary SCI and must be avoided.

Circulation

It is essential to avoid hypotension of any kind in patients with SCI given its contribution to secondary injury. Care must be taken to ensure that hypotension from other causes is excluded, especially that attributable to occult hemorrhage, which can be challenging to detect in patients with sensorimotor deficits.

Fluid administration is generally considered first-line therapy in this situation; however, a restricted heart rate makes these patients susceptible to fluid overload. Early consideration of vasoactive agents is recommended in people and so should be considered in veterinary patients where appropriate.

Specific Management Considerations

Medical Therapy

Pain Management Analgesic therapy is essential in the management of the neurotrauma patient. The degree of analgesia and sedation must be balanced with preservation of blood pressure and ventilatory status, as depression of each of these parameters can contribute to secondary injury, and if possible should not impede reassessment of neurologic status.

Opioids are the analgesic drugs of choice in critical care medicine, because of their ease of reversal and relative safety when titrated to effect. Several studies suggest that bolus infusion of opioids should be avoided, and constant-rate infusions (CRIs) are preferred. Because of the ease of reversal, it is recommended that full agonist opioids be used.

Table 69.1 lists the recommended analgesics and their respective doses.

Corticosteroids The use of corticosteroids in the treatment of acute SCI remains controversial despite extensive clinical investigation. Proposed mechanisms supporting the use of corticosteroids in SCI include free radical scavenging, antiinflammatory effects, and improved local blood flow. Unfortunately, there are no studies demonstrating a benefit of steroids in improving outcome after SCI in humans or veterinary patients. Given the potential for significant adverse side-effects, such as gastrointestinal ulceration, immunosuppression, and compromise of renal perfusion in hypovolemic patients, the routine administration of high-dose corticosteroids in the acute phase of injury is not recommended.

Table 69.1 Analgesic drugs suggested for use in patients with spinal cord injury

Analgesic	Recommended dose
Fentanyl	Dogs: 2 µg/kg, then constant-rate infusion (CRI) at 2–5 µg/kg/h Cats: 1 µg/kg, then CRI at 1–2 µg/kg/h
Morphine	Dogs: 0.15–0.5 mg/kg slow, then CRI at 0.1–1 mg/kg/h
Ketamine	0.1–1 mg/kg, then CRI at 2–10 µg/kg/min
Lidocaine	Dogs: 1–2 mg/kg, then CRI at 25–80 µg/kg/min
Dexmedetomidine	0.5–1 µg/kg/h

Cellular Transplantation Therapy Intraspinal olfactory glial cell transplantation in dogs with thoracolumbar SCI has been shown to have promise with respect to improved functional outcome. The rationale for this approach stems from the unique ability of these cells to promote regeneration in experimentally induced injured spinal cord and foster a more hospitable environment for axonal growth, increase tissue sparing after SCI, increase tissue bridging and reduce cavity formation following experimental SCI, and improve angiogenesis within the injured spinal cord. Olfactory ensheathing glia can be harvested from the olfactory epithelium and transplanted in the same animal, thereby minimizing the likelihood of rejection. Autologous bone marrow stromal cell transplantation has been evaluated in dogs with vertebral fracture luxation and found to be feasible and safe, with no complications noted.

Although such techniques are currently in the early stages of development, they may represent the future for patients with acute SCI.

Surgical Therapy

A significant body of animal research has demonstrated neurologic benefit from early decompression of the injured spinal cord; however, such benefit is less clear in polytrauma patients, who are often medically unstable in the acute postinjury phase. Despite the fact that early spine surgery appears to be safe in polytrauma patients, the question of whether early decompression for acute SCI is or is not beneficial for neurologic recovery remains incompletely answered. Cord compression can be due to displaced vertebral fragments, herniated intervertebral disk or hematomas. Decompression may be achieved by realignment of vertebrae alone; a laminectomy or hemilaminectomy may be necessary to remove material from the vertebral canal. Decompressive procedures could produce or exacerbate instability in the injured spine, thus requiring surgical stabilization.

Instability can be addressed surgically, by placement of an external splint, or simply by cage rest (Table 69.2). Surgical stabilization is the most effective method of stabilizing an unstable spine, but is associated with significant surgical risks. A variety of different techniques are used; in one of the most easily adaptable techniques, screws or pins are placed in the vertebral bodies adjacent to the injury and cement is applied to hold the structure in alignment (Figure 69.7). Another popular technique, sometimes known as "spinal stapling" or "segmental stabilization," uses pins wired to articular facets and dorsal spinous processes to stabilize dorsally. Different plates can be used; difficulty contouring plates to the vertebral bodies limits options, but more recently locking plates such as the string of pearls (SOP) plate have been described which can offer more flexibility.

Sacrocaudal luxations in cats are typically addressed by amputation of the tail if the tail is paralyzed and has no nociception. Prompt removal of the tail may limit

Table 69.2 Advantages and disadvantages of different stabilization techniques

Technique	Advantages	Disadvantages	Indications
Cage rest	• Inexpensive • No anesthetic or surgical risk	• No stability provided • No decompression	• Stable fracture (articular facet, dorsal spinous and transverse processes) • No spinal cord compression • Mild neurologic deficits
External splint	• Inexpensive • No anesthetic or surgical risk	• Splint complications • Limited protection against axial or rotational forces • No decompression	• Unstable fracture • Limited spinal cord compression • Mild neurologic deficits
Screws/pins and PMMA; plates	• Excellent stabilization • Can combine with decompression	• Cost • Risk of iatrogenic injury during implant placement • Infection • Implant failure	• Unstable fractures
Segmental stabilization	• Good stabilization against flexion and extension. • Reduced risk of iatrogenic injury. • Readily applied in the lumbosacral region	• Suboptimal protection against rotational and axial forces • Implant failure/migration • Infection	• Unstable lumbosacral/caudal lumbar fractures

PMMA, polymethylmethacrylate cement.

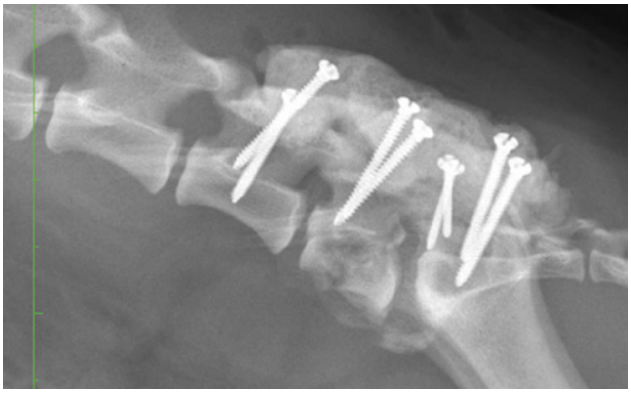


Figure 69.7 Multiple internal fixation materials and methods exist to stabilize vertebral fractures and luxations. This lateral radiograph demonstrates the use of screws and polymethylmethacrylate to stabilize a lumbosacral vertebral fracture luxation.

ongoing damage to the sacral nerve roots that could result from inadvertent movement of the tail.

Surgical complications from any spinal stabilization procedure can be serious and include iatrogenic injury to the spinal cord, damage to the vasculature immediately ventral to the vertebral column, failure of the fixation (Figure 69.8), and infection.

Placement of the splint is achieved by wrapping the appropriate part of the body in cast padding and then forming the splint from a material such as Vetcast® (3M) to cover the dorsal aspect of the thoracolumbar spine or the ventral aspect of the neck (from below the chin to the sternum). Following padding of the splint to ensure that there are no sharp edges, it is incorporated into the bandage with a cover of bandaging material such as Vetwrap®. Pressure points, particularly between thoracic and pelvic limbs, should be checked and padded carefully. The patient should always be hospitalized overnight after the first placement of a splint to ensure that the splint is tolerated, and to allow adjustment for any splint movement that occurs in the first 24 hours. Splints should be checked daily by the owner for development of decubital ulcers and should be checked and potentially changed by the veterinarian after the first 3–5 days and then on a weekly basis for six weeks. Splints do not protect from compressive loading of the spine, and offer poor protection against rotatory forces. In addition, it is not possible to stabilize the lumbosacral spine with an external splint. Splints are inappropriate if there are open wounds affecting areas that would be incorporated into the bandage.

Bladder Management

Urinary tract infections (UTI) in dogs being treated for SCI should be considered. Female dogs, dogs that cannot ambulate or voluntarily void urine, dogs which are not given antimicrobials during surgery, and dogs whose body temperature falls below 35 °C during surgical decompression of the spinal cord all have an increased likelihood of developing a UTI. The frequency of UTIs in dogs with an indwelling urinary catheter may approach 50%. Indiscriminate antimicrobial use for animals with an indwelling catheter should be avoided, though intraoperative antimicrobials should be administered at the time of surgical decompression of the spinal cord.

If the patient is unable to urinate, the owner must be able to express or catheterize their pet three times a day. Addition of phenoxybenzamine (0.25–0.5 mg/kg orally q8–12h) or prazosin (dog: 1 mg if less than 15 kg body weight or 2 mg if over 15 kg PO q8–12h; cat: 0.25–0.5 mg PO q12–24h) and diazepam (0.5 mg/kg orally 20 min prior to expression) may help to reduce urethral sphincter tone and facilitate expression. Since marked hypotension can result from prazosin, patients should be monitored for lethargy, collapse, pallor, syncope or seizures. Skin should be kept clean and dry and checked regularly for development of decubital ulcers over pressure points, or urine scald.

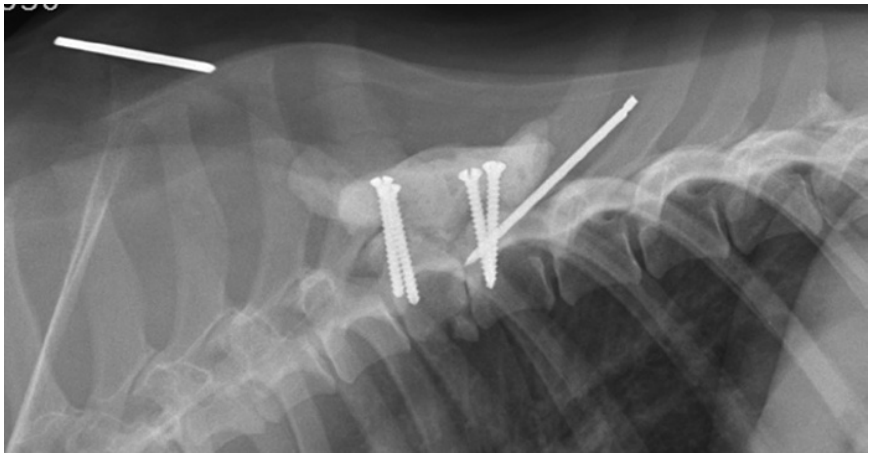


Figure 69.8 Fixation failure can be due to breakage or migration of the implants as can be seen to have occurred with these transarticular pins which needed to be removed.

Prognosis for Animals with Spinal Trauma

Prognosis associated with SCI is influenced by the severity of cord injury and the presence of injuries to other organs (e.g., lungs, heart, and bladder). The form of treatment (surgical versus conservative) does not appear to influence outcome, although in published case series, the more severely affected patients tend to be treated surgically, and so a true comparison is difficult. Prognostic indicators based on the neurologic examination are somewhat different for different regions of the spine.

- Thoracolumbar injuries carry a guarded to grave prognosis for recovery of pelvic limb function and fecal and urinary continence if the animal is paraplegic with loss of nociception to its pelvic limbs. If nociception is still present, these animals do have a good chance of recovery.
- Cervical injuries are associated with a guarded to grave prognosis if the animal is tetraplegic and unable to ventilate adequately. If treated surgically, the risk of perioperative death can be as high as 36% in cervical injuries. Note that it is extremely unusual to see tetraplegic animals that lack nociception because cervical spinal cord transection usually causes death by respiratory failure and bradyarrhythmias. Delaying referral, diagnosis, and treatment does worsen the prognosis. Less severe injuries carry a much better prognosis, with the majority of cases making a recovery if managed appropriately.
- The prognosis for recovery of fecal and urinary continence in lumbosacral and sacrocaudal fractures is approximately 50% if there is absent anal tone and no nociception in the perineal region or the tail at the time of presentation. Positive tail base sensation is useful to identify cases that will recover within 30 days of the injury, but it is not very useful to discriminate the cases that will recover despite not having tail base sensation. Because the cauda equina is largely composed of peripheral nerves, displacement of fracture fragments is less likely to cause complete transection but severe pain due to nerve root entrapment is common and can be a reason for euthanasia.

Head Trauma

Traumatic brain injury in veterinary patients occurs most commonly secondary to automobile accidents. Other common causes of traumatic brain injury include kicks to the head, falls, gunshot wounds, and animal bites. Immediate and appropriate treatment is critical to potentiate an acceptable recovery. Although treatment recommendations remain controversial, there are several guidelines for head trauma management. Accurate and frequent assessment of both systemic and neurologic injuries can allow for a successful outcome. Additionally, treatment strategies should remain flexible, adjusting to the patient's needs and changes in neurologic status. A complete understanding of intracranial physiology and the effects of injury will aid in the management of dogs and cats with head trauma.

Injury-Related Intracranial Physiology

Following injury, cerebral blood flow is often significantly reduced due to associated elevations of intracranial pressure (ICP) (>/= (greater than or = to)12–20 mmHg). Specific factors that decrease cerebral blood flow (CBF) include the presence of edema, hematomas, compression of vessels from mass effect, and vasospasm. Additionally, trauma significant enough to cause brain injury likely causes some degree of systemic shock and hypotension. The presence of hypotension further reduces cerebral blood flow.

Reduction of CBF due to elevation of ICP can lead to brain ischemia. A series of physiologic responses are in place to try to prevent this when CBF declines. Reduced blood flow to the vasomotor centers in the brainstem leads to reduced carbon dioxide removal. A subsequent elevation in local carbon dioxide concentrations stimulates the sympathetic nervous system to increase mean arterial pressure. The result is systemic hypertension in an effort to maintain blood flow to the brain. However, as the baroreceptors located in the aorta and carotid sinus both detect systemic hypertension, a signal is sent to the vagal centers of the brainstem. A reflex bradycardia occurs as a consequence. This phenomenon is referred to as the Cushing reflex. Therefore, concurrent systemic hypertension and bradycardia can indicate elevated ICP in head trauma patients.

Additionally, an elevation in ICP and the subsequent reduction of cerebral perfusion pressure (CPP) stimulates the release of catecholamines. This catecholamine surge can lead to the brain–heart syndrome, which causes arrhythmias and myocardial ischemia.

Pathophysiology of Brain Injury

After trauma, the brain parenchyma is susceptible to two types of injury: primary injury and secondary injury.

Primary or Biomechanical Injury

This is injury to the brain tissue from direct trauma and the forces applied to the brain at impact. An impact to the skull exerts the following forces on the brain: acceleration, deceleration, and rotational forces. The brain is unable to tolerate these forces because of its composition and lack of internal support. The superficial gray matter is most susceptible to the forces of acceleration, leading

to hemorrhage or contusion and tearing of neuronal tissue. The rotational forces have more of an impact on the deeper white matter of the brain, causing concussive injuries and axonal damage. The spherical shape of the skull and the propagation of rotational forces after injury direct these forces into the deeper tissues of the brain.

Additionally, penetrating injuries can cause direct damage to the brain parenchyma, fractures, and hemorrhage.

Skull Fractures

Skull fractures are described based on pattern (depressed, comminuted, linear), location, and type (open vs closed). A depressed fracture is one where the inner shelf of bone is driven into the brain to a depth equivalent to the width of the skull. Depressed fractures are most common on the dorsal and lateral aspects of the skull. Fractures may also occur at the base of the skull, middle ear, and temporomandibular joint; however, fractures in these locations are difficult to evaluate. Bullae fractures can result in neurologic signs such as vestibular syndrome, facial paresis/paralysis, and Horner syndrome on the side of the fracture. Fractures of the temporomandibular joint, mandible, and zygomatic arch may require additional treatment, but are unlikely to cause neurologic signs alone.

Brain Hemorrhage

Hemorrhage following trauma may be located in an extraparenchymal or intraparenchymal location. Extraparenchymal hemorrhage may occur in the epidural, subarachnoid, or subdural space. The most common location of hemorrhage following trauma is within the brain parenchyma (intraaxial) or subarachnoid space. Epidural hemorrhage is frequently secondary to bleeding from meningeal arteries, resulting in blood between the skull and dura. Hematomas located in the subdural space (between the arachnoid and dura) are typically secondary to venous bleeding, resulting in slow accumulation of blood.

Hemorrhage into the cranial cavity has several deleterious effects. The presence of hematomas contributes to elevations in ICP and reduction of CBF. Additionally, hemorrhage provides a substrate for oxygen free radical formation and promotes inflammation. Finally, hemorrhage promotes the release of excitatory amino acids exacerbating secondary brain injury.

Secondary Injury

After impact, a cascade of biomolecular events occurs causing continued and progressive brain pathology. The presence of hematomas and edema from the primary injury distorts normal brain parenchyma, and decreases CBF. Additionally, a series of cellular reactions begins at the time of impact and continues after the injury. This secondary brain injury has a significant effect on outcome and can lead to continued death of neurons and glial cells. The primary mediators involved in secondary brain injury include oxygen free radicals, excitatory amino acids (i.e., glutamate), and nitric oxide.

Cerebral Edema

Edema develops after primary brain injury and continues to develop as secondary brain injury ensues. Typically, brain edema is most severe 24–48 hours after injury. There are two main types of edema: vasogenic and cytotoxic (intracellular).

- *Vasogenic* edema occurs secondary to failure of the blood–brain barrier and vasodilation. Vasodilation is frequently secondary to hypercapnia, which is often associated with head injury. Initially, the brain is able to compensate for this increase in fluid through the compliance strategies discussed earlier.
- *Cytotoxic* edema occurs secondary to failure of cellular ion pumps and damage to cellular membranes. Cytotoxic edema can lead to cellular death.

Intracranial Pressure

The brain is protected within the bony confines of the skull, where it exists in equilibrium with cerebrospinal fluid (CSF) and blood. The pressure exerted between the brain and the skull is the ICP, which is normally 5–12 mmHg in dogs and cats. The skull is relatively inelastic, limiting the volume that can exist within the cranial cavity. The space within the cranial vault is occupied primarily by three components: brain parenchyma, CSF, and blood.

The Monro–Kellie hypothesis describes the relationship between these compartments and their ability to compensate for increases in volume within the cranial cavity. After head trauma, the volume of the intracranial contents within the skull may increase due to hemorrhage, edema, or CSF accumulation. The brain has the capacity to tolerate small increases in volume by adjusting the size of one of the three components, primarily the CSF compartment. Shunting CSF to the spinal subarachnoid space, decreasing CSF production, and increasing CSF absorption can rapidly decrease the CSF compartment. CSF production does not typically affect elevations in ICP unless its drainage is obstructed, leading to obstructive hydrocephalus. Additionally, venous blood can be redirected out of the cranial cavity and cerebral blood flow will decrease to compensate for ICP elevation. The ability of the brain to adjust for increases in intracranial pressure by decreasing the volume of CSF and blood is called compliance. During this time of compensation, the patient's clinical signs will remain relatively normal, unless the trauma primarily injured the parenchyma via laceration, puncture wounds, etc. Once

compliance is exhausted, small increases in volume will result in dramatic elevations in ICP, which will be accompanied by a rapid decline in the patient's neurologic status.

This ability to compensate is more effective if the increase in volume occurs slowly. With continued elevation of ICP, brain herniation can result. There are four types of brain herniation.

- *Falcine herniation*: herniation of one cerebral hemisphere ventral to the falx cerebri.
- *Transtentorial herniation*: herniation of the parahippocampal gyrus below the tentorium cerebelli which causes compression of the midbrain, leading to mydriatic, unresponsive pupils, loss of consciousness, and subsequent failure of the cardiorespiratory centers. A sign of developing transtentorial herniation is asymmetric mydriasis followed by symmetric mydriasis as the parasympathetic portion of the cranial nerve III nucleus is compressed. Transtentorial herniation can be life-threatening, leading to sudden cardiopulmonary arrest.
- *Foramenal herniation*: cerebellar herniation into the foramen magnum (see Figure 69.9). This is frequently fatal, causing respiratory arrest by compressing the respiratory centers of the medulla.
- *Calvarial herniation*: the brain can also herniate through a defect in the skull.

Clinical Assessment

The ability to recognize signs consistent with elevated ICP or a declining neurologic status is critical in the management of dogs and cats following head trauma. Trauma significant enough to cause brain injury will have systemic effects, which may be life-threatening. Additionally, systemic injuries and shock will cause continued decline in the head trauma patient. Therefore, a complete systemic evaluation and stabilization is required in addition to a thorough neurologic assessment (Table 69.3).

Systemic Assessment

Initial assessment should involve evaluation of the patient's respiratory and cardiovascular system. An airway must be established, if necessary through endotracheal intubation. Breathing patterns may be affected by thoracic trauma, but may also be secondary to brain injury. Auscultation of the thorax may detect pulmonary pathology or cardiac arrhythmias. Oxygen support should be given as necessary and mechanical or manual ventilation may be required with severe pulmonary injuries. Traumatic pneumothorax may require thoracocentesis or chest tube placement to allow proper ventilation. The cardiovascular system should be evaluated by monitoring heart rate, blood pressure, and electrocardiography. An electrocardiogram may demonstrate cardiac arrhythmias secondary to traumatic myocarditis, systemic shock, or brain injury. Arterial blood analysis and lactate concentrations may provide additional information regarding systemic perfusion and respiratory function.

Temperature assessment on a frequent basis is important in all patients. Cerebral metabolic rate is proportional to body temperature and increases 5–7% per degree centigrade. Hyperthermia should be avoided in all patients and cooling techniques should be considered if this is noted. Hypothermia reduces the cerebral metabolic rate and although this may be advantageous to the injured brain, it also increases the risk of cardiac abnormalities.

Once the patient is stable, CT or radiographs of the chest and abdomen are recommended to evaluate for pulmonary

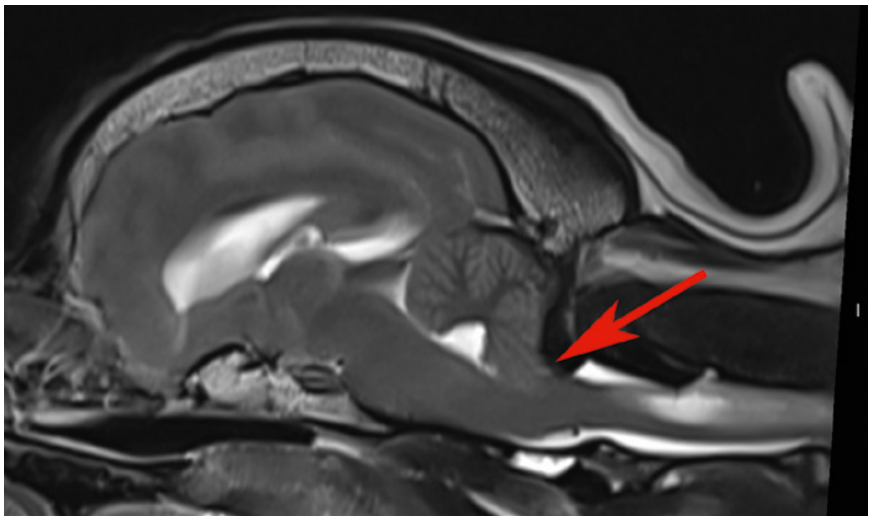


Figure 69.9 A sagittal T2-weighted MRI confirms cerebellar vermal herniation through the foramen (*arrow*).

Table 69.3 Monitoring parameters for the cat and dog following head trauma

Monitoring parameters	Suggested goal	Suggested treatment
Neurologic examination	MGCS >15	Ensure head elevation (30°) Ensure all points below are addressed Consider mannitol (see below) Consider surgery (see text)
Blood pressure	MAP 80–120 mmHg	Adjust fluid therapy Pressor support (dopamine 2–10 μg/kg/min)
Blood gases	PaO_2 >/=90 mmHg $PaCO_2$ <35–40 mmHg	Oxygen supplementation Consider active ventilation
Pulse oximetry (SpO_2)	SpO_2 >/=95%	Oxygen supplementation Consider active ventilation
Heart rate and rhythm	Avoid tachy- and bradycardias Avoid arrhythmias	Adjust fluid therapy Treat for pain Address ICP Treat arrhythmias specifically
Central venous pressure	5–12 cmH_2O	Adjust fluid therapy
Respiratory rate and rhythm	10–25/min	Ventilate if necessary
Body temperature	37–38.5 °C	Passive warming or cooling NSAIDs if hyperthermic
Electrolytes	See individual laboratory normal values	Adjust fluid therapy
Blood glucose	4–6 mmol/L	Adjust fluid therapy Consider dextrose administration
Intracranial pressure	5–12 mmHg	As for MGCS abnormalities

ICP, intracranial pressure; MAP, mean arterial pressure; MGCS, Modified Glasgow Coma Scale; NSAID, nonsteroidal antiinflammatory drug.

contusions, pneumothorax, and abdominal injuries. Pulmonary contusions are common following trauma and may not be most severe until 24 hours after injury. Trauma can also result in injury to abdominal organs. The abdomen should be evaluated with CT or radiography and ultrasonography for the presence of free fluid, blood, or urine, which may require additional therapy. Radiographs of the cervical vertebrae should also be considered as head trauma can often be accompanied by fractures and luxations of these bones.

Neurologic Assessment

Neurologic assessment should be undertaken on any animal which has experienced a trauma. Assessment of neurologic status in a patient after head trauma should initially be performed every 30–60 minutes. Frequent assessment allows for monitoring the efficacy of treatment and early recognition of deteriorating status. Primarily, neurologic evaluation of the patient serves to determine whether there are deficits suggesting structural neurologic lesions, where the lesions are located (i.e., at least intracranial, spinal, and peripheral nerve), and the severity of the lesion(s). Detection of a spinal and/or peripheral nerve (e.g., brachial plexus) lesion can affect the prognosis of any patient with head trauma. Without any extracranial lesions, the prognosis associated with head trauma is dependent on the location and severity of the parenchymal lesions.

The assessment should include evaluation of state of consciousness, motor function and reflexes, pupil size and responsiveness, position and movement of the eyes, and breathing pattern. The evaluation of pupil and eye function is the most accurate manner in which brainstem function can be assessed and this is the most important part of the examination prognostically. A scoring system has been developed in veterinary patients to provide an objective assessment and allow for rational diagnostic and treatment decisions.

Modified Glasgow Coma Scale

The Glasgow Coma Scale (GCS) is used in human medicine to assess head trauma patients by evaluating eye, verbal, and motor responses. This scale has been modified and applied to veterinary patients. The Modified Glasgow Coma Scale (MGCS) evaluates motor activity, brainstem reflexes, and level of consciousness in veterinary patients, enabling initial and serial monitoring following injury. The three categories evaluated using the MGCS provide objective standards for scoring a patient between 1 and 6, with lower scores assigned to

Table 69.4 Modified Glasgow Coma Scale

	Score
Motor activity	
Normal gait, normal spinal reflexes	6
Hemiparesis, tetraparesis	5
Recumbent, intermittent extensor rigidity	4
Recumbent, constant extensor rigidity	3
Recumbent, constant extensor rigidity with opisthotonus	2
Recumbent, hypotonia of muscles, depressed or absent spinal reflexes	1
Brainstem reflexes	
Normal pupillary light reflexes and oculocephalic reflexes	6
Slow pupillary light reflexes and normal to reduced oculocephalic reflexes	5
Bilateral unresponsive miosis with normal to reduced oculocephalic reflexes	4
Pinpoint pupils with reduced to absent oculocephalic reflexes	3
Unilateral, unresponsive mydriasis with reduced to absent oculocephalic reflexes	2
Bilateral, unresponsive mydriasis with reduced to absent oculocephalic reflexes	1
Level of consciousness	
Occasional periods of alertness and responsive to environment	6
Depression or delirium, capable of responding but response may be inappropriate	5
Semicomatose, responsive to visual stimuli	4
Semicomatose, responsive to auditory stimuli	3
Semicomatose, responsive only to repeated noxious stimuli	2
Comatose, unresponsive to repeated noxious stimuli	1

more severe clinical signs (Table 69.4). The score from each category is added together to determine a patient's coma score ranging from 3 to 18, which may be used to guide treatment decisions and prognosis.

Assessment of Limb Function The first category of the MGCS describes a patient's motor activity, limb tone, and posture. Voluntary motor activity is characterized as normal, paretic, or recumbent. Patients typically maintain some degree of voluntary motor activity even in altered states of consciousness unless they are comatose. Abnormal motor function usually reflects either brainstem injury or spinal cord injury; the latter may complicate the assessment of head trauma

Tone is evaluated by placing the limbs through passive range of motion. Increased tone can be seen following cranial trauma, as CNS inhibitory modulation to the lower motor neurons is lost. However, severe brain injury leading to coma will be associated with decreased tone in all limbs. Spinal reflexes are evaluated to primarily assess nerve function, but may provide some information regarding cerebral activity. Animals may have exaggerated reflexes following cerebral injury and absent reflexes when comatose.

An animal's posture after head trauma can also provide information about location and degree of brain injury. Decerebrate rigidity can occur following cerebral trauma and suggests severe brain injury and a poor prognosis as this posture reflects loss of communication between the cerebrum and the brainstem. Animals with decerebrate rigidity have opisthotonus with hyperextension of all four limbs and are stuporous or comatose, with abnormal pupillary light reactions (Figure 69.10). Decerebellate rigidity suggests acute cerebellar damage and may cause either flexion or extension of the pelvic limbs; however, consciousness may be normal.

Assessment of Brainstem Reflexes Pupil size, the pupillary light reflex, and the oculocephalic reflex should all be immediately evaluated in all head trauma patients. Pupil size, symmetry, and reactivity can provide valuable information about severity of brain injury and prognosis. These parameters should be frequently assessed as they can signal a deteriorating neurologic status. Response of the pupils to a bright light indicates sufficient function of



Figure 69.10 Extensor rigidity of the limbs as seen in this cat can be compatible with severe brain injury following trauma.

the retina, optic nerves, optic chiasm, and rostral brainstem. The presence of miosis may indicate a lesion in the diencephalon, as the sympathetic innervation to the eye originates in the hypothalamus. The peripheral sympathetic innervation to the eye can also be affected by injury anywhere along its pathway through the brachial plexus, anterior mediastinum, cervical soft tissues, and tympanic bulla which often causes concurrent third eyelid elevation, enophthalmos, and ptosis as part of a Horner syndrome. A miotic pupil may also be seen with ocular injury and spasm of the ciliary muscles of the iris; therefore, an ocular cause of miosis should be investigated.

Bilateral mydriasis that is unresponsive to light can indicate permanent midbrain damage or brain herniation and a poor prognosis. Other causes of mydriasis include decreased cerebral perfusion, postictal changes, trauma to the iris or retina, periorbital trauma or hematoma and previous ocular abnormalities.

Progression from miosis to mydriasis indicates a deteriorating neurologic status and is an indication for immediate, aggressive therapy. Unilateral changes in pupil size may be seen early in deterioration. Paralysis of cranial nerve (CN) III can lead to mydriasis, loss of direct pupillary light reflex, ptosis, and ventrolateral strabismus. The CN III nucleus is located in the midbrain so damage to this nucleus can be seen as a result of midbrain injury or compression secondary to transtentorial herniation.

The oculocephalic reflex (physiologic nystagmus) is tested by moving the animal's head in vertical and horizontal planes to assess brainstem function and function of the cranial nerve nuclei innervating the extraocular eye muscles. If the animal's head cannot be moved without risk, a visual stimulus such as food or the owner should move around the animal. Absence of the oculocephalic reflex reflects injury to the brainstem. This reflex may also be delayed with cerebral injuries.

Assessment of Consciousness

A patient's level of consciousness provides information regarding function of the cerebral cortex and the ascending reticular activating system (ARAS) of the brainstem. Consciousness can be described as normal, depressed or obtunded, stuporous, or comatose. An animal in a stupor is partially or completely unconscious, but will respond to noxious stimuli. A patient in a coma is unconscious and cannot be roused with noxious stimuli. Coma typically indicates severe cerebral injury or brainstem damage, which carries a guarded prognosis. These terms describe different levels or "quantities" of consciousness and provide information regarding degree of cerebral impairment. The quality of consciousness may be more difficult to objectively evaluate. Inappropriate activity suggesting confused or exaggerated responses to routine stimuli often confirms prosencephalon damage. It is important to note that the patient's blood pressure, oxygenation status, and temperature may all affect its level of consciousness and so the latter should be reevaluated after correction of the former vital parameters.

After evaluation, the patient should be assigned a score for each category to determine its overall coma score. This score can be used to monitor for improvement or deterioration of neurologic status, guide diagnosis and treatment decisions (see later), and provide information about prognosis.

Confirmation of Injury and Diagnosis

A diagnosis of head trauma is based primarily on a compatible history and clinical signs of intracranial neurologic dysfunction. However, additional tests can be used to confirm location and extent of injury. It is important to understand that advanced imaging of the brain (computed tomography and magnetic resonance imaging) should be reserved for patients that do not respond to initial treatment or who deteriorate despite aggressive therapy. Both of these imaging modalities require anesthesia, which can destabilize the head trauma patient, unless the patient is in a coma on presentation.

Significant injury to the brain can occur, leading to neurologic signs without causing skull fractures or hematoma formation. Advanced imaging of the brain may be performed to evaluate for fractures, hemorrhage, or parenchymal lesions; however, changes may not be seen even in a patient with severe neurologic deficits. Imaging modalities available include skull radiography, ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI). Advanced imaging can be helpful in identification of hematomas (extraaxial vs intraaxial), calvarial fractures, edema, and parenchymal contusions.

Skull Radiographs

Skull radiography may reveal calvarial fractures, but provides no information regarding the brain parenchyma (Figure 69.11). Radiographs of the skull can be difficult to interpret due to the irregularity of the skull bones and require anesthesia for accurate positioning, which may be contraindicated in the acutely injured patient. Radiography should not be limited to the skull following head trauma. Radiographs of the vertebral column, thorax, and abdomen are indicated to evaluate for evidence of other injuries.

Advanced Imaging

Computed tomography allows superior evaluation of bony structures and is preferred over conventional

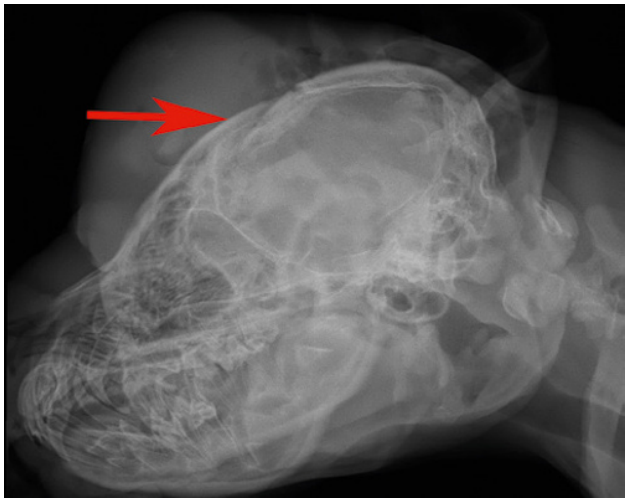


Figure 69.11 A lateral skull radiograph shows a frontal bone fracture (*arrow*) in this dog after being bitten by another dog.



Figure 69.12 A transverse bone windowed CT scan of the dog in Fig. 69.11 confirms a comminuted frontal bone fracture associated with soft tissue damage and air pockets dorsal to the skull.

radiography, especially considering the 3D reconstruction capabilities (Figure 69.12). Additionally, CT can be used to diagnose intracranial hemorrhage, alterations in ventricular size or shape, midline shift of the falx cerebri, and edema. CT does not provide good soft tissue detail of the brain parenchyma, but is frequently the preferred modality for evaluation of human head trauma patients for surgical intervention because of the speed of image acquisition. Typically, hemorrhage is hyperattenuating (hyperdense) on a CT in the acute stages. Over time, the

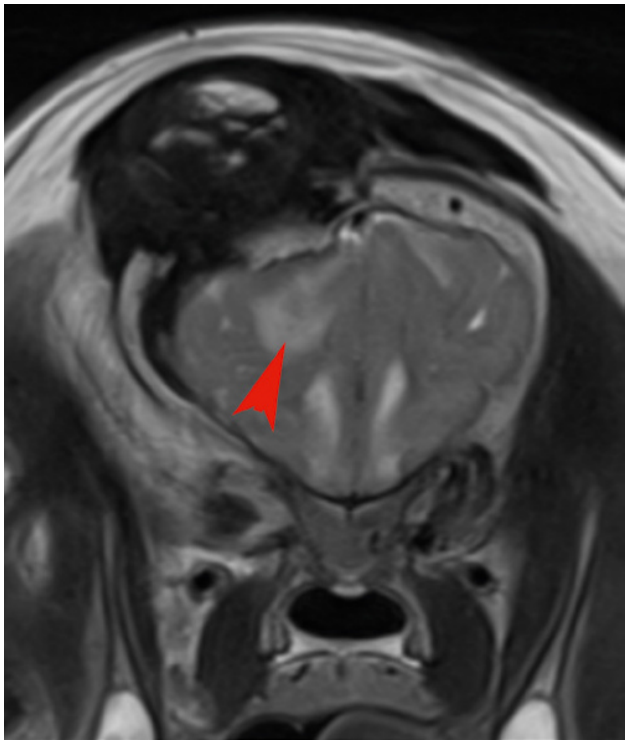


Figure 69.13 A transverse T2-weighted MRI of the dog in Fig. 69.11 confirms the extent of the soft tissue injury associated with frontal bone fractures. Hyperintensity seen in the brain (*arrow*) is compatible with edema secondary to the bite injury.

density decreases, with clot resorption creating a hypoattenuating lesion similar to edema. A CT can provide images for surgical planning, but should only be pursued in patients who are severely affected or deteriorating requiring surgical intervention.

Magnetic resonance imaging allows superior soft tissue detail and is preferred for evaluation of the brain, especially the caudal fossa which does not image well with CT (Figure 69.13). MRI can detect more subtle parenchymal changes that may be missed on a CT and may provide information about prognosis. Hematomas or hemorrhage, parenchymal contusions, and edema are readily apparent on MRI images. Although CT is preferred for evaluation of bony structures, fractures can also be identified on an MRI, most proficiently using STIR and gradient echo sequences.

Typically, CT and MRI are only pursued in patients who fail to respond to aggressive medical therapy or who deteriorate and may require surgical intervention. Both MRI and CT findings were recently correlated with prognosis in veterinary head trauma patients so their use may be of specific additional benefit.

Intracranial Pressure Monitoring

Intracranial pressure may be monitored through placement of a pressure transducer or fiberoptic transducer

into the epidural, intraaxial, or intraventricular space. ICP monitoring is frequently pursued in human head trauma patients, but may have its limitations in veterinary patients. ICP monitoring is not without risks and may lead to development of edema, hemorrhage, parenchymal damage, and infection.

Treatment of Head Trauma Patients

Treatment strategies should be directed toward both systemic and neurologic stabilization in an effort to minimize secondary damage. Several aspects of treatment exist. Systemic stabilization involves correction of systemic shock and respiratory abnormalities with fluid therapy and oxygen therapy/management of ventilation respectively. The second aspect of treatment involves measures to reduce elevations in intracranial pressure and cerebral metabolic rate. Finally, some animals require surgical intervention because of lack of improvement or a declining neurologic status.

Although once used as a treatment following head trauma, corticosteroids are no longer recommended in head trauma patients. Their use has been extensively evaluated in people and has shown no beneficial effect and may even result in worse morbidity and mortality rates. Detrimental effects of corticosteroids include immunosuppression, hyperglycemia, and gastrointestinal disturbances.

Fluid Therapy

The goal of fluid therapy of the head trauma patient is to restore a normovolemic state. It is deleterious to dehydrate an animal in an attempt to reduce cerebral edema. Aggressive fluid therapy and systemic monitoring are required to ensure normovolemia to maintain adequate cerebral perfusion pressure.

Crystalloid, hypertonic, and colloid fluids should be given concurrently to help restore and maintain blood volume following trauma. Crystalloids are usually given initially for the treatment of systemic shock. These balanced electrolyte solutions may be given at shock doses (90 mL/kg for dogs, 60 mL/kg for cats). Typically, it is recommended that the shock dose be given in fractions starting with one-third to one-fourth of the calculated volume, frequently reassessing the patient for normalization of mean arterial blood pressure, mentation and central venous pressure, if monitored, and giving additional fractions if needed. Unfortunately, crystalloid solutions will extravasate into the interstitium within one hour of administration, requiring additional fluid resuscitation.

Hypertonic and colloid fluid therapy can rapidly restore blood volume using low-volume fluid resuscitation; additionally, colloids remain in the vasculature longer than crystalloid fluids. These fluids should be used with caution as without concurrent administration of crystalloid solutions, hypertonic and colloid solutions can lead to dehydration. Other benefits of hypertonic fluids include the ability to improve cardiac output, restore normovolemia, and reduce inflammation after trauma. Hypertonic saline may be preferred in hypovolemic, hypotensive patients with increased ICP.

Hypertonic saline improves cerebral perfusion pressure and blood flow by rapidly restoring intravascular blood volume. Additionally, the high sodium content of hypertonic saline draws fluid from the interstitial and intracellular spaces, subsequently reducing intracranial pressure. Contraindications to administration of hypertonic saline include systemic dehydration and hypernatremia. Hypertonic saline only remains within the vasculature for about one hour so it should be followed by colloids to maximize its effects. A dose of 5–6 mL/kg (dogs) and 2–4 mL/kg (cats) of 7.5% NaCl should be given over 5–10 minutes.

Colloids (i.e., Hetastarch, Dextran-70) allow for low-volume fluid resuscitation, especially if total protein concentrations are below 50 g/L or 5 g/dL. These fluids also draw fluid from the interstitial and intracellular spaces, but have the added benefit of staying within the intravascular space longer than crystalloids. Hetastarch is typically given at 5–6 mL/kg boluses in dogs and 2–4 mL/kg in cats over 5–10 minutes, with frequent patient reevaluation. A total dose of 20 mL/kg/day may be given. In addition to volume resuscitation, oxygen-carrying capacity should be considered, especially if the packed cell volume <30%. The use of oxyglobin and other hemoglobin-based oxygen carriers has not been well evaluated in head trauma but initial studies suggest that they could play a valuable role.

Systemic blood pressure may require additional treatment to maintain adequate cerebral perfusion pressure. A mean arterial pressure of 80–100 mmHg should be the target. Hypotension should initially be treated with fluid resuscitation but persistent hypotension may require treatment with vasoactive agents (i.e., dopamine 2–10 μg/kg/min). Additionally, systemic hypertension may occur as a sequela to intracranial hypertension as a result of the Cushing reflex. Systemic hypertension secondary to ICP elevation should be treated by aggressively treating elevated ICP; the use of additional drugs to modulate the blood pressure should be avoided unless all attempts to lower ICP have been exhausted.

Head trauma patients should be positioned to maximize arterial circulation to the brain and improve venous drainage. This goal is best achieved by elevating the animal's head at a 30° angle. It is important to ensure the jugular veins are not occluded and that no restrictive collars are placed around the neck, which would elevate ICP.

Oxygen Therapy and Management of Ventilation

Oxygen supplementation is recommended in all patients following head trauma. Control of PaO_2 and $PaCO_2$ is mandatory and will affect both cerebral hemodynamics and ICP. Permissive hypercapnia should be avoided because of its cerebral vasodilatory effect that increases ICP. Hypocapnia can produce cerebral vasoconstriction through serum and CSF alkalosis. Reduction in CBF and ICP is almost immediate although peak ICP reduction may take up to 30 minutes after PCO_2 has been changed.

The amount of oxygen within the blood can be assessed by measuring oxyhemoglobin saturation with a pulse oximeter (SpO_2), measuring the PaO_2 with blood gas analysis in conjunction with measurement of circulating haemoglobin concentration. Calculation of oxygen delivery to the tissues requires measurement of both arterial oxygen content and cardiac output. Measurement of mixed venous oxygen can provide an indirect measure of adequacy of oxygen supply to the tissues. The amount of carbon dioxide within the blood can also be assessed by arterial blood gas analysis as well as via capnography. Capnography provides breath-by-breath assessment of adequacy of ventilation assuming normal cardiovascular function. This technique measures CO_2 in the expired patient gases (P'$ETCO_2$), which approximates the CO_2 tension in the alveoli. As alveolar gases should be in equilibrium with arterial blood, P'$ETCO_2$ can be used to approximate $PaCO_2$ unless severe pulmonary dysfunction is present.

The goal of oxygen therapy and management of ventilation is to maintain the partial pressure of oxygen in the arterial blood supply (PaO_2) greater than or equal to 90 mmHg and the $PaCO_2$ below 35–40 mmHg. If the patient is able to ventilate spontaneously and effectively, supplemental oxygen should be delivered via "flow-by"; confinement within an oxygen cage prevents frequent monitoring. Facemasks and nasal catheters should be avoided if possible as they can cause anxiety which may contribute to elevations of intracranial pressure.

Patients with severe head injury require mechanical ventilation to maintain these arterial blood gas concentrations at their optimal levels. The absolute indications for mechanical ventilation include loss of consciousness, rising $PaCO_2$ of >50 mmHg and falling SPO_2 despite appropriate treatment.

There are no contraindications to the use of positive end-expiratory pressure (PEEP) in hypoxemic patients. With adequate volume resuscitation, PEEP does not increase ICP nor does it lower CPP, and it may actually decrease ICP as a result of improved cerebral oxygenation. Assessment of adequacy of ventilation can be made by measurement of arterial CO_2 or alternatively using capnography.

Diuretics

Intracranial pressure can be aggressively addressed with the administration of osmotic diuretics. Osmotic diuretics such as mannitol should not be given to any patient without being certain that the patient has been volume resuscitated. If not, their use can precipitate acute renal failure. For this reason, they are reserved as tier 2 therapies.

Mannitol improves CBF and reduces ICP by decreasing edema. After administration, mannitol expands the plasma volume and reduces blood viscosity, which improves CBF and delivery of oxygen to the brain. Additionally, mannitol assists in scavenging free radicals, which contribute to secondary injury processes. Vasoconstriction occurs as a sequela to the increased partial pressure of oxygen, leading to an immediate decrease in ICP. Additionally, the osmotic effect of mannitol reduces extracellular fluid volume within the brain.

Mannitol (0.5–2.0 g/kg) should be given as a bolus over 15 minutes to optimize the plasma-expanding effect. Continuous infusions of mannitol increase the permeability of the blood–brain barrier, exacerbating edema. Lower doses of mannitol are as effective at decreasing ICP as higher doses, but may not last as long. Mannitol reduces brain edema over about 15–30 minutes after administration and has an effect for approximately 2–5 hours. Repeated dosing of mannitol can cause diuresis, leading to reduced plasma volume, increased osmolarity, intracellular dehydration, hypotension, and ischemia. Therefore, adequate isotonic crystalloid and colloid therapy is critical to maintain hydration. Additionally, administration of mannitol should be reserved for the critical patients (MGCS of <8), a deteriorating patient, or a patient failing to respond to other treatment. Administration of furosemide (0.7 mg/kg) prior to administration of mannitol has a synergistic effect at lowering ICP. Currently, there is no evidence to indicate that mannitol is contraindicated in the presence of intracranial hemorrhage, as has been suggested.

Seizure Therapy

Seizures should be aggressively treated to prevent worsening of the secondary effects in the brain parenchyma due to associated brain hypoxia and subsequent development of edema. Seizure activity may occur immediately following trauma or may be delayed in onset. The need for antiseizure prophylaxis after severe brain trauma remains controversial in human medicine. Human patients treated in the first seven days after head trauma with anticonvulsants have a significantly lower risk of posttraumatic seizures within this time period than if not treated. Beyond seven days from injury, there appears to be no benefit to prophylactic treatment.

Diazepam (0.5–2.0 mg/kg) can be given intravenously to treat seizures. Additionally, phenobarbital (2–3 mg/kg) may also be given intravenously or intramuscularly and continued parenterally following a loading dose (18–24 mg/kg over a 24–48-hour period) if necessary. Recently, the use of intravenous levetiracetam (20–60 mg/kg) has been described for emergency seizure treatment as it may be effective for up to eight hours without causing much sedation and without needing hepatic metabolism. Refractory seizures at the time of head trauma may require additional therapy such as a continuous infusion of diazepam (0.5–1.0 mg/kg/h) or propofol (4–8 mg/kg bolus to effect followed by 1–5 mg/kg/h CRI).

Some patients may require long-term management of seizure activity with antiepileptic medications. However, if maintenance therapy is continued beyond seven days and seizure activity is not noted over a 3–6-month period, antiepileptic treatment may be slowly withdrawn. Therapy should be reinstituted if seizures return with an unacceptable frequency.

Refractory Head Trauma

Failure of fluid therapy, oxygenation and ventilation strategies, and osmotic diuretics to stabilize the patient and/or improve the neurologic status significantly warrants radical therapy and such cases should be considered for advanced imaging such as MRI. The treatments discussed here have not been evaluated in veterinary medicine in terms of their efficacy and remain controversial or unproven in human head trauma.

Hyperventilation

Hyperventilation has been suggested as a method of quickly lowering ICP. Hypercapnia causes vasodilation and subsequent increases in ICP so hypoventilation should be avoided. Mechanical or manual ventilation may be used to lower partial pressure of carbon dioxide in the arterial blood ($PaCO_2$ <35 mmHg) to reduce ICP in deteriorating patients responsive to no other treatment and with no surgical lesions. The prolonged use of hyperventilation should be avoided as reduction in cerebral $PaCO_2$ less than 30–35 mmHg causes vasoconstriction which ultimately leads to decreased cerebral blood flow and ischemia.

Hypothermia

At this time, hypothermia is an experimental treatment which has not been validated in veterinary medicine and remains controversial in human medicine. Following trauma, the cerebral metabolic rate may be increased, leading to exacerbating secondary effects. Controlled hypothermia and induction of coma reduce cerebral metabolic rate and have been reported in human head trauma patients and recently in a veterinary patient. Hypothermia can be achieved by cooling a patient to a rectal temperature of 32–35 °C, which reduces cerebral metabolic rate and oxygen consumption, leading to decreased CBF and ICP. However, reduction of core body temperature carries risks and may lead to the development of cardiac arrhythmias, coagulopathies, electrolyte disturbances, hypovolemia, and insulin resistance. Coma may also be induced using barbiturates, but this prevents neurologic evaluation and requires induction of mechanical ventilation.

Surgery

Surgical intervention is reserved for patients that do not improve or deteriorate despite aggressive medical therapy. Advanced imaging (CT or MRI) is necessary for surgical planning and is also reserved for similar patients. Surgery may be indicated to remove hematomas, relieve intracranial pressure, or address skull fractures. Ventricular obliteration and mass effect identified on advanced imaging should be considered strong indicators for surgical treatment in any animal which does not improve with medical therapy.

Extraaxial hematomas can be removed through a generous craniectomy. Surgery in these patients may lead to significant hemorrhage requiring blood transfusions. Removal of hematomas may exacerbate bleeding as compression of bleeding vessels is removed, leading to reaccumulation of blood even after surgery. Intraaxial hematomas are typically managed conservatively. Surgery may be indicated in a deteriorating patient with subacute enlargement of a previously small hematoma.

Hemorrhagic parenchymal contusions can cause severe neurologic signs, depending on their location. They are typically managed conservatively. Cerebellar contusions causing fourth ventricle and brainstem compression are an indication for surgery in humans in an effort to reduce continued compression and the risk of herniation. Surgery for cerebellar contusions may be indicated prior to neurologic deterioration because these signs are less reversible with conservative management.

Intracranial hypertension should be treated initially with the therapies discussed previously. However, in about 20% of human head trauma patients, additional decompressive surgery is also required. Surgery is beneficial in deteriorating patients before irreversible brain damage occurs indicated by bilateral pupillary dilation. Surgical intervention for intracranial hypertension involves creation of a large craniectomy over the most affected site followed by a durectomy or duraplasty to allow the brain to swell.

Typically, skull fractures do not require surgical intervention. However, significantly contaminated, comminuted fractures may require surgical debridement, especially if

open. In dogs, such fractures of the frontal sinus may be associated with traumatic pneumocephalus and this should be considered in any dog deteriorating despite aggressive medical therapy. If surgical intervention is pursued, aggressive debridement should include removal of all devitalized tissues and bone and should be guided by imaging. Large bone fragments may be spared and replaced after thorough debridement, cleaning, and soaking in an antibiotic solution.

Following surgery, seizure and antibiotic prophylaxis are recommended. Phenobarbital at 2–3 mg/kg IV every 6–8 hours for 48 hours followed by maintenance parenteral therapy is advised. An alternative approach is to use levetiracetam at 20–60 mg/kg IV every 8 hours followed by 20 mg/kg orally every 8 hours.

Prognosis for Animals with Head Trauma

Prognosis is dependent on severity of neurologic signs and response to treatment. Potential complications associated with brain trauma include coagulopathies, pneumonia, sepsis, transient or permanent central diabetes insipidus, and seizures. Treatment in brain trauma patients should be immediate and aggressive if the animal is to survive and recover to a level that is functional and acceptable to the owner. The ultimate goal in the management of brain trauma in veterinary medicine is for the pet to maintain a good quality of life. Many patients can recover if systemic and neurologic abnormalities are identified and treated early. Dogs and cats have a remarkable ability to compensate for the loss of cerebral tissue, making it important not to make rapid prognostic conclusions based on the initial appearance of a pet suffering from brain injury.

Predicting the outcome for an individual patient can be difficult. Multiple prognostic factors have been identified in human medicine. The most important factors identified include age, cause of injury, Glasgow Coma Scale motor score, pupil response to light, and CT scan characteristics, including the presence of subarachnoid hemorrhage. Secondary insults of hypotension and hypoxia have also been found to add important predictive information.

The association between a patient's score using the MGCS and prognosis has been evaluated. This evaluation showed an almost linear correlation between score and probability of survival within the first 72 hours. Therefore, patients with a high score had a high probability of survival while patients scoring low on the MGCS were unlikely to survive. A score of 8 on the MGCS was associated with about a 50% chance of survival. The MGCS was recently evaluated with long-term survival at one and six months following injury. Again, a linear trend between MGCS and survival at one and six months was demonstrated. An association between MGCS and long-term patient outcome could allow prediction of acceptable patient recovery and aid in decision making at the time of injury.

In humans with head trauma, hyperglycemia on admission is a frequent component of the stress response to the injury, a significant indicator of severity of injury, and a potent predictor of the patient's outcome. A recent study in dogs and cats suggests that head trauma in these species may be associated with hyperglycemia and that the degree of hyperglycemia can be associated with severity of head trauma. However, the degree of hyperglycemia does not seem to be associated with outcome for dogs and cats with head trauma. Because hyperglycemia can potentiate neurologic injury, iatrogenic hyperglycemia should be avoided in patients with head trauma.

70

Seizures and Movement Disorders

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Seizures

Pathophysiology

Epilepsy is a heterogeneous disease of diverse etiology, electrophysiologic and behavioral seizure patterns, and responses to treatment. As such, the pathogenesis of epilepsy is multifactorial. Genetically determined seizure susceptibility factors play a crucial role in the response of the brain to triggering or precipitating factors, also known as the seizure threshold.

A basic tenet in the mechanism of epilepsy is the presence of an imbalance in excitatory and inhibitory neurotransmission. A seizure develops when the balance shifts towards excessive excitation. Glutamate is the principal excitatory neurotransmitter and gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter involved in this process in the brain. Conditions leading to excessive excitation or loss of inhibition result in depolarization of neurons without normal regulatory feedback mechanisms. The result is a paroxysmal depolarization shift of a neuronal aggregate. In response to this sudden change in brain activity, local surrounding inhibitory zones are established to try to prevent the spread of this epileptogenic activity. If inhibition is unsuccessful, other neuronal aggregates are excited through thalamocortical recruitment, intrahemispheric association pathways or interhemispheric commissural pathways. Successful recruitment of a critical number of areas with synchronized depolarization then leads to a seizure (Figure 70.1).

History and Clinical Signs

Classification of seizures and epilepsy into a universally accepted, coherent and relevant scheme for clinicians has been an ongoing dynamic process in human epilepsy since the early 1980s. The standardized classification scheme for seizures and epilepsy established by the International League Against Epilepsy (ILAE) in the 1980s provided the first basis for a taxonomic foundation for an analytic approach in the diagnosis and treatment of epilepsy. The proposed diagnostic scheme consists of five levels or axes as proposed by Engel and revised by Berg *et al*. for people and Podell for dogs (Box 70.1).

Axis 1: Seizure (Ictal) Phenomenology

A seizure can be defined as a nonspecific, paroxysmal, abnormal event of the body. An epileptic seizure is defined by the ILAE as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Thus, an epileptic seizure has a specific neural origin. Absolute confirmation that a seizure is epileptic may be difficult as it requires simultaneous observation of behavioral and electroencephalographic changes. As a result, historical information is often used to diagnose an epileptic seizure. The clinical features of epileptic seizures can be separated into four components.

1) The prodrome is the period prior to the onset of seizure activity. Owners report that they can "predict" the onset of their pet's seizures based on behavior exhibited during this time, such as increased anxiety-related behavior (i.e., attention seeking, whining), reluctance to perform normal activity patterns, and increased hiding (especially in cats).
2) The aura is the initial manifestation of a seizure. During this period, which can last from minutes to hours, animals can exhibit stereotypical sensory or motor behavior (e.g., pacing, licking), autonomic patterns (e.g., salivating, urinating, vomiting) and even unusual psychiatric events (e.g., excessive barking, increased/decreased attention seeking).

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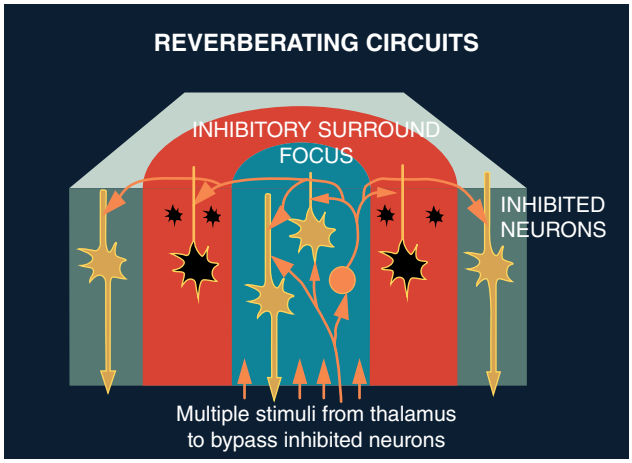


Figure 70.1 Pathophysiology of epileptic seizure generation. Reverberating circuitry between the cerebrocortical epileptic focus and the subcortical thalamic pathways provides a mechanism to overcome the natural inhibitory surround defense against seizure propagation that leads to expanding and propagating epileptic seizure foci in epileptic patients. This process can become a feed-forward, self-propagating mechanism of drug-resistant epilepsy when antiepileptic drug treatment is delayed.

3) The ictal period is the actual seizure event, manifested by involuntary muscle tone or movement and/or abnormal sensations or behavior, lasting usually from seconds to minutes.
4) The postictal period follows the actual seizure and can last from minutes to days. During this time, an animal can exhibit unusual behavior, disorientation, inappropriate bowel and/or bladder activity, excessive or depressed thirst and appetite, or actual neurologic deficits including weakness, blindness, and sensory/motor disturbances. Often, owners observe only the postictal period as evidence that their pet has had a seizure.

Regardless of the cause, a patient's epileptic seizures may be recurrent over time or may occur as a single event. If the patient has a chronic brain disorder characterized by recurrent epileptic seizures, then that patient has epilepsy. Status epilepticus can be defined as a state of continuous seizure activity lasting for five minutes or longer, or repeated seizures with failure to return to normality within 30 minutes.

Box 70.1 Diagnostic categorization for epilepsy

Axis 1: Seizure (ictal) phenomenology

- Seizure:
  - Epileptic seizure
  - Nonepileptic episodes
- Epilepsy
- Status epilepticus

Axis 2: Seizure type

- Focal:
  - Without impairment of consciousness or awareness
    - Sensory only (olfactory, hallucinatory)
    - Motor and/or autonomic components
      - Focal motor with or without automatisms
      - Autonomic only
  - With impairment of consciousness or awareness
    - Altered sensory and/or motor activity
    - Evolving to generalized seizure
- Generalized:
  - Tonic-clonic
  - Tonic only
  - Clonic only
  - Atonic only
  - Myoclonic (or any combination with tonic, clonic, and/or atonic)
- Absence
- Unknown cause

Axis 3: Epilepsy syndromes

- Electroclinical syndromes by age of onset
  - Neonatal
  - Infancy
  - Childhood
  - Adult
- Structural or metabolic syndromes
- Epileptic encephalopathies (progressive neurologic dysfunction)
- Unknown cause (idiopathic)

Axis 4: Etiology

- Genetic
- Structural (symptomatic)
  - Congenital
  - Acquired
- Metabolic
- Unknown
  - Cryptogenic
  - Idiopathic

Axis 5: Impairment from epilepsy

- Temporary (<1 week) vs prolonged (>1 week)
  - Motor: paresis, fatigue
  - Sensory: vision loss, somatosensory deficits
  - Behavioral: change in obedience, housebreaking, altered attention seeking, agitation, anxiety

Axis 2: Seizure Type

Epileptic seizures are divided into focal and generalized types. Focal seizures are the manifestation of a discrete, epileptogenic event in the cerebral cortex. The focal nature of this seizure type is associated with a higher incidence of focal intracranial pathology. Focal seizures can be associated with or without impaired consciousness or awareness and are typically characterized by motor or sensory disturbances.

Focal motor seizures are commonly seen as facial muscle twitching whereas sensory focal seizures are manifested by more abnormal behavioral disorders.

More complex behavior patterns with focal seizures include impaired consciousness, often with bizarre behavioral activity. Previously termed complex partial or psychomotor seizures, these events are now classified as automatisms or automotor seizures. Animals may show "fly-biting" behavior patterns, become aggressive without provocation, howl incessantly, become restless or exhibit a variety of motor disturbances. Cats may show a variety of abnormal behaviors or motor signs, including drooling, hippus, excessive vocalization or random, rapid running behaviors indoors. Whenever a focal seizure is suspected, the clinician should be suspicious of a focal cerebral disturbance and plan the diagnostic workup accordingly.

Generalized seizures are subdivided into tonic-clonic, tonic, clonic, myoclonic, atonic or absence types. The terms *convulsive* (grand mal) and *nonconvulsive* (petit mal) seizures are no longer in use. Generalized seizures originate from both cerebral hemispheres from the start, or more commonly progress secondarily from focal seizures. Unlike focal seizures, generalized seizures are not necessarily associated with focal cerebrocortical disease.

Epileptic spasms are currently classified as a discrete seizure type, as it has yet to be determined whether these events have a focal or generalized onset based on electroclinical data from humans.

Axis 3: Syndrome

By definition, a syndrome is a group of signs or characteristics that defines a particular combination of clinical abnormalities, often due to a specific genetic disorder. Epilepsy syndromes are not well defined in veterinary medicine, although familial epilepsies are now being identified with segregation analysis.

Axis 4: Etiology

Genetic (Idiopathic) Epilepsy

A diagnosis of genetic epilepsy is most common in purebred dogs with the first onset of seizures between 1 and 5 years old, a normal interictal neurologic examination, and if there is a lengthy initial interictal period (>4 weeks). A high percentage of these patients also exhibit cluster seizures. A genetic basis has been reported in numerous dog breeds, including Belgian shepherd dogs, border collies, poodles, beagles, springer spaniels, Shetland sheepdogs, vizslas, Irish wolfhounds, lagotto Romagnolos, and retrievers. True genetic epilepsy is much less common in cats due to their more diverse genetic background. As such, all cats should be evaluated for underlying structural or metabolic seizures before a diagnosis of genetic epilepsy is made.

Structural or Symptomatic Epilepsy

These types of epileptic seizures are the direct result of either structural brain pathology or metabolic disease. Younger animals are more prone to developmental and encephalitic diseases, while older dogs (>7 years of age) are more likely to develop intracranial neoplasia. As expected with underlying cerebral pathology, these animals are more likely to exhibit focal or multifocal neurologic deficits. However, focal lesions in "silent" cortical areas of the brain (e.g., olfactory, pyriform and occipital lobes) may have seizures as the only neurologic problem. This presentation has been seen in cats due to feline infectious peritonitis (FIP) and meningioma. Metabolic (formerly reactive) epileptic seizures are a reaction of the normal brain to transient systemic insult, toxic reaction or physiologic stresses. Animals of any age may be affected. Small-breed dogs are more predisposed to develop seizures secondary to portosystemic shunts at a younger age. Typically, a higher seizure frequency occurs initially until the underlying metabolic or toxic insult is corrected, but evidence of systemic illness is often present concurrently.

Unknown Cause of Epileptic Seizures

A variety of epileptic seizures arise without an apparent cause but are thought to have a more specific etiology. Previously termed or cryptogenic epileptic seizures, these events are believed to be due to an underlying unidentified brain disease. Many of these dogs are over the age of 7 without identifiable brain lesions but with a high prevalence of drug-resistant epilepsy, with close to 90% of the cases requiring more than one antiepileptic drug (AED) for treatment.

Axis 5: Impairment from Epilepsy

The majority of postictal signs in cats and dogs are transient, such as disorientation, visual impairment, salivation, incontinence, and altered behavior. More prolonged or recurrent seizure activity can lead to permanent sensory deficits (vision deficits), cognitive changes (altered obedience), and loss of normal personality. Chronic seizures have been shown to induce microglial activation and cerebral angiogenesis in Shetland sheepdogs with familial epilepsy.

Diagnosis

The most important component in approaching a seizure case is acquiring a thorough and accurate history. The purpose is to establish overall frequency, seizure type, patterns of occurrence, relationship to daily activity (e.g., exercise, sleep) and severity of postictal effects. Inquiries regarding the seizure event should address a description of the event, time of day, duration, and postictal effects. Video segments of events can be extremely helpful for clinicians to determine whether an epileptic event has occurred. Owners should be encouraged to video an event if possible and to try and distract the animal to determine whether the event can be terminated with external stimuli. Distractability often implies a nonepileptic event. A charting technique measuring seizure frequency and severity should be developed to aid objective evaluation of future therapeutic success. Owners should be provided with a calendar to record the frequency and description of all observed and suspected seizures.

The interictal status of cerebrocortical function (between seizures and after the postictal period) can be evaluated by asking questions concerning the animal's behavior, vision, gait, and sleep/wake patterns. For example, if the dog is more withdrawn or attention seeking, showing any unusual episodes of aggression or irritability, or fails to follow simple commands, then a structural cerebral problem should be suspected. Likewise, subtle gait disturbances (stumbling up or down the stairs), visual disturbances (occasionally bumping into objects on one side) and restless sleep patterns may indicate forebrain problems.

The sequence of diagnostic testing for any animal with seizures should proceed from the least to the most invasive (and expensive) modality. A complete blood count (CBC), biochemistry panel, urinalysis, and blood pressure measurement should be performed for all animals being evaluated for an epileptic seizure.

For dogs, additional testing is based upon the age, breed, seizure type, seizure frequency, and neurologic examination findings.

Advanced Metabolic and Infectious Disease Testing

Pre- and postprandial serum bile acid study with serum ammonia levels in dogs less than 1 year of age and those being started on hepatic metabolized antiepileptic drug (AED) therapy.

Other individual tests for toxin exposure (e.g., plasma lead, serum cholinesterase assay), parasitic or rickettsial infection, or systemic illness are based on the clinical picture at the time of presentation. For cats, basic screening should include a retroviral screen for feline leukemia and feline immunodeficiency virus and testing for serum antibodies to *Toxoplasma gondii*. Testing for the virus that causes feline infectious peritonitis is not recommended, as the correlation between a positive titer and active CNS infection is low.

Magnetic Resonance Imaging (MRI) Brain Scan

- All dogs 7 years of age or older and all cats with an initial onset of seizure(s), regardless of the seizure pattern or frequency or outcome of neurologic examination.
- Patients with an abnormal interictal exam or behavior.
- Drug-resistant epileptic patients.
- Cerebrospinal fluid (CSF) analysis is recommended in any animal with multifocal neurologic deficits or lesions observed on MRI scans or if the scan is normal.

Electroencephalogram (EEG)

Electroencephalogram analysis is beneficial for identifying underlying epileptic foci in the dog but the overall usefulness of this test for determining diagnosis and treatment has yet to be proven.

Therapy

Management of epilepsy in cats and dogs often requires a lifetime commitment by the owners. The owner must be willing to medicate their pet several times per day, travel to emergency clinics at unpredictable times, follow up with periodic reevaluations and diagnostic testing, and watch their pet carefully for adverse effects of therapy.

Despite all the time, financial, and emotional commitment, a significant number of dogs may still continue to have seizures. Thus, proper client education is critical in preparing owners for understanding their pet's condition and the potential associated lifestyle changes. In particular, owners need to know that a diagnosis of epilepsy implies an increased risk of premature death with the prognosis dependent on a combination of veterinary expertise, therapeutic success, and owner motivation.

Decision-Making Strategies for AED Therapy

The decision regarding when to start AED treatment is based on a number of factors, including etiology, risk of recurrence, seizure type and its effect on the patient, as well as the risk of treatment. Risk factors for seizure recurrence are not well established for cats and dogs. A number of relative risk factors have been identified in epileptic people, including current or previously defined cerebral lesions or trauma, the presence of interictal EEG epileptic discharges (up to 90% recurrence rate) and a history of marked postictal adverse effects (Todd paralysis). Evidence-based guidelines from several international groups are well established for humans based on the risk:benefit ratio and predictability factors of drug

effect. From these guidelines, several commonalities exist for guiding clinical practice, including confirmation of an epileptic seizure event and seizure type, obtaining a definitive diagnosis, knowledge that recurrent seizure activity is correlated with poorer long-term treatment success, and the influence of treatment on the patient's quality of life. Thus, the decision to treat is a reflection of the treatment goals to reduce or eliminate epileptic events, reduce seizure severity, avoid adverse effects, and reduce seizure-related mortality and morbidity.

Initiating Treatment

Overwhelming evidence exists in humans that there is no benefit in starting treatment after a single unprovoked event However, the earlier AED therapy is initiated, the better the potential outcome may be for seizure control.

Reasons to initiate AED therapy include the following.

- Structural epilepsy is diagnosed.
- Status epilepticus has occurred (ictal event of five minutes or longer).
- Two or more isolated seizures occur within a six-month period.
- Two or more cluster seizure events (two or more seizures within a 24-hour period) occur within a 2–3-month period.
- The first seizure is within one month of a traumatic event.
- Severe or unusual postictal effects are present (e.g., prolonged blindness, aggression).

Drug Selection

Selection of AED is based on a number of factors, including seizure type, efficacy, and tolerability. No evidence exists that any single AED provides a better outcome for adults with unprovoked epilepsy when early treatment is initiated. Monotherapy is still the recommendation for new-onset epilepsy. The use of a single AED has the advantages of no drug interactions, more predictable pharmacokinetic and pharmacodynamic properties, less potential for adverse effects, and less expense to the client.

Antiepileptic drugs are classified into three broad mechanistic categories which decrease either the seizure onset or spread of seizures:

- enhancement of inhibitory processes via facilitation of GABA action
- reduction of excitatory transmission
- modulation of membrane cation conductance.

Success Parameters

The treatment of epilepsy should be goal oriented and approached in an objective fashion. Eliminating or significantly reducing the number and severity of seizures and maintaining a normal lifestyle for both the patient and owner are all important considerations. Whilst many drugs may provide initial improvement in seizure control, long-term efficacy is dependent on many factors. With only approximately 60–80% of human and canine epileptic patients responding to treatment, evaluating the reasons for recurrent seizure activity (refractory epilepsy) is important.

These factors can be separated into three "Ds": Disease-related, Drug-related or Dynamic-related factors. Disease-related factors include the presence of an undiagnosed underlying brain disease, such as cortical dysplasia, prior trauma or an active disease process. Occult conditions can lead to localization-related epilepsy, where epileptic foci develop drug resistance due to architectural brain changes.

Drug-related factors include an ineffective mechanism of action, development of tolerance and alteration of the drug target or uptake over time. Seizure-specific therapy targets a drug for a specific seizure type, and inappropriate drug selection may result in poor control. The reasons for drug tolerance or loss of effectiveness can be categorized as either metabolic (pharmacokinetic) or functional (pharmacodynamic). Metabolic tolerance is due to altered drug metabolism, which occurs in an unpredictable fashion. As such, a change in drug dosage does not result in a parallel change in serum drug level. During this time, autoinduction of the cytochrome P450 enzyme system increases drug clearance and is not dose dependent. Serum drug levels decline over time with the same dose until steady-state clearance is achieved. Concomitant drug usage that either inhibits or stimulates the P450 system also alters hepatic metabolized AED levels. Functional drug tolerance, also known as pharmacoresistance, is due to reduced drug transport through the blood–brain barrier, long-term downregulation of the target receptor or genetic factors that alter cellular metabolism of the drug.

Dynamic-related factors are now being discovered in relation to gene polymorphisms that affect AED pharmacokinetic or pharmacodynamic properties. As a result, altered drug metabolism or action is no longer predictable when compared with the general patient population. In addition, a placebo effect has been demonstrated in epileptic dogs, indicating that nonpharmacologic therapeutic effects may play a role in canine epilepsy treatment.

First-Generation AEDs

Phenobarbital

Phenobarbital (PB) has the longest history of chronic use of all AEDs in veterinary medicine. It is a relatively inexpensive, well-tolerated drug and has documented success in preventing seizures. Phenobarbital has a high

bioavailability, being rapidly absorbed within two hours and with a maximal plasma concentration obtained within 4–8 hours following oral administration. Almost one-half of the drug is protein bound. The majority of phenobarbital is metabolized by the liver, with approximately one-third excreted unchanged in the urine. Phenobarbital is an autoinducer of hepatic microsomal enzymes (P450 system), which can progressively reduce the elimination half-life with chronic dosing.

Adverse Effects Overall, phenobarbital is well tolerated at therapeutic serum concentrations in the dog and cat. Idiosyncratic drug reactions to phenobarbital can be either behavioral or biochemically mediated. A more serious idiosyncratic reaction is development of an immune-mediated neutropenia or thrombocytopenia in dogs, as well as anemia. Rare acute, idiosyncratic hepatotoxic reactions may also be present, as evidenced by a rapid elevation of alanine aminotransferase (ALT) and abnormal dynamic bile acid levels. The drug should be stopped immediately if either neutropenia or dramatic elevations in ALT are noted and replaced with a nonhepatic metabolized AED.

The most serious and potentially life-threatening complications that can occur with long-term phenobarbital therapy are hepatotoxicity and development of superficial necrolytic dermatitis in dogs. Documentation of a serum phenobarbital concentration >35 µg/mL had the highest correlation with the development of hepatotoxicity. All animals on chronic phenobarbital therapy should have a routine biochemistry panel performed every 6–12 months to monitor for the development of chronic hepatotoxicity. A bile acid tolerance test should be performed to evaluate liver function if ALT levels suddenly increase or if the serum albumin level starts to decrease. Hepatotoxicity is uncommon to occur in cats.

Dosage and Monitoring The appropriate starting dose of phenobarbital is 2.5 mg/kg orally q12h in dogs and 2.5 mg/kg q24h in cats. An intravenous loading dose can be used to produce a rapid rise in serum blood concentration. This starting dose is the only time a weight-based dosage is used. All future adjustments should be based on serum drug concentrations in conjunction with clinical assessment.

The goal of drug level monitoring is to be proactive rather than reactive in seizure prophylaxis. Serial serum trough phenobarbital concentrations should be evaluated at 14, 60,180, and 360 days after the initiation of treatment, at six-month intervals thereafter, if the pet has more than two seizure events between these time points, and at two weeks after a dosage change. Although blood level fluctuations may not be dramatic throughout the day in dogs with steady-state concentrations, blood samples are best taken in the early morning, prior to dosing, in a fasted dog, to increase consistency in comparison with published information, maintain consistency in interpretation, and remove diurnal or dietary-induced fluctuations of absorption.

Adjustments in AED dosages are undertaken either to enhance the effect or to reduce the adverse effects. The most efficacious and safe trough therapeutic phenobarbital range is 15–30 µg/mL. An optimal starting level is between 20 and 25 µg/mL. Increments of 5 µg/mL are beneficial if seizures are occurring at an equal frequency or worsening after 30 days of therapy. Cats in general can tolerate higher serum levels in the 30–45 range without complications.

Adjustments of the trough phenobarbital levels can be calculated with the following formula:

$$\left(\text{Desired concentration} / \text{Actual concentration}\right) \times \text{total mg PB per day} = \text{Oral daily dose of PB}\left(\text{mg}\right)$$

Potassium Bromide

Potassium bromide can be used as either monotherapy or as an add-on AED of choice in the dog. Concomitant potassium bromide and phenobarbital administration decreased seizure number and severity in the majority of dogs in several studies, with seizure-free status ranging from 21% to 72% of all treated dogs. In general, many canine refractory idiopathic epileptic patients may benefit from potassium bromide. By allowing a reduction in the use of drugs metabolized by the liver, potassium bromide therapy may also reduce the incidence of hepatotoxicity. Bromide is not recommended for use in cats due to potential for life-threatening allergic asthmatic reaction.

Pharmacology A starting dose of 40 mg/kg/day potassium bromide is slowly metabolized in the dog, with a median elimination half-life of 15.2 days, Steady-state concentrations fluctuate between dogs, most likely due to individual differences in clearance and bioavailability. Dietary factors also alter serum drug concentrations, with high-chloride diets resulting in excessive renal secretion and lower serum concentrations.

Adverse Effects Potassium bromide is generally well tolerated in the dog. The most common adverse effects seen with potassium bromide and phenobarbital combination therapy are polydipsia, polyphagia, increased lethargy, and mild ataxia with increasing serum concentration. Pancreatitis and gastrointestinal intolerance have also been reported. Chronic use at higher serum concentations can result in pelvic limb ataxia and excess sedation.

Administration and Monitoring Potassium bromide can be administered at a starting dose of 40 mg/kg/day when used as sole therapy or 30 mg/kg/day when used as an add-on drug to phenobarbital. Potassium bromide serum concentration should be measured at one month and at the first steady-state concentration (approximately 8–12 weeks). The recommended goal is to achieve steady-state trough serum concentrations of 25 µg/mL for phenobarbital and 2000 mg/L for potassium bromide. The range is highly individualized according to the seizure pattern of each dog. Further reductions in phenobarbital can be attempted if a seizure-free period is maintained for six months. The dosage is adjusted according to the formulae given below.

Potassium bromide monotherapy is recommended for dogs with underlying liver disease, less frequent seizure activity (<3 per year) and for some dogs with idiopathic epilepsy. The use of potassium bromide monotherapy is not recommended for high initial frequency seizure activity, if secondary epilepsy is present, or if unwarranted adverse effects persist (e.g., weakness, extreme polydipsia).

Adjustment of bromide dose can be calculated with the following formula:

$$\begin{aligned}&(\text{Target Css} - \text{Actual Css}) \times (\text{Clearance/Bioavailability})\\ &= (2000\ \text{mg/L} - \text{Actual Css}) \times 0.02\\ &= \text{New mg/kg/day added to existing dose}\end{aligned}$$

where Css = steady-state concentration.

Second-Generation AEDs

Zonisamide

This is a substituted 1,2-benzisoxazole derivative that works by both blocking the propagation of epileptic discharges and suppressing focal epileptogenic activity. Broad-spectrum antiepileptic activity has been reported against a variety of seizure types, with particular improvement in the treatment of adult myoclonus epilepsy. Zonisamide can be an efficacious and well-tolerated drug in dogs with recurrent generalized seizures refractory to phenobarbital or potassium bromide therapy. Over 70% of dogs with refractory idiopathic epilepsy responded well to zonisamide add-on therapy in one study, with 58% responding favorably in another.

Pharmacology Zonisamide is well absorbed, has a relatively long half-life (18–28 hours) and high protein-binding affinity (70%) in dogs. In cats, zonisamide is more slowly metabolized, with a half-life of 33 hours. Zonisamide is hepatic metabolized and thus influenced by concurrent administration of other similarly metabolized drugs. Phenobarbital dosages should be reduced by 25% at the time of starting zonisamide due to the enhanced hepatic enzyme induction and clearance of zonisamide.

Adverse Effects The major adverse effects include sedation, dry eye, ataxia, inappetence, and vomiting, often related to metabolic and renal tubular acidosis. Cats are more likely to develop adverse effects of anorexia, vomiting, diarrhea, and ataxia at doses over 10 mg/kg/day. A decrease in circulating total serum T4 levels can occur and acute idiosyncratic hepatic necrosis has been reported in the dog. Patients with a history of sulfa drug hypersensitivity should not be prescribed zonisamide.

Dosage and Monitoring Zonisamide is available as a generic medication in dosages of 25 mg, 50 mg, and 100 mg. The starting dose in dogs is 10 mg/kg every 12 hours and 5 mg/kg once daily in cats. Trough serum drug levels should be obtained at 14 and 45 days, then every six months if no seizures are observed or in 10 days after a drug adjustment.

Levetiracetam

This is the *S*-enantiomer of the ethyl analogue of piracetam and has a unique mechanism of action mediated by binding to the presynaptic vesicular protein, SV2A, which decreases glutamate neurotransmitter. The drug has shown to be an effective add-on AED in the cat but not as conclusive in the dog.

Pharmacology In dogs, the drug is well absorbed, is rapidly metabolized with an estimated elimination half-life of 4–8 hours, and is predominantly renal excreted (>80%). However, wide fluctuations of drug metabolism occur in the dog. The oral dose should be increased when dogs are receiving phenobarbital concurrently as lower serum levels can potentially be related to the induction of serum hydrolases. A new extended-release formulation of levetiracetam has been shown to have a half-life in excess of seven hours in dogs following oral administration, giving rise to the potential for twice-daily administration

Adverse Effects Levetiracetam is the best tolerated of all the current AEDs used in veterinary medicine. Sedation is the most common initial adverse effect that typically dissipates over time.

Dosage and Monitoring The initial dose of 10–20 mg/kg orally q12h is gradually incremented to ≥20 mg/kg orally q8h. The therapeutic range is not well defined and drug monitoring is recommended only to establish the pharmacokinetic pattern of the individual patient.

Drug tolerance over time, known as the "honeymoon effect," can occur. However, wide individual patient drug metabolism may be associated with this phenomenon. As such, this author advocates incremental escalation by 10 mg/kg/dose per week when seizures persist to a maximal tolerated dose. No upper limit dosage exists due to a high therapeutic index (safety) for this drug. A parenteral formulation is available for intravenous loading at 40–60 mg/kg over 15–30 minutes in a 1:1 diluted saline solution.

Third-Generation AEDs

Lacosamide

This is a functionalized amino acid proven to decrease neuronal discharge frequency and synaptic excitability. The postulated mechanisms of action include selective slow inactivation of sodium channels and novel binding to collapsin response mediator protein-2. In humans, the drug is well absorbed, has minimal first-pass effect with predominant renal excretion, low protein binding, favorable drug–drug interactions with other AEDs, and is well tolerated. Clinical trials in humans have demonstrated a comparable decrease in seizure frequency with that of levetiracetam and zonisamide at a dose of 100–200 mg orally q12h. A parenteral formulation is available for intravenous loading. The author has used lacosamide to successfully treat refractory idiopathic epilepsy in dogs at a dose range of 5–10 mg/kg q12h.

Rufinamide

This novel drug is structurally unrelated to any other AED. Its main mechanism of action is related to prolongation of the inactive state of the sodium channel, thus preventing neuronal depolarization. In humans, the drug is absorbed slowly and has low bioavailability. Renal excretion is high and no induction of the hepatic P450 system has been found, although other hepatically metabolized drugs decrease the serum concentration. Of a total of nine double-blinded studies in humans, five revealed a positive effect of rufinamide to treat refractory partial seizures but not generalized seizures. In beagle dogs, the mean terminal half-life ranged between five and 14 hours. In people, dose-dependent adverse effects include sedation, fatigue, and dizziness. Initial dosing in the dog is 20 mg/kg q12h. Serum concentration can be monitored to achieve a therapeutic range of 10–25 μg/mL. A parenteral formulation is not currently available.

Imepitoin

This drug is the first AED that acts as a low-affinity partial agonist at the GABA-A benzodiazepine receptor site. The advantage is that imepitoin is associated with fewer adverse effects of sedation and ataxia, and is less likely to develop functional drug tolerance or physical dependence, compared to the full agonist AED drugs like phenobarbital and diazepam. Imepitoin was recently approved for use in canine epilepsy in Europe and is undergoing clinical investigation for FDA approval in the United States.

A summary of AED therapy is shown in Table 70.1.

Movement Disorders

Cats and dogs can develop a variety of unusual movement disorders that bewilder even the most seasoned clinicians due to the difficulty in determining their neuroanatomic origin and etiology. Movement disorders include a wide range of neurologic disturbances, characterized by either excess (hyperkinesia) or reduced (bradykinesia) movements. These abnormal involuntary movements (AIMs) refer to a number of muscle jerks, twitches, postures, and oscillations that have been classified in human neurology with official terms such as tic, chorea, tremor, dystonia, and myoclonus. Uncontrolled muscle contractions may be of muscle or neuronal origin.

History

The saying "A picture is worth a thousand words" is made for movement disorders. The ability to visualize the characteristics of AIMs should be supplemented with a detailed history to characterize the nature of the movement disorder. Information regarding anatomic distribution, rhythmicity, amplitude, frequency, speed of onset and offset of the movement, relationship to posture and activity, situations that alleviate or exacerbate the movement, presence or absence during sleep, and affected littermates are all essential to help determine the neuroanatomic localization and potential etiology. If the movement disorder is not present at the time of the examination, owners should be encouraged to video the events for future review. Many times, the initial few minutes of observation will solidify the clinical perspective, allowing an accurate diagnostic and therapeutic course of action to proceed.

Etiology and Pathophysiology

The process of initiation and completion of voluntary movement is a complex one that relies on coordination of serial communications between multiple components of the central and peripheral nervous system. Failure of any of these components to complete their assigned tasks can result in either loss of the desired movement or excessive, abnormal movements. A summary of movement disorders in dogs is provided in Box 70.2.

Table 70.1 Summary of antiepileptic drug therapy in the dog

	Clinical pharmacology								
Drug	**$T_{1/2}$ (h)**	**Tss (d)**	**Vd (L/kg)**	**Protein binding (%)**	**Therapeutic range**	**Dosage**	**IV load dose**	**Monitor**	**Guidance advice**
Bromide	20–46 days	100–200	0.45	0	Monotherapy: 1000–3000 mg/L; with phenobarbital at 1500–2500 mg/L	40–60 mg/kg orally q24h	3 % Sodium bromide 800 mg/kg/24h	At 1 and 3 months and then q6 months or q1 month post dose change	Synergistic effect with PB No hepatotoxicity Inexpensive
Clorazepate	5–6	1–2	1.6	85	20–75 µg/mL (nordiazepam)	2–4 mg/kg PO q12h	No	NR	Longer acting than diazepam Complex partial seizure therapy Inexpensive
Felbamate	5–6	1–2	1.0	25	25–100 mg/L	20 mg/kg PO q8h	No	NR	Complex partial seizure therapy Risk of blood dyscrasia Expensive
Gabapentin	2–4	1	0.2	0	4–16 mg/L	10–20 mg/kg PO q8–12h	No	NR	For use with liver compromised patients
Levetiracetam	4–8 and 2–4 with PB	2–3	0.5	<10	Variable	10–40 mg/kg orally q8–12h	30–60 mg/kg/15 min	Only to establish if elimination half-life is very short	Very well tolerated Minimal liver metabolism Use in older patients first
Phenobarbital	24–40	10–14	0.8	40	15–35 mg/dL Optimal level is 20 mg/dL	2.5 mg/kg orally q12h	16 mg/kg/5 min	At 14, 45 and 180 days, then q months or 14 day post dose change	Effective and predictable all seizure types Close monitoring first 3 months is essential
Zonisamide	15–20	3–4	1.5	50	10–40 µg/mL	5–10 mg/kg PO q12h	No	At 2 and 6 weeks then q6 months or 14 day post dose change	Effective and predictable all seizure types Well tolerated Generic available
Lacosamide	ND	ND	ND	ND	ND	5 mg/kg q12h	3 mg/kg/15 min	ND	Well tolerated Very expensive
Rufinamide	5–14	2–4	ND	ND	ND	20 mg/kg PO q12h	No	At 1 week and q6 months	Well tolerated Very expensive

IV, intravenous; ND, not determined; NR, not recommended; PB, phenobarbital; PO, by mouth (*per os*).

Box 70.2 Classification of hyperkinetic movement disorder types

Neuromuscular disorders
- Myotonia
- Tetany and tremor
  - Hypocalcemia
- Fasciculations
  - Benign
    - Exercise
    - Stress
  - Toxicity
  - Metabolic: hypercalcemia
  - Other causes of neuropathy
- Myokimia
- Environmental (hypothermia)

Central nervous system disorders
- Noncerebellar
  - Myoclonus
    - Spinal
    - Proprioceptive
    - Epileptic
    - Toxicity
  - Tetanus
  - Tremor
    - Essential
    - Toxicity
    - Idiosyncratic drug-induced
    - Metabolic
      - Hypoglycemia
      - Hepatic or uremic encephalopathy
    - Degenerative disease
- Cerebellar-related tremor disorders
  - Congenital
    - Neonatal syndromes
      - Hypoplasia
      - Malformation
      - Granuloprival degeneration
      - Hypo-dysmyelinogenesis
      - Axonopathy
    - Postnatal syndromes
      - Abiotrophy
      - Lysosomal storage diseases
  - Acquired
    - Inflammatory
      - Infectious
      - Immune-mediated
    - Neoplasm
    - Vascular/traumatic
    - Toxin
    - Idiopathic

Hyperkinetic Movement Disorders

Myotonia

Myotonia is a sustained muscle contraction with delayed relaxation. Myotonia congenita has been reported in the chow chow and miniature schnauzer dog breeds, and seen sporadically in a number of other breeds. The disease is due to a failure of normal myocyte chloride conductance resulting in delayed muscle hyperpolarization, and therefore delayed relaxation. As an inherited autosomnal recessive disease, puppies are affected from birth. Clinical signs are seen within the first few months of life and characterized by a stiff, "sawhorse" stance upon ambulation, with improvement in gait as exercise time increases. Some dogs may suffer from dysphagia and respiratory problems due to contraction of the tongue and oropharyngeal muscles. Affected dogs have hypertrophied glossal and proximal appendicular muscles that exhibit percussion dimpling upon being struck with a percussion hammer.

Electromyographic recordings demonstrate the classic myotonic discharge of a high-frequency waxing-waning spontaneous discharge that produces a "dive-bomber" or revving motorcycle sound. Muscle biopsy is typically normal. Treatment revolves around avoiding excessive exercise in the cold and maintaining a normal exercise routine, as drug therapy has not been shown to be effective.

Tetanus and Tetany

Tetanus is a continuous sustained extensor muscle contraction. The cause is the tetanus toxin released by *Clostridrium tetani* bacterial infection of domestic animals. The disease occurs when the tetanus spores localized to an anaerobic environment, such as a necrotic wound, transform into the toxin-producing form. The exotoxin, tetanospasm, travels from the infected site via peripheral nerves to the central nervous system. The toxin prevents the release of the inhibitory neurotransmitter glycine from interneurons in the spinal cord and brain, resulting in excessive excitation of brainstem and motor neurons.

Both cats and dogs are fairly resistant to tetanus. When infected, they can exhibit an extreme stiffness progressing to extensor rigidity of all limbs, spastic facial muscles and trismus within 5–10 days of infection. A "grimacing" expression with the ears pulled back is usually seen. Occasionally, localized tetanus may affect only a single limb or be confined to the facial muscles. Many

animals are hypersensitive to external stimuli. The diagnosis is based predominantly on a history of recent wounds and clinical signs. Initial treatment consists of aggressive wound debridement, parenteral penicillin or metronidazole treatment, muscle relaxant therapy (diazepam constant-rate infusion at 0.3 mg/kg/h or pentobarbital 3–10 mg/kg IV to effect) and nutritional support. Tetanus antitoxin (100–1000 IU/kg IV) has been reported to reduce the duration of clinical effects. A test dose of 0.2 mL SC should be given first to test for anaphylactic reaction. Careful attention should be given to hydration and nutritional support, as the trismus can prevent adequate fluid and food intake. Complete remission of clinical signs will usually occur within several weeks to months.

Tetany is a variable and intermittent extensor muscle contraction. It may accompany both central and peripheral nervous system diseases. In dogs, tetany is most commonly seen with hypocalcemia-associated parturition or hypoparathyroidism. Total calcium is typically below 7.0 mg/dL. Dogs will often suffer from an inability to rise, extensor muscle contractions, and hyperthermia (from muscle contractions). Secondary hypoglycemia may also be seen due to the excessive muscle movements. Treatment is focused on initial muscle relaxation with benzodiazepines, followed by calcium and vitamin D supplementation.

Myoclonus

Myoclonus is defined as a sudden, rapid, involuntary muscle movement of short duration caused by active muscle contractions (positive myoclonus) or pauses in muscle activity (negative myoclonus). Classification can be by clinical presentation, site of origin, or etiology. Reflex myoclonus to auditory stimuli has been reported in the retriever dog breeds. Spinal myoclonus arises from abnormal neuronal discharges originating in the spinal cord and is of two main types: segmental and propriospinal. Segmental myoclonus can occur in canine distemper-infected dogs, producing a repetitive, myoclonic jerk motion of one or more limbs, even during sleep. Epileptic and drug-induced myoclonus in dogs are examples of an etiologic classification.

Fasciculations and Myokimia

Muscle fasciculations are spontaneous contractions of muscle fibers within a motor unit and arise from ectopic electrical activity in the distal axons. Fasciculations typically are the manifestation of irritability of the neuronal cell body (motor neuron) or its accompanying axons. As such, they are most often associated with motor neuron disease and peripheral nerve disorders. Fasciculations can be more readily observed in the distal appendicular muscles and the tongue but can be difficult to detect in more obese animals. One can usually detect a fine "rippling" movement of the muscle as a sign of fasciculation.

The differential diagnoses of muscle fasciculations range from the benign to the more severe neuromuscular disease. Benign, or contraction, fasciculations can be seen after strenuous exercise and possibly in very tense animals. Other transient muscle fasciculations can be associated with hypercalemia, hypomagnesemia, and certain toxic drug reactions, to include theophylline, terbutaline, caffeine and methylxanthine (chocolate toxicity), and anticholinesterase agents (i.e., pyridostigmine and neostigmine used for the treatment of myasthenia gravis). Fasciculations associated with neuromuscular disease are most likely to be present after the onset of clinical signs of weakness. Degenerative feline and canine motor unit disease and more advanced cases of distal axonopathy in the dog are conditions that are more likely to be associated with muscle fasciculations.

Myokimia is a pattern of abnormal muscle contraction that produces a "rippling" or "writhing" appearance of the area involved. The change is the result of spontaneous discharges of large motor units. Myokimia is an indication of neuronal disease followed by sprouting of the motor unit territory in response to the denervation. Myokimia or myokimia-like syndrome has been described in Jack Russell terriers and is associated with hyperthermia and collapse.

Tremor Syndromes

A number of tremor syndromes have been described in affected humans that are also seen in small animals. Tremor is defined as a rhythmic oscillation of a body part and classified according to its anatomic distribution, frequency (tremors/s, or Hertz) amplitude (fine or coarse with increasing severity), presence at rest, standing (posture), or movement or performance of specific tasks (intention), The degree of tremor (amplitude) is often variable, and can be exacerbated with emotional (anxiety) and physical activity and stimulant drugs (e.g., caffeine). The two main types of tremor are known to occur either at rest or with action. Rest tremor describes an involuntary, rhythmic oscillation of a body part completely supported against gravity. This tremor could be seen in a leg with the animal lying down and not supporting weight. Action tremor occurs during voluntary contraction of skeletal muscle and is classified as postural, kinetic, isometric or task-specific. Kinetic tremor describes oscillation during guided voluntary movement, also known as an intentional tremor, and is the most common type seen with cerebellar disease in small animals.

Essential Tremors

Physiologic and essential tremor syndromes are the most common in people and can occur in older dogs, in

particular aging terrier breeds. In dogs, it is a pure clinical syndrome characterized by progressive action tremor of pelvic limbs, starting with posture that worsens with activity and excitement. Severity can range from barely perceptible tremor to altered gait and balance problems. Signs can progress as the dog ages.

Tremor Associated with Neuromuscular Disease

Tremor attributed to weakness is almost always associated with underlying nerve disease. Most likely, this type of tremor is an exaggeration of the normal physiologic tremor that results from the synchronized discharge of enlarged motor units in patients with a reduced number of surviving motor neurons. Dogs with advanced peripheral neuropathies can present with this type of tremor in the pelvic limbs. The tremor is exaggerated after exercise and while standing. Other conditions that directly affect nerve function with this type of tremor include compressive neuropathy from lumbosacral disk disease or stenosis, nerve sheath tumors, and other mass effects or entrapment syndromes involving the nerve.

Drug-Induced Tremors

Drug-induced tremor has been reported in the cat and dog. Predictable tremor can be seen with stimulant toxicity (e.g., caffeine, amphetamines, cocaine, etc.). Other potential drugs that have induced tremor in humans include valproic acid, amiodarone, procainamide, and lithium. Tardive dyskinesia represents a wide variety of involuntary movements in humans, including chorea, dystonia, akathisia, myoclonus, tremor, and stereotypies. Stereotypy, or rhythmic involuntary movements, is the most common manifestation resulting from exposure to dopamine receptor-blocking agents, such as phenothiazine (e.g., acepromazine) or antiemetic drugs (e.g., metoclopramide).

Cerebellar-Related Tremors

By far the most common cause of tremor in small animals is cerebellar syndromes and disease. Cerebellar diseases are often associated with a conglomeration of signs related to abnormal motor activity to include any or all of the following: tremors, bilaterally symmetric ataxia without paresis, dysmetria, vestibular signs (head tilt, nystagmus, falling), absent menace with preservation of vision, and pupillary changes. An altered resting posture is often present, with affected animals demonstrating truncal ataxia (swaying of the body back and forth or side to side) and compensatory broad-based stance for balance, known at titubation (cerebellar postural tremor). Cerebellar tremors are associated with diffuse cerebellar cortical diseases. These intention tremors are characterized by a fine head tremor that worsens with initiation of voluntary head movements. The more acute-onset diseases affecting the cerebellar cortex usually result in more pronounced tremor disturbances. Severe action-related tremors may affect the entire body, with complete loss of all muscular coordination, and failure to posture and prehend food. Ensuing hyperthermia, rhabdomyolysis, and related complications from continuous muscle activity require that these patients be aggressively treated on an emergency basis (see later). Fortunately, many "pure" cerebellar diseases can be treated and/or compensated for by the patient.

Cerebellar syndromes associated with tremor can be divided into congenital and acquired diseases (see Box 70.2). Congenital neonatal syndromes represent diseases of the newborn animal in which the clinical signs are present from birth and nonprogressive. In contrast, the clinical signs of congenital postnatal diseases begin in the pediatric animal after birth and are slowly progressive. Acquired cerebellar diseases can be either acute or chronic in onset, with rapid progression most commonly seen with inflammatory diseases and toxic exposures (e.g., mycotoxins, metaldehyde, macadamia nuts).

Diagnosis

The diagnostic approach to an animal with AIMs starts with an evaluation of whether the movement disorder is hyperknetic, hypokinetic or paroxysmal (Figure 70.2). The next step is to determine if the animal exhibits any signs of tremor of the head, neck or other areas of the body. Animals without tremor should then be evaluated for signs of excessive rigidity or stiffness. Constant extensor muscle rigidity is more likely to be a sign of tetanus, while variable extensor muscle rigidity is associated with tetany. An initial metabolic evaluation of a complete blood count, serum chemistry panel, ionized calcium, and creatine kinase should be performed. Tetanus is diagnosed predominantly on clinical signs and history, while tetany is diagnosed typically on the presence of hypocalcemia or other metabolic disorder.

If no extensor muscle rigidity is detected, then signs of abnormal muscle movement of myotonia, fasciculation, or myokimia should be suspected. These signs are all indicators of underlying neuromuscular disease, and as such merit further specific diagnostic testing for either peripheral neuropathy or myopathy. Again, an initial metabolic evaluation of a complete blood count, serum chemistry panel, ionized calcium, and creatine kinase should be performed. The next level of testing would be electrodiagnostic evaluation with electromyography and nerve conduction testing. Electromyography (EMG) tests the stability of the muscle membrane.

If tremor is present as part of the history or clinical examination, then the next step is to determine if any paresis is present. Care must be taken not to confuse

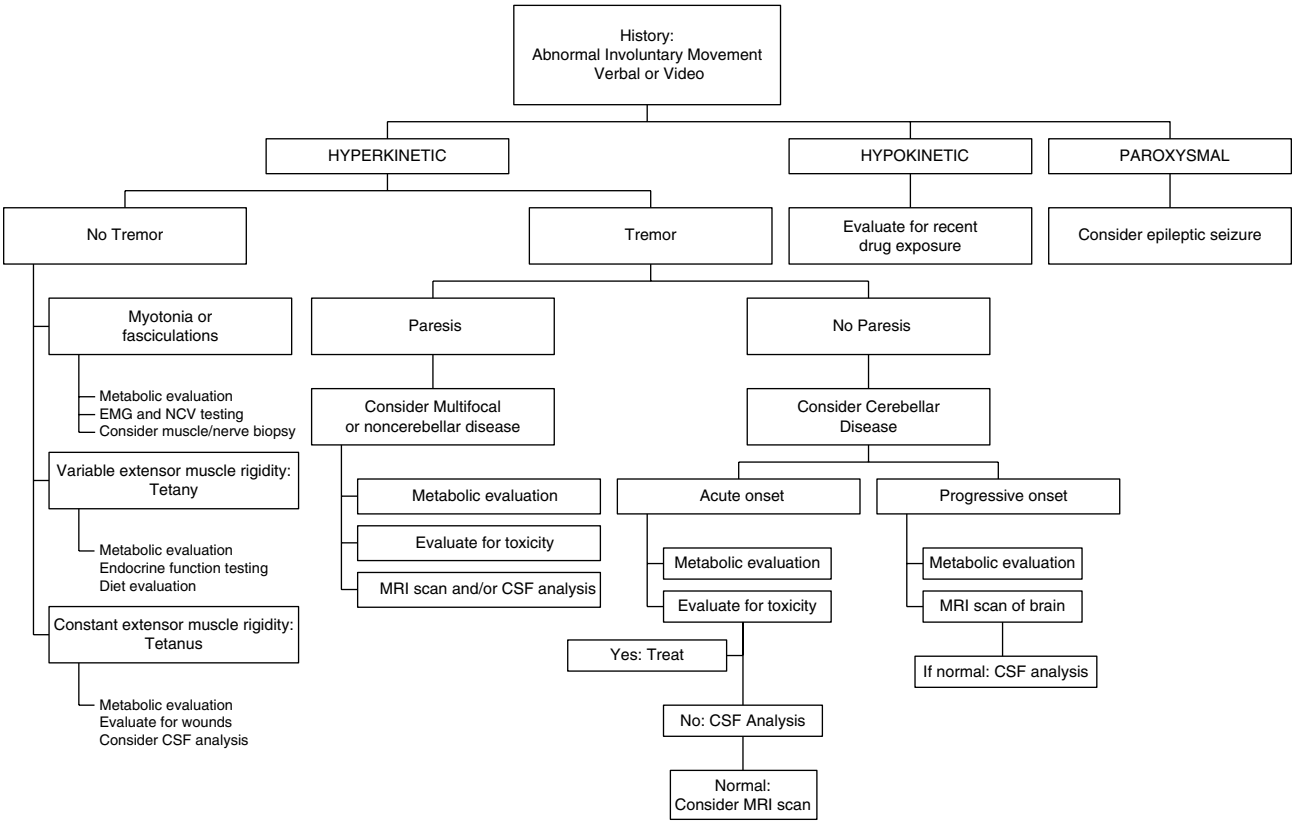


Figure 70.2 Diagnostic paradigm for hyperkinetic movement disorders.

weakness with falling from incoordination. A reliable test is to hop an animal on each leg individually to see if it will collapse on that leg during testing. A weak animal will not be able to support weight on that limb, while an uncoordinated one will. If paresis is present, then one should consider either a multifocal or noncerebellar central nervous system disease. A history of possible toxicity exposure should be ruled out prior to pursuing more advanced testing. If the metabolic evaluation is normal as stated above, then a MRI scan of the brain and/or spinal cord with possible cerebrospinal fluid (CSF) analysis is warranted to evaluate for the underlying etiology.

If paresis is not present with the tremor syndrome, then it is most likely that the animal is suffering from a pure cerebellar disease process. Acute onset of clinical signs is now more suggestive of either a toxic reaction or inflammatory disease process. If toxicity is documented, then no further diagnostic testing may be needed, and symptomatic therapy can be instituted. If toxicity cannot be documented, then a CSF analysis is recommended. If the CSF is normal, then MRI scanning of the brain may be necessary. If the disease process is more chronic and progressive in nature, then the patient should be evaluated for a possible mass lesion of the cerebellum with an MRI scan prior to collection of CSF for analysis.

Treatment

The goal for the control of tremors in small animals is to determine the etiology, remove any inciting cause (toxin or iatrogenic), and provide immediate and prolonged symptomatic relief for acquired diseases. A number of treatments for essential tremor have been proposed for people, with varying results. First-line treatments useful in the dog include phenobarbital at 2.5 mg/kg PO BID, or a beta-adrenergic antagonist (propranolol 2.5–10 mg PO BID to TID). Benzodiazepines appear not be effective in humans or dogs (personal experience). Topiramate, has recently been shown to be efficacious in refractory essential tremor cases in humans at a dose range of 100–200 mg/day.

Recommended emergency treatment for acute onset of suspected acquired tremor disease should be based on an IV loading dose of diazepam or midazolam at 0.5 mg/kg IV followed by constant-rate infusion (CRI) of either drug at 0.5 mg/kg/h in 0.9% saline at 1.5 times the maintenance fluid rate. This situation can be life-threatening and requires a rapid therapeutic approach. Adjuvant therapy to stabilize hyperthermia should be given.

Further Reading

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71

Disorders of the Forebrain

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Anatomy/Function

The forebrain, also known as the prosencephalon, encompasses the two cerebral hemispheres, together with the diencephalon (the most rostral part of the brainstem, itself consisting of the thalamus, hypothalamus, and epithalamus). It is regarded as a region of the brain separate from the rest of the brainstem because it is separated in part by the tentorium cerebelli from the other main compartment within the cranial vault, the caudal fossa. In addition, the forebrain is responsible for those functions in both animals and humans which are commonly thought of as the "higher" functions: memory, behavior, personality, learning, and integration. It is the forebrain that receives information from the outside world, integrates it with memory and other functions, makes decisions based on this information and predicts the outcomes of those decisions in order to select the most appropriate one. Anatomically, this occurs within what are known as the association areas. Rather than being a distinct area of the brain, the association areas are a dense, interconnecting network of interneurons with short axons and widespread dendrites that essentially have no beginning and no end. In dogs and cats, the association areas represent approximately 20% of the cerebral cortex compared with approximately 85% in humans.

The other main areas within the cerebral cortex are the projection areas. These regions are the primary sensory and motor cortex (responsible for receiving sensation and generating motor program output), the primary visual and auditory centers (for receiving vision and hearing), and the rhinencephalon (responsible for receiving olfactory information – evolutionarily this is the most primitive part of the brain).

Sitting between and below the cerebral hemispheres, and connecting them to the rest of the brainstem, is the diencephalon. The most important functional components of the diencephalon are the thalamus, a major gateway for all information entering and leaving the cortex, and the hypothalamus, which houses higher control over the major endocrine systems such as the pituitary–adrenal axis and thyroid function, amongst others, as well as regulating temperature, appetite, and sodium homeostasis.

The clinical significance of these anatomic structures is that disorders affecting the forebrain result in the clinical signs detailed in Table 71.1.

Etiology/Pathophysiology

Lesions within the forebrain can arise as one of a number of pathologic processes, often categorized using the DAMNIT-V system (Degenerative, Anomalous, Metabolic, Neoplastic/Nutritional, Inflammatory, Traumatic/Toxic and Vascular). A complete list of differential diagnoses is provided in Box 71.1.

It is important to note that clinical signs are dependent not on the nature of the lesion/disease, but on where it arises (and how rapidly). A patient presenting with signs of right-sided forebrain disease (e.g., circling, unilateral blindness in the left eye with normal pupillary light reflexes, left-sided proprioceptive deficits) may be suffering from any one of the following diagnoses: an ischemic infarct, a primary brain tumor, granulomatous meningoencephalitis, or a bacterial abscess. For this reason, details of history and signalment are extremely important to collect since they provide the only way of narrowing this list of differentials.

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Table 71.1 Clinical signs of forebrain disease

Clinical sign	Notes
Seizures	Can occur with lesions in the cerebral hemispheres, thalamus or hypothalamus
Propulsive walking	
Circling	Patients with forebrain disease circle towards the side of the lesion, but without signs of vestibular disease (no head tilt or nystagmus present)
Head pressing	
Obtundation	Obtundation describes decreased responsiveness to normal stimuli. This is often a sign of bilaterally symmetric, global cerebral hemisphere disturbance. Further disturbance of level of consciousness (i.e., stupor or coma) is more likely to signify the presence of a brainstem lesion
Contralateral cortical blindness	Absent menace response (as a result of absent vision) with normal consensual and indirect pupillary light reflex occurs as a result of lesions in the occipital cortex or affecting the internal capsule, caudal to the level of the lateral geniculate nucleus, on the side opposite the affected eye
Proprioceptive deficits	Patients with forebrain disease often have a relatively normal gait but significant proprioceptive deficits that are only evident on testing or on negotiating stairs or other difficult terrain
Decerebrate rigidity	Decerebrate rigidity (increased extensor tone in all four limbs with opisthotonus) indicates severe, bilateral forebrain disease and is a reflection of functional disconnection of the cerebral peduncles from the brainstem
Hemi-inattention syndrome	This occurs rarely as a result of lesions affecting the sensory cortex and is most commonly evident while eating. Patients with hemi-inattention syndrome will eat one half of a bowl of food, apparently ignoring the other half unless it is rotated 180°. The lesion is situated within the cerebral hemisphere contralateral to the "ignored" side of the body
Behavioral/memory changes	The most commonly noted behavioral and memory changes seen in patients with forebrain disease include loss of toilet training, loss of recognition of family members or toys, and changes in personality
Vestibular signs	Lesions in the thalamus will rarely produce vestibular signs. This is most commonly reported in patients with cerebrovascular accidents

Box 71.1 Differential diagnoses for forebrain disease according to underlying etiology

Degenerative	Lysosomal storage diseases
	L2-hydroxyglutaric aciduria in Staffordshire terriers
Anomalous	Hydrocephalus
	Lissencephaly
	Porencephaly
	Hydranencephaly
	Meningoencephalocele (Dandy-Walker syndrome)
Metabolic	Hepatic encephalopathy
	Renal (uremic) encephalopathy
	Hypoglycemia
	Electrolyte abnormalities: hypo/hypernatremia
	Hypothyroid myxedema coma
Neoplastic	Meningiomas
	Glial tumors:
	Oligodendrogliomas
	Astrocytomas
	Ependymomas
	Choroid plexus tumors
	Pituitary tumors
	Metastatic disease
	Lymphosarcoma
Nutritional	Thiamine deficiency
Infectious/inflammatory	Viral: distemper, feline infectious peritonitis, rabies, Borna disease virus
	Protozoal: *Toxoplasma*, *Neospora*
	Fungal: *Cryptococcus*, *Aspergillus*, blastomycosis, others (pheohyphomycotic encephalitis)
	Rickettsial: Rocky Mountain spotted fever, *Ehrlichia*
	Bacterial: abscess; meningitis
	Parasitic: *Cuterebra*, verminous encephalitis
Inflammatory (noninfectious)	Granulomatous meningomyeloencephalitis
	Necrotizing encephalitides
Idiopathic	Idiopathic epilepsy
Toxins	Lead
	Organophosphate
	Metronidazole
	Cyanide, sodium fluoroacetate, hydrocarbons, other heavy metals
Vascular	Hemorrhagic and ischemic infarcts
	Feline ischemic encephalopathy

Degenerative and Developmental Causes

Storage Diseases

There are a large number of diseases caused by congenital deficiencies in the enzymatic pathways that are involved in degrading lysosomal waste products within cells. The biochemical pathways involved are complex but the majority of described storage diseases involve a deficiency of a lysosomal acid hydrolase enzyme. A deficiency in any one enzyme leads to a build-up of undegraded products within lysosomes in the cell's cytoplasm which ultimately enlarge and cause the death of the cell. Although cells in all body organs are affected, neurons are especially vulnerable since they are postmitotic, permanent cells. Most of these conditions affect young animals at early ages, affect both males and females, and are autosomal recessively inherited. Most commonly, the initial clinical signs are referable to cerebellar dysfunction but two in particular, alpha-fucosidosis and ceroid lipofuscinosis, may show up with signs of forebrain disease initially, including behavioral changes, dullness and vision abnormalities (typically abnormal depth of vision or inability to focus rather than blindness), followed by generalized ataxia, dementia, tetraparesis, tremors, and seizures. Affected breeds include border collies, Tibetan terriers, English setters (ceroid lipofuscinosis), and springer spaniels (alpha-fucosidosis).

In alpha-fucosidosis, the diagnosis can occasionally be made on hematologic examination (40% of lymphocytes may have cytoplasmic vacuoles) or genetic testing. In ceroid lipofuscinosis, skin biopsy and demonstration of autofluorescent pigment may confirm the diagnosis. Imaging studies and cerebrospinal fluid (CSF) taps are typically normal and CSF may be normal or show vacuolated macrophages (alpha-fucosidosis). Generally, these diseases are progressive and nontreatable, with death occurring by the second or third year of life, although gene therapy has been shown to reverse clinical signs in a feline model of alpha-mannosidosis, suggesting gene therapy may one day become available.

L2-Hydroxyglutaric Aciduria

This is a poorly characterized condition reported over the past 10 years in young to middle-aged Staffordshire terriers. Initially reported in the UK, the disease has now been seen worldwide. Clinical indications include vague prosencephalic signs – abnormal behavior, anxiety, difficulty/slowness in learning (owners may describe these dogs as dull), and an abnormal, ataxic gait (difficult to localize). Signs may also include seizures in some cases. The onset of the condition is from 6 months onwards, with both males and females affected and with some dogs presenting in middle age.

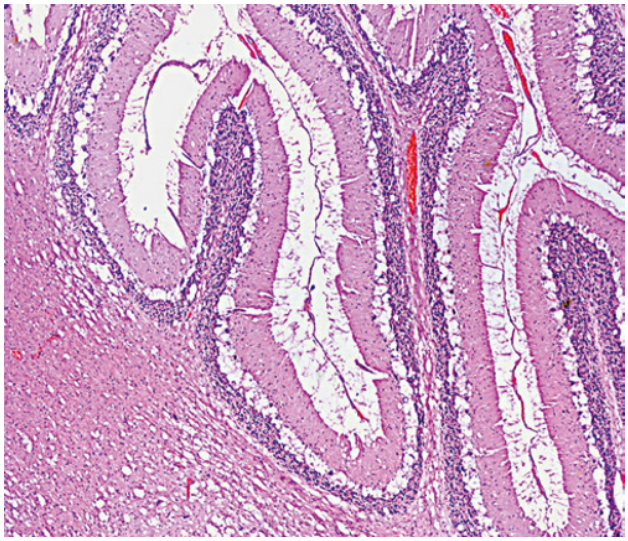


Figure 71.1 Histopathology of the cerebellum of a dog with L2-hydroxyglutaric aciduria. Note the vacuoles in the Purkinje cell layer and molecular layer as well as the deep cerebellar white matter.

The condition is caused by an inborn error of metabolism leading to widespread vacuolation within neurons in the brain with excess secretion of L2-hydroxyglutaric acid in the urine (organic acid). Diagnosis may be suggested by magnetic resonance imaging (MRI) finding (lack of distinction between gray and white matter on T2-weighted MRI scans with diffuse cerebral atrophy) and demonstration of excess organic acid in the urine, and genetic testing is now available (Figure 71.1). Overall, the long-term prognosis is guarded as the condition is untreatable but some dogs with mild signs may live a relatively normal life if seizures are controlled with anticonvulsant medication.

Anomalous Causes

Hydrocephalus

Hydrocephalus is a pathologic enlargement of the ventricles as distinct from ventriculomegaly which describes enlargement of the ventricles which may or may not be pathologic (there is considerable breed-related variation in ventricular size, with brachycephalic dogs such as boxers and bulldogs often having larger ventricles than other breeds). True hydrocephalus may occur due to obstruction in the ventricular system (obstructive or noncommunicating form; most common) or overproduction of CSF from tumors of the arachnoid granulations and choroid plexus (nonobstructive or communicating hydrocephalus; less common).

Causes of obstruction may be either congenital (stenosis of the mesencephalic aqueduct, failure of opening of the lateral apertures of the fourth ventricle) or acquired (secondary to inflammatory disease or neoplasia or other cysts obstructing part of the system). Dilation of the ventricular system upstream of the obstruction results in clinical signs. In mature animals with acquired hydrocephalus, the cause may not be determinable and is often presumed to be the result of clinically inapparent inflammation or hemorrhage within the ventricular system. Enlargement of the ventricular system can also occur with age – as the cerebral cortex tissue volume decreases, so ventricles get larger to take up the extra space available (this is also known as hydrocephalus *ex vacuo*).

Clinical signs predominantly refer to the area affected, most commonly the forebrain but potentially also hindbrain if the fourth ventricle is affected. Seizures, behavioral changes, cortical blindness, dullness, head pressing, and circling are all reported in association with this condition. Occasionally vestibular signs are also present. Diagnosis requires imaging – either MRI or CT, or ultrasound in dogs where an open fontanelle is present for placement of the ultrasound probe. This applies to congenital cases in particular, and often the skull is abnormally large and dome-shaped with divergent strabismus as a result of displacement of the orbits. On all imaging modalities, the lateral ventricles appear abnormally enlarged, and in congenital cases a very thin rim of cerebral cortex may surround these (Figure 71.2). Depending on the level of obstruction, the third and/or fourth ventricle and mesencephalic aqueduct may also be enlarged. MRI may reveal the presence of increased fluid signal (on T2-weighted or FLAIR scans) in the periventricular tissue if the development of the hydrocephalus is acute. The septum pellucidum which normally separates the lateral ventricles on midline may be absent.



Figure 71.2 Dorsal plane CT scan of the brain of a dog with obstructive hydrocephalus. Note the extreme paucity of cerebral cortex.

Treatment is either medical or surgical; reasonable long-term management is possible with corticosteroid therapy at antiinflammatory doses. Carbonic anhydrase inhibitors have also been used in acute stages of disease but cause significant electrolyte disturbances in the long term so are not recommended for chronic management. Recently, some authors have described omeprazole in some cases of acquired hydrocephalus based on experimental studies that suggest it may reduce CSF production by 26% but no evidence supports its use in dogs with hydrocephalus. Surgical treatment is also commonly performed which involves placement of a ventriculoperitoneal shunt via a small craniotomy which transfers fluid via a one-way, pressure-sensitive valve into the abdominal cavity for absorption by mesentery.

Long-term prognosis is generally good, with approximately 75% of cases improving or resolving following shunt placement. However, up to 22% may require subsequent revision to deal with blockage or infection which are common complications

Metabolic Causes

Hepatic and Uremic Encephalopathy

The pathogenesis of hepatic encephalopathy (HE) is poorly understood. Hepatic insufficiency from a number of causes, including acute liver failure, chronic liver failure (including cirrhosis), congenital portosystemic shunts and congenital urea cycle enzyme abnormalities, can all result in secondary prosencephalic disease. As a consequence, various substances pass from the portal circulation directly into the systemic circulation without undergoing detoxification. These include ammonia (probably integral to the pathogenesis of dysfunction), various amino acids (especially the aromatic amino acids phenylalanine, tyrosine, and tryptophan), short-chain fatty acids, mercaptan and various biogenic amines, indoles and skatoles, incriminated in causing HE. Increased intracellular osmolality from too-rapid glutamine accumulation (ammonia is metabolized by astrocytes to glutamine) may result in cerebral edema, which also may play a role in development of cerebral hyperemia and increased intracranial pressure. Glutamine, short-chain fatty acids, aromatic amino acids, and mercaptans are sodium/potassium ATPase inhibitors.

Other theories pertaining to the pathogenesis of HE include perturbed monoamine neurotransmission as a result of altered plasma amino acid metabolism; imbalance between excitatory amino acid neurotransmission (glutamate) and inhibitory amino acid neurotransmission (gamma-aminobutyric acid, GABA); and increased cerebral concentration of an endogenous benzodiazepine-like substance.

Clinical signs relate to prosencephalic disease: behavioral changes (vocalizing, aggression), dullness, ataxia, circling, aimless wandering, blindness, seizures, and head pressing. In severe cases this can progress to stupor or coma. Diagnosis is made on biochemistry panels together with pre- and postprandial bile acid tolerance tests. Ammonia levels can also be measured but are very labile and should only be relied on if quality control standards associated with performing the test are high. If imaging studies are performed, MRI may show (precontrast) T1-weighted hyperintensities in the caudate nucleus, amgydala and hippocampus and/or cingulate gyrus. Treatment is directed at the underlying hepatic disease. Ligation of portosystemic shunts (or coil embolism) is the treatment of choice for animals with congenital shunts.

It is also important to note that when treating animals with seizures secondary to hepatic insufficiency, anticonvulsants that are metabolized by the liver should be avoided (e.g., phenobarbitone, diazepam). Potassium bromide or levetiracetam are preferable as first-line therapy. In addition, animals that have portosystemic shunts ligated may develop seizures shortly postoperatively, for reasons that are poorly understood (and independent of whether the patient has HE prior to shunt ligation). Various causes have been postulated, including the existence of endogenous benzodiazepine-like ligands within the brain of these patients. These seizures are frequently very difficult to control if they occur; potassium bromide at 100 mg/kg PO QID for 24 hours followed by 30 mg/kg PO SID dosing has been recommended but is not always effective, and levetiracetam has also been proposed as a useful treatment. Propofol constant-rate infusions (CRIs) have also been reported to be effective.

In addition to HE, a rare encephalopathy associated with end-stage renal disease is also reported, with clinical signs including depression or stupor, seizures, muscle fasciculations, and myoclonic head-bobbing movements. The diagnosis is usually straightforward, with profound uremia evident on biochemistry panels, usually with accompanying hyperphosphatemia. The underlying cause is unknown, with suggested mechanisms including depressed cerebral oxygen consumption, cerebral hypoxia, increased brain calcium levels, and increased blood levels of parathyroid hormone (PTH). In experimental uremia, the electroencephalogram (EEG) changes associated with disease can be abolished if parathyroidectomy is performed before induction of uremia. Prognosis is poor as a result of the underlying renal disease but treatment with calcitriol (1.5–3.4 ng/kg/day PO) can reduce signs of neurologic depression in animals with chronic uremia, as long as phosphate levels are normal to prevent renal mineralization.

Electrolyte Disturbances

Hypoglycemia

There are two main causes for hypoglycemia: insulin-secreting tumors (insulinomas) of the pancreas, and overdosage of diabetic patients with insulin (especially when not eating). Young puppies (less than 3 months of age) are also prone to hypoglycemia in association with cold, starvation or gastrointestinal (GI) disease, and hypoglycemia may also be seen in animals with portosystemic shunts. Clinical signs associated with hypoglycemia include behavioral changes, weakness, ataxia, collapse, transient blindness, and seizures. Signs are often intermittent, becoming more frequent as the disease progresses, and may be associated with periods of fasting, exercise or excitement. Rarely, polyneuropathies may also occur with hypoglycemia; tetraparesis/plegia, facial nerve signs, hyporeflexia, and hypotonia are the most commonly seen signs associated with these. Central nervous system (CNS) signs occur because neurons are unable to synthesize or store glucose and rely almost entirely on glucose derived from the blood.

Diagnosis of hypoglycemia secondary to insulinoma requires demonstration of hypoglycemia in a fasting blood sample, together with elevated insulin levels (from paired samples). Treatment is directed at removing the underlying cause of hypoglycemia plus administration of dextrose solutions (5%). In animals with inoperable insulinomas, prednisolone and diazoxide can be used but the prognosis is guarded to poor, with survival of 90 days only (vs 12–14 months for resectable tumors).

Sodium Abnormalities

Neurologic signs may be seen in association with both hypernatremia and hyponatremia.

Hypernatremia

Hypernatremia occurs with sodium >156 mEq/L (dogs) or >161 mEq/L (cats). Causes include:

- *excess water loss*: diabetes insipidus (central or nephrogenic), burns, fever, osmotic diuresis (acute/chronic renal failure, diabetes mellitus, diuretics, or IV solute administration such as mannitol, glucose or urea), osmotic diarrhea (lactulose therapy, malabsorption syndromes, infectious enteritides), hot weather

- *excess salt intake*: salt poisoning, administration of IV hypertonic solutions (NaCl), sodium bicarbonate, or saline emetics
- *insufficient water intake*: lack of access, inability to drink, CNS disease resulting in primary adipsia (absence of thirst), mental depression, congenital adipsia.

Marked hypernatremia may induce cerebral signs, such as depression, weakness, irritability, uncharacteristic aggression, confusion, propulsive circling, dementia, seizures, coma, and death as the result of cellular dehydration of neurons. Neurologic signs may not occur until serum Na levels exceed 170–175 mEq/L (>350 mOsm/kg), although the severity of neurologic signs depends especially on the rate of increase, with signs being most severe in animals with rapidly developing hyperosmolality.

Treatment depends on the rate at which hypernatremia develops; overrapid correction can lead to worsening clinical signs (due to a relative hyponatremia and movement of water from the vascular spaces into the brain). Replacement of the water deficit should be undertaken using 5% dextrose with the aim of correction of the deficit over 24 hours (or longer). In animals with acute-onset hypernatremia, correction of Na levels at a rate of 1.0 mEq/h is acceptable. However, if the hypernatremia is more chronic, Na levels should not be allowed to change at more than 0.5 mEq/h. In animals with excess salt intake, diuretics should be given in conjunction with fluid therapy to avoid pulmonary edema.

Hyponatremia

Hyponatremia occurs when serum Na levels are less than 146 mEq/L in dogs (151 mEq/L in cats). Hyponatremia can be further divided into *true hyponatremia* (associated with total body water in excess of Na – serum osmolality is low, <290 mOsm/L) and *pseudohyponatremia* (low Na with normal or increased serum osmolality).

Clinical signs of hyponatremia relate primarily to the rate of onset of hyponatremia. In acute hyponatremia, sodium levels within the brain are relatively normal while sodium levels within the vascular spaces are low. Water flows down its concentration gradient into the brain, producing cerebral edema and raised intracranial pressure (ICP). Signs include generalized weakness, depression, stupor, coma, seizures, and dementia. Treatment is aimed at increasing sodium levels: use hypertonic saline (3–5%) when serum Na <115 mEq/L. The Na deficit is calculated using:

$$\text{Defect}\,(\text{mEq/l}) = (140 - \text{measured Na}) \times \text{bodyweight}\,(\text{kg}) \times 0.3$$

The replacement fluid should be given slowly over 12–24 hours. For animals with hypovolemic hyponatremia, normal isotonic saline can be used. For animals with normovolemic or hypervolemic hyponatremia associated with excessive water intake or renal retention, water restriction (i.e., limiting water intake to less than urine output) can be performed. In instances where severe neurologic signs are seen associated with normal or excessive intravascular fluid, frusemide (2–4 mg/kg IV) can be used to promote renal water excretion.

Chronic hyponatremia may be more difficult to treat since overrapid correction of the deficit can result in a worsening of clinical signs associated with central pontine myelinolysis. Lesions appear in white matter associated with death of oligodendrocytes and loss of myelin, resulting in bilaterally symmetric lesions in the pons and rarely (10% of cases) thalamus, subthalamic nuclei, striatum, internal capsule, amygdala, lateral geniculate body, white matter of the cerebellum and deep layers of the cerebral cortex. The postulated hypothesis is that with chronicity, cells within the brain extrude intracellular electrolytes followed by organic osmolytes ("idiogenic osmoles"), in order to reduce the risk of brain edema. When sodium is replaced intravascularly as part of fluid therapy, osmotic attraction of water out of cells in the brain results in dehydration of brain tissue. Clinical signs occur several days after fluid treatment: ataxia, weakness, hypermetria, visual deficits, depressed menace response (with normal pupillary light response [PLR]), reduced proprioception, exaggerated licking movements, episodic myoclonus, whole-body spasms, obtundation, and tetraparesis. Prognosis for recovery is reasonable; in one study of two dogs, one died but the other recovered over 4–7 weeks. As a result, it is important to stick to the guideline of replacing Na at a rate no greater than 0.5 mEq/L/h.

Neoplastic Causes

Brain Tumors

Tumors affecting the brain can arise as one of several forms.

- Primary tumors arise from cells and structures of the brain itself.
- Secondary tumors arise from cells and structures adjacent to the brain.
- Metastatic tumors arise from spread of a tumor at a distant site.

The most common tumors that affect dogs (and humans) are primary tumors. They occur with a slightly greater incidence than in people (14–15 per 100 000 dogs vs 8–9 per 100 000 people at risk). The most common types include:

- meningiomas
- astrocytomas

- oligodendrogliomas
- choroid plexus papillomas
- pituitary macroadenomas
- ependymomas
- primitive neuroectodermal tumors (PNETs).

Meningiomas are the most common brain tumors seen in both dogs and cats (approximately 45% of all primary brain tumors in dogs). They are thought to arise from arachnoid cap cells of the meninges and occur anywhere along a meningeal surface (e.g., cerebral convexity, falx cerebri, at the cerebellopontine angle, in the olfactory lobe), or within a ventricle. They can occur as a discrete focal mass, as an *en plaque* form or with large cystic components within them. On imaging, they have a broad-based dural attachment and are often associated with hyperostosis of the overlying bone (approximately 50% of the time in cats). Contrast enhancement is typically homogenous. Noncontrast-enhancing areas associated with necrosis are not uncommon in dogs. Histopathologically, they appear benign; in cats, they are often well encapsulated and removable surgically but in dogs tend to creep into the Virchow-Robin spaces surrounding meningeal vessels so microscopic disease usually remains after debulking.

Astrocytomas and oligodendrogliomas together are often referred to as gliomas. Astrocytomas are thought to arise from an astrocyte precursor cell while oligodendrogliomas are thought to arise from an oligodendrocyte precursor, although this is by no means certain. They occur with approximately equal frequency – approximately 17% and 14% of all primary brain tumors in dogs, respectively. Astrocytomas in humans are graded using a four-grade classification scheme created by the World Health Organization, WHO Grade I being a very small subset (pilocytic astrocytomas), grade II encompassing most astrocytomas, Grade III anaplastic astrocytoma, and Grade IV glioblastoma multiforme.

Oligodendrogliomas may occur more frequently in boxers and more commonly in periventricular white matter. They can also spread along CSF pathways. Imaging features of both types suggest an intraaxial tumor (arising from within the brain tissue). On MRI, oligodendrogliomas are frequently hypointense on T1-weighted scans and hyperintense on T2-weighted scans, as befitting their gross mucinous appearance. Astrocytomas tend to be more solid in appearance on imaging with greater and more heterogenous contrast uptake.

Choroid plexus papillomas arise from the choroid plexus of the lateral, third or fourth ventricles. Since they arise from essentially a collection of blood vessels, they tend to enhance very strongly and uniformly following contrast administration on imaging studies. Most are histologically benign but a few can be anaplastic (choroid plexus carcinoma). They can also seed along CSF pathways and implant in other parts of the neuraxis.

Pituitary macroadenomas arise from the hypophyseal stalk and expand dorsally into the thalamus/hypothalamus, and on imaging appearance commonly look like "mushroom clouds."

Ependymomas and PNETs occur relatively uncommonly; ependymomas arise from ependymal cells lining the ventricular system, whilst the PNET's origin is currently unknown.

Secondary tumors most commonly include adenocarcinomas arising from the nasal epithelium and invading the brain, and osteosarcomas, fibrosarcomas or multilobulated tumors of bone arising from the skull that compress the brain.

Metastatic tumors arise from tumors that spread hematogenously (since there is no lymphatic drainage within the brain). Common candidates include lymphoma, metastatic carcinoma (from mammary gland, lung, and GI tract, most commonly) and hemangiosarcoma. Histiocytic sarcoma can also occur in the brain (both as a metastatic tumor and as a primary brain tumor).

Clinical signs associated with tumors reflect their site of origin. In the case of meningiomas, it is common for tumors to have been present for several months before the onset of clinical signs as these tumors grow slowly, allowing the brain to accommodate. Tumors arising in the prosencephalon often cause seizures and cortical blindness. Seizures without interictal abnormalities may be seen with tumors arising on the ventral midline or in the rostral parts of the prosencephalon.

Diagnosis requires either MRI or computed tomography (CT) scanning. CSF taps may show albuminocytologic dissociation (increased protein with normal cell counts) in tumors with significant necrosis, and very occasionally may reveal neoplastic cells (with lymphoma most commonly, but also metastatic carcinomas and very occasionally with oligodendrogliomas or choroid plexus papillomas).

Treatment requires surgical debulking (where location allows) followed by irradiation with megavoltage sources. Typical hyperfractionated dose schedules include 2–3 Gy daily doses up to a maximum of approximately 50 Gy. Survival times in dogs are reported to approach a median of two years, with some patients living three or four years following diagnosis. At present, there is little evidence to support different treatment modalities for different tumor types, with the exception of meningiomas in cats, for whom surgical debulking alone often results in survival times of up to 4–5 years. However, in people some tumor types (particularly oligodendrogliomas) are chemosensitive, associated with particular patterns of genetic rearrangements in these tumors (loss of heterozygosity of the short arm of chromosome

1 and the long arm of chromosome 19) and it may be that in the future the same features may be identified in canine oligodendrogliomas.

Nutritional Causes

Thiamine Deficiency

Thiamine (vitamin B1) deficiency occurs sporadically in dogs and cats either if commercial rations are naturally low in thiamine or if food is treated with excessive heat or sulfites/sulfur dioxide preservatives. One recent report also describes a series of cats fed a commercial dry-food diet without any obvious problems in formulation. All-fish diets in particular are a risk factor since many species of fish contain thiaminases. Thiamine is essential for carbohydrate metabolism (especially glucose) via the Krebs cycle and deficiency leads to increased levels of pyruvate and lactate, together with reduced red blood cell transketolase activity. The brain is particularly susceptible since it is dependent on glucose or lactate-pyruvate for energy.

Clinical signs of thiamine deficiency include anorexia, vomiting, depression, wide-based hindlimb stance, ataxia, progressive paraparesis, crouching hindlimb gait, torticollis, head ventroflexion, circling, generalized tonic-clonic seizures, weakness, opisthotonus, coma, and death. Proprioceptive and menace deficits may be seen, along with tremors and occasionally nystagmus. Some dogs show signs of hysteria. In cats, vestibular signs, head tremors, dilated poorly responsive pupils and absent menace response are common. With severe lesions, semicoma, persistent crying, opisthotonus, limb spasticity, and death may occur. Lesions consist of polioencephalomalacia, bilaterally symmetric in periventricular gray matter, brainstem nuclei (the red nucleus and vestibular nuclei are commonly affected), cerebellar peduncles, and cerebral cortex.

Treatment requires prompt administration of thiamine hydrochloride 25–50 mg/day IM in dogs (10–20 mg IM cats) over several days. Complete remission of clinical signs usually occurs if treatment is initiated promptly, although some cats have been reported to have residual visual and proprioceptive deficits.

Inflammatory/Idiopathic Causes

Noninfectious Inflammatory Diseases

Meningoencephalomyelitis of Unknown Origin

Meningoencephalomyelitis of unknown origin (MUO) in the dog comprises a variety of conditions that are thought to be immune mediated in nature and which involve inflammation of the brain, meninges, and/or spinal cord. MUO is the umbrella term used to encompass granulomatous meningoencephalomyelitis (GME), necrotizing leukoencephalitis (NLE), and necrotizing meningoencephalitis (NME). GME is an angiocentric, mixed lymphoid, infiltrative process that predominantly affects the CNS white matter and leptomeninges. The clinical signs of all these conditions vary depending on those parts of the nervous system where the lesions are most severe. Commonly, however, the clinical picture is one of multifocal, asymmetric, intracranial disease seen in a young to middle-aged (or older) small-breed dog.

Granulomatous Meningoencephalitis

Three forms of GME have been described based on morphologic and clinical characteristics: disseminated, focal, and ocular. The disseminated form typically manifests with acute onset of rapidly progressive clinical signs suggestive of a multifocal CNS disorder whereas focal GME is associated with clinical signs suggestive of a single space-occupying mass with an insidious onset and slowly progressive course. The ocular form of GME manifests with acute onset of visual impairment and dilated nonresponsive pupils caused by optic neuritis. Dogs with the ocular form can subsequently develop CNS lesions.

The cause of GME is unknown, with immune-mediated, infectious, and neoplastic causes proposed as possible etiologies. Historically, GME was once classified within a group of conditions known as reticulosis, the neoplastic form of which has since been reclassified as B cell lymphoma occurring within the brain, suggesting that there are features of the disease which are common to cancer. Other investigations have focused on the nature of the immune system attack on the brain which appears to be similar to a delayed-type hypersensitivity and which involves antibodies directed at astrocytes. So far, efforts to identify an underlying infectious trigger for the immune response have been unsuccessful.

Necrotizing Leukoencephalitis and Necrotizing Meningoencephalitis

Necrotizing leukoencephalitis and NME both started out as conditions identified in certain breeds, with NLE being called Yorkshire terrier encephalitis and NME called pug encephalitis. Since these early reports in specific breeds, an increasing number of dogs of other (and mixed) breeds have been identified with these conditions, including Yorkshire terriers with pug encephalitis and vice versa. The necrotizing meningoencephalitides differ from those in GME in distribution and severity. Both are characterized by extensive necrosis and nonsuppurative inflammation. In NME, the lesions tend to involve more of the cerebral gray and subcortical white matter. The neurologic signs are acute and progressive

and reflect a forebrain disorder, with seizures observed in most dogs. NLE is characterized histologically by multifocal areas of extremely severe mononuclear inflammation surrounding a large malaciac gliotic center, predominantly affecting the brainstem and periventricular cerebral white matter. Brainstem signs with central vestibular dysfunction predominate, although a mixture of forebrain and brainstem signs also occurs.

The etiopathogenesis of GME, NME, and NLE likely is multifactorial: familial predisposition, infectious agents, and immunopathologic mechanisms all may play roles in disease pathogeneses. GME is responsible for up to 25% of canine CNS disease.

Diagnosis and Treatment

A female predisposition for GME has been reported and the disease is most common in young to middle-aged dogs. Most cases of the necrotizing meningoencephalitides described so far have occurred in young and adult animals (6 months to 7 years) with no gender predisposition.

Confirmation of a diagnosis of GME, NME, and NLE requires histopathologic confirmation, and as such is infrequently achieved antemortem. Extraneural signs such as hyperthermia are rare. Blood examination may be normal or reveal a stress leukogram. CSF findings include a pure mononuclear pleocytosis or a mixed cell population (particularly in acute cases), bearing in mind that cytology cannot discriminate between immune-mediated, infectious, and neoplastic considerations for canine meningoencephalitis. Similarly, the absence of CSF abnormality does not rule out the possibility of GME, particularly in dogs pretreated with corticosteroids or where the lesions are not in close proximity to the ventricular system and subarachnoid space. CSF findings in dogs with NME or NLE reveal a moderate pleocytosis with mononuclear cells or mixed cell pleocytosis and mild to marked elevation of protein concentration.

Imaging findings in MUO are nonspecific but can help to support the suspected clinical diagnosis. CT scan may reveal hyperdense lesions after injection of contrast medium intravenously. Most frequently, the diagnosis is made following MRI scans. The most consistent MRI finding in dogs with the multifocal form of GME is the presence of multiple hyperintense T2-weighted (T2W) and fluid-attenuated inversion recovery (FLAIR) lesions scattered throughout the cerebral white matter. Contrast enhancement may be present and may be strong (occasionally with ring enhancement) or mild. Central nervous system lymphosarcoma and, less commonly, glial neoplasms and metastatic neoplasia can present with similar clinical and imaging findings and should therefore be part of the differential diagnosis list. The focal form of GME presents on CT or MRI as a nonspecific single space-occupying mass. The more characteristic distribution of the lesions observed in breed-specific meningoencephalitis (NLE or NME) may aid in the imaging diagnosis of these conditions.

At present, immunosuppression is the mainstay of therapy for MUO. Most clinicians treat with corticosteroids together with adjunctive immunosuppression, although whole-brain radiation therapy has also shown promise in the treatment of GME in some cases (supporting the hypothesis that neoplasia might be part of the etiopathogenesis). Response to corticosteroids is variable and may be temporary, but dogs often have a favorable initial response to steroid monotherapy. Typically, secondary immunomodulatory agents are added once negative serology and PCR results have ruled out other disease.

In a clinical setting, steroid monotherapy may resolve signs associated with MUO in some dogs, but insufficiently or only transiently provides resolution in others. Most studies suggest that longer survival is achieved with additional therapy. The most commonly used additional immunomodulatory drugs include cytosine arabinoside (CA) at 50 mg/m^2 q12h SC for two days (using a regime that involves therapy initially at three-weekly intervals, then reducing to every four weeks, every five weeks, and continuing every six weeks thereafter), ciclosporin at 5–10 mg/kg q12h PO, procarbazine at 25–50 mg/m^2 q24h PO, azathioprine at 2 mg/kg q24h PO for 14 days before tapering to every other day, mycophenolate 10–20 mg/kg q12h PO, and leflunomide at 2–4 mg/kg q24h PO. A prednisone/vincristine/cyclophosphamide (COP) protocol has also been described, although this has not been shown to provide longer survival than a prednisone/CA protocol and is associated with more adverse effects. Treatment is monitored by clinical response and regression of neurologic deficits and occasionally repeated CSF analysis and MRI.

The prognosis for long-term remission in proven cases of GME and the breed-specific meningoencephalitides has been reported as being poor. However, such reports have been limited to histopathologically confirmed cases of GME that died or were euthanized as a result of the severity of their disease, so the poor prognosis in these studies may be biased. Most recent studies have reported several years survival in dogs with MUO with aggressive immunosuppression, and potentially cure, although ultimately other side-effects (predominantly hepatic failure) may be life-threatening.

Infectious Diseases

Encephalitis and meningitis often exist concurrently in dogs and cats with infection of the CNS. Numerous

infectious agents have been incriminated and include viruses (distemper, rabies, parvovirus, parainfluenza, herpes, feline leukemia, feline immunodeficiency virus), bacteria, rickettsia (*Ehrlichia*, Rocky Mountain spotted fever), protozoal (*Toxoplasma*, *Neospora*), fungi (blastomycosis, histoplasmosis, cryptococcosis, aspergillosis, coccidioidomycosis), and spirochetes (Lyme disease, leptospirosis). Adding to this list, a number of parasites have been reported to affect the brain during aberrant migration (*Toxocara*, heartworm, *Cuterebra* larvae) and the incidence of these depends mainly on geographic location. CSF and infectious titers or DNA testing performed on serum or CSF are the most reliable antemortem diagnostic tests for identifying infectious CNS diseases.

Canine Distemper Virus Encephalomyelitis

Canine distemper virus (CDV) is a paramyxovirus that commonly infects the CNS of dogs and other carnivores. Unvaccinated and vaccinated dogs are at risk for this disease, and although the prevalence of infection seems to be decreasing in some countries, sporadic outbreaks have been reported in several countries, particularly where vaccination coverage is incomplete. Systemic signs of disease such as respiratory and gastrointestinal involvement are reported to precede the neurologic signs by 2–3 weeks. However, many dogs have no previous history of disease prior to the onset of neurologic signs. Many dogs probably develop transient CNS infections without concurrent clinical signs. Lesions may be found in gray (polioencephalomyelopathy, PEM) and/or white matter (leukoencephalomyelopathy, LEM). Since the lesions are predominantly demyelinating in nature, it has been proposed as a model for the study of multiple sclerosis. PEM is more frequently seen in immature dogs while a combination of PEM and LEM is more common in mature animals.

Infected dogs can present with a variety of neurologic signs that tend to be progressive. Clinical signs in dogs with chronic CDV encephalomyelitis may have a chronic insidious or waxing and waning course, and are often not associated with systemic signs of CDV. The classic syndrome of distemper myoclonus (repetitive and continual myoclonic jerks that affect the whole body or just one body part with a characteristic 1 Hz frequency) can be pathognomonic.

The diagnosis of CDV can be difficult. CSF analysis is often the most helpful diagnostic test. However, an inflammatory response is often lacking in the acute stage of the disease, with mononuclear pleocytosis more often observed in the chronic stage. Immunofluorescent staining of conjunctival tissues, urine sediment, tracheal wash or CSF leukocytes for CDV antigen is variably successful, but positive results are occasionally obtained in dogs with chronic CDV encephalomyelitis. Identification of neutralizing CDV antibodies in serum is of questionable value in previously vaccinated dogs, and demonstration of CDV antibodies in CSF can be complicated if CSF is contaminated with peripheral blood. Several PCR techniques have been described for the detection of CDV in various tissues and body fluids, some of which are now commercially available, and these can be applied to CSF; this is probably the most specific and sensitive test for the antemortem diagnosis of CDV encephalomyelitis regardless of the clinical form of disease present.

The chronic form of the disease is typically slowly progressive, although clinical signs may be well tolerated for long durations. Therapy is mainly supportive and symptomatic. Overall, prognosis is poor although the disease is not fatal in all dogs and some may recover.

Feline Infectious Peritonitis (FIP)

Two biotypes of feline coronavirus (FCoV) exist: feline infectious peritonitis virus (FIPV) that causes FIP, and feline enteric coronavirus (FECV) that induces mild enteritis from which cats typically recover. FIPV has been shown to arise within individual patients from a spontaneous mutation of existing FECV infection. FIP is a clinical disease that arises due to infection of macrophages by FIPV, which subsequently results in the immune-mediated formation of pyogranulomatous lesions with an affinity for serosal, pleural, uveal, meningeal, and ependymal membranes (surface-related disease).

The neurologic clinical variant of FIP is the most common infectious cause of meningoencephalomyelitis in the cat, as well as being the most prevalent spinal cord disease of cats. Although the effusive form is about four times more common than the noneffusive form, neurologic involvement is more common with the noneffusive (or "dry") form of the disease and develops in cats with humoral immunity, but with partial cell-mediated immunity (immunity sufficient to induce granulomatous inflammatory reaction around virus present in macrophages, but not quite adequate to eliminate the infection). The pathogenesis involves FIP virus inducing a pyogranulomatous and immune complex-mediated vasculitis involving the meninges, ependymal lining, periventricular brain tissue, and choroid plexus of the CNS. As a result, clinical signs most commonly arise as a result of hydrocephalus secondary to obstruction of the ventricular pathways.

Cats with FIP are typically young (<3 years of age), pure-bred, from multiple cat households and the disease is more common in sexually intact males. The main route of infection with FCoV is oronasal from contact with infected feces. Asymptomatic carriers are not common.

Clinical signs most commonly relate to hydrocephalus and associated forebrain syndrome (seizures, cortical blindness, obtundation) although central vestibular signs are often also reported, as the meningitis caused by FIP may be more severe in the ventral brainstem and at the base of the cerebellum, and choroid plexitis and ependymitis are frequently severe in the caudal fossa.

The diagnosis of FIP is challenging, especially when signs are restricted to the CNS. Hematology findings may include anemia, leukocytosis, and hyperglobulinemia. Serum tests for anticoronavirus antibodies have a low specificity and a negative serum titer does not exclude the possibility of FIP-associated neurologic disease because soluble antibodies can form immune complexes and escape detection by standard tests. There is also considerable overlap in titers in cats with and without FIP (some cats with FIP have low titers, while many cats with high titers never develop FIP). The CT and MR abnormalities present in the brains of cats are well described and include meningeal contrast enhancement, choroid plexitis (contrast enhancement), ependymitis, granuloma formation, and obstructive hydrocephalus, most commonly due to blockage of the mesencephalic aqueduct. CSF analysis may reveal a predominantly neutrophilic or mixed cell pleocytosis, but can be normal. CSF total protein concentration is often markedly elevated (>200 mg/dL). Documentation of elevated coronaviral antibody concentrations, especially in cerebrospinal fluid, confirms exposure and is supportive of the diagnosis. However, this result must be interpreted with respect to the integrity of the blood–brain barrier. Positive coronavirus-specific PCR performed on CSF can be used as a relatively reliable antemortem diagnostic tool.

Treatment of FIP is immunosuppressive or immunomodulatory in nature, but the disease should be considered terminal in virtually all affected cats. Corticosteroids, chlorambucil, cyclophosphamide, and interferons have been used with variable efficacy in FIP cases.

Protozoal Encephalitis

Toxoplasmosis and neosporosis are polysystemic protozoal diseases capable of causing heterogeneous signs of peripheral and CNS dysfunction. Natural infection with *Toxoplasma gondii* is more common in cats, but also occurs in dogs. Ingestion of tissue from infected intermediate hosts (ingestion of encysted bradyzoites) is the most common cause of infection in both species. Other forms of infection include fecal contamination and *in utero* infection. With *Neospora caninum*, dogs are affected, most commonly via *in utero* transmission, although they may also be infected by ingestion of intermediate host tissue.

Following acute systemic infection in intermediate hosts in which the organism can be disseminated to many body organs (this phase may be subclinical), tissue cysts form most commonly in the CNS, skeletal muscle, and heart muscle. The parasites are mainly intracellular and subclinical infection may persist for the life of the host, although activation of toxoplasmosis may occur in association with severe immunosuppressive disorders. These protozoal organisms have the potential to cause an extremely variable number of clinical neurologic syndromes. Two main forms are observed:

- encephalomyelitis – neurologic signs associated with protozoal encephalomyelitis are variable and may reflect a focal or multifocal disease process
- *Neospora* myositis-polyradiculoneuritis – this is probably the most commonly reported infectious myositis in dogs and presents with severe pelvic limb paresis and skeletal muscle fibrosis in young dogs, especially those less than six months of age.

A tentative antemortem diagnosis of toxoplasmosis is established in dogs most commonly through elevated IgM titers, IgG seroconversion, or documentation of a positive clinical response to an antiprotozoal treatment regimen. In cats, an elevated serum or CSF IgM titer is considered diagnostic for toxoplasmosis. However, a positive titer can be found in animals previously subclinically infected with either organism and demonstration of a rising titer with serial (monthly) testing may be required to confirm a diagnosis of active disease. Neosporosis is diagnosed by serologic detection of indirect fluorescent antibody titers in dogs. Demonstration of tachyzoites of either organism in various tissues or body fluids is also diagnostic but rarely achieved. CSF analysis typically demonstrates pleocytosis with a mixed population of neutrophils and the presence of small and large mononuclear cells. Eosinophils may also be seen. Sensitive PCR assays have been reported for the detection of both *Neospora caninum* DNA and *Toxoplasma gondii* DNA in biological samples. Muscle biopsy is indicated in dogs with polyneuropathy/polymyositis and may reveal nonsuppurative inflammation and tachyzoites within myocytes.

Treatment for both diseases is identical. Clindamycin (10–15 mg/kg PO q812h for a minimum of 12 weeks) is the preferred therapy. However, TMS (15 mg/kg PO q12h) in combination with pyrimethamine (1 mg/kg/day PO) may also be effective. Folic acid or brewer's yeast supplementation should be considered (5 mg/dog/day) in animals receiving this latter therapy. The prognosis for survival is fair to good, but recovery of neurologic function may be incomplete in those animals with severe clinical signs. In the author's experience, some cases may require long-term (a year or possibly longer) therapy,

suggesting selective immunodeficiency in some animals contributing to the presence of infection.

Bacterial Meningoencephalitis

Bacterial infection of the CNS is a relatively rare cause of encephalitis and/or meningitis in dogs and cats compared with other species. Bacterial infection of the brain can be the consequence of hematogenous spread (metastasis from distant foci of infection), penetrating injury to the skull (bite wound, bullet, surgery) or direct extension of infection from the middle/inner ear, eyes or nasal sinuses. Infection of the CNS may result in an abscess and/or, much less frequently, collection of pus (empyema) in subdural or epidural locations. Brain abscesses are life threatening due to systemic and local toxicity (in the early stages of cerebritis) and increased intracranial pressure (during/after capsule formation). Clinical signs are largely the result of the inflammatory reaction that the bacteria provoke.

Affected animals can present with a wide variety of neurologic signs of intracranial disease that reflect a focal anatomic diagnosis suggesting a space-occupying lesion or a multifocal syndrome associated with many small microabscesses. These signs are usually rapidly progressive and frequently fatal if left untreated. Fever is present in approximately 50% of cases at presentation. Hematology usually reflects an inflammatory process (leukocytosis with or without left shift) or can be normal. Imaging of the brain (CT or MRI) may be suggestive of an inflammatory process and may reveal a defect in the skull suggestive of a penetrating injury or signs suggestive of otitis media/interna.

Cerebrospinal fluid analysis usually reveals an elevated nucleated cell count, with the majority of cells being degenerate neutrophils, and marked elevation in total protein concentration. Bacteria may be visible in the spinal fluid. In some cases, CSF can be normal or may show nonspecific inflammatory changes. CSF should be cultured if it contains degenerate neutrophils although it is uncommon for culture to be positive. Urine and blood culture should also be considered in animals in which there is no obvious source of infection.

Treatment of abscesses centers around antibiotic therapy, often for long periods, based on culture and drug sensitivity testing of organisms isolated from the abscess. When cultures cannot be obtained, a broad-spectrum antibiotic, such as third-generation cephalosporins and enrofloxacin or metronidazole, can be used. In the early stages antiinflammatory doses of corticosteroids to reduce surrounding edema are indicated, and seizure control with anticonvulsants may be required. Antibiotic therapy should be maintained for several weeks after clinical signs have resolved. Surgical decompression by craniectomy is indicated in cases of brain abscess that do not respond to medical management.

Mycotic Meningoencephalitis

Fungal CNS infections other than cryptococcosis are uncommon in dogs and cats. Small animals with mycotic CNS infections can have neurologic signs that range from peracute in onset to insidiously progressive, and lesion localization is often suggestive of multifocal disease.

Cryptococcus neoformans is the most commonly implicated systemic mycotic agent causing CNS signs in both dogs and cats. Extraneural organ involvement is often present, but may be clinically occult, or absent in some cases. Brainstem disease resulting in signs of vestibular dysfunction is frequently reported. Peripheral vestibular disease has also been reported to be a sequel of cryptococcosis in cats.

The diagnosis of cryptococosis is best established by cytologic or histologic demonstration of the organism, with its characteristic capsule, from tissue aspirates or biopsies, or in body fluids, such as urine or CSF; organisms can be identified in the CSF of more than 90% of dogs with CNS signs. In cases in which organisms cannot be demonstrated, serologic testing using the latex agglutination procedure that identifies cryptococcal capsular antigen is recommended. Serologic testing can be performed on blood or CSF, although CSF is preferred. Latex agglutination testing is generally considered to be both highly sensitive and specific. CT and MRI imaging of the brain in cats and dogs with cryptococcosis have demonstrated numerous and variable abnormalities including single or multifocal mass lesions, meningeal enhancement, intraparenchymal ring enhancement associated with "punch hole" lesions in the gray matter, and choroid plexus enhancement.

The recommended therapy for CNS cryptococcosis is fluconazole (5 mg/kg PO q12h), as this agent effectively penetrates CNS tissues. Intrathecal administration of amphotericin B has also been described. The length of therapy required is often protracted, and serial serologic monitoring has been recommended. Treatment should ideally be continued until clinical signs have resolved, CSF analysis has normalized, and two consecutive titers performed one month apart have been negative. However, relapses have occurred after consecutively negative serum titers, and it has been suggested that when possible, treatment should continue until the patient is seronegative and all previously documented intracranial MR abnormalities have resolved. Newer antifungal agents, such as voriconazole, offer advantages including excellent CNS penetration, a broader antifungal spectrum, and greater potency than either fluconazole or itraconazole, and thus may prove to be beneficial for the treatment of CNS cryptococcosis in dogs and cats.

Vascular Causes

Cerebrovascular Accidents

Cerebrovascular accident (CVA), also known as stroke, is defined as a sudden onset of nonconvulsive and nonprogressive focal brain signs secondary to cerebrovascular disease (any pathology affecting the blood supply of the brain). By convention, these signs must remain for more than 24 hours to qualify for the diagnosis of CVA; if the clinical signs resolve within 24 hours, the episode is called a transient ischemic attack or TIA.

Causes and Pathophysiology

Ischemic strokes result from occlusion of cerebral blood vessels by a thrombus or embolism while hemorrhagic strokes result from rupture of blood vessel walls within the brain parenchyma or subarachnoid space.

Ischemic Stroke

Ischemic strokes have been reported infrequently in the veterinary medical literature when compared with the human medical literature. Suspected underlying causes identified in histopathologically confirmed cases include:

- septic thromboemboli associated with bacterial endocarditis or other sources of infection
- atherosclerosis associated with primary hypothyroidism and miniature schnauzers with hypertriglyceridemia
- aberrant parasite migration (*Cuterebra*) or parasitic emboli (*Dirofilaria immitis*)
- embolic metastatic tumor cells
- intravascular lymphoma
- fibrocartilaginous embolism
- aortic or cardiac embolism.

However, in those cases which are not severe enough to warrant admission to the postmortem room, a concurrent medical condition can be found in just over 50% of dogs. The most commonly encountered conditions are:

- hyperadrenocorticism
- chronic kidney disease
- hypothyroidism
- hypertension.

Chronic kidney disease and hyperadrenocorticism were the most commonly suspected underlying causes for the hypertension in one study. No underlying cause could be identified antemortem in nearly half of the dogs; this type of infarct of unknown origin is referred to in humans as cryptogenic. No age, sex or breed predisposition has been identified in dogs but Cavalier King Charles spaniels (CKCS) and greyhounds appear to be overrepresented.

Reports of ischemic stroke in cats are scarce. The term *feline ischemic encephalopathy* (FIE) has been used to describe cases of peracute onset of clinical signs consistent with a unilateral cerebral or brainstem problem caused by ischemia. Although the cause remains unknown in most cases, some of them have been linked to *Cuterebra* migration. It is believed that the migrating parasite, or the host response to it, leads to vasospasm in the cerebral vasculature (typically middle cerebral artery).

Failure of blood supply (which results in decreased perfusion pressure within one area of the brain) leads to the development of ischemia, progressing to infarction if this is severe and persists. An infarct describes the area of compromised brain parenchyma that results from this process. The initial drop in perfusion pressure may occur either secondary to vascular obstruction that develops within the occluded vessels (thrombosis) or due to obstructive material that originates from another vascular bed and travels to the brain (thromboembolism). Two distinct regions of an infarct can be distinguished: the core, where ischemia is severe and infarction develops rapidly; and the penumbra surrounding the core, which shows a more moderate decrease of cerebral blood flow (CBF), allowing longer durations of ischemic stress to be tolerated. Tissue within the penumbra has the potential for recovery and therefore is the target for interventional therapy in acute ischemic stroke.

Hemorrhagic Stroke

In contrast to the high incidence in humans, intracerebral hemorrhage resulting from spontaneous rupture of vessels is considered rare in dogs and cats. Secondary hemorrhage has been reported in dogs in association with:

- rupture of congenital vascular abnormalities
- primary and secondary brain tumors
- inflammatory disease of the arteries and veins (vasculitis)
- intravascular lymphoma
- brain infarction (hemorrhagic infarction)
- impaired coagulation.

Nontraumatic subarachnoid hemorrhage has been reported in dogs but remains very rare when compared to its occurrence in humans, where aneurysmal rupture is the most common underlying cause.

In hemorrhagic stroke, blood leaks from the vessel directly into the brain, forming a hematoma within the brain parenchyma, or into the subarachnoid space. The mass of clotted blood causes physical disruption of the tissue and pressure on the surrounding brain. This alters CNS volume/pressure relationships with the possibility of increasing intracranial pressure and decreasing cerebral blood flow. In addition, the tissue downstream of the ruptured vessel(s) undergoes ischemia as a result of the loss of blood supply. As the volume of the hematoma

initially develops, ICP typically remains constant due to a system of compensation known as cerebrovascular autoregulation. However, with progressive expansion of the hematoma, these mechanisms become exhausted, after which further increases in the volume of the clot become associated with a dramatic increase in ICP. In severe cases, this increase in ICP causes a decrease in perfusion of the brain and ultimately fatal herniation of the brain at the level of the foramen magnum.

Clinical Presentation

Neurologic signs seen in stroke patients are characteristically peracute or acute in onset and nonprogressive or regressive in their evolution. Initially, deficits observed are usually focal, often asymmetric and ultimately related to the area of the brain involved. The combination of abrupt onset and focal, often asymmetric localization should raise the index of suspicion for vascular disease. The initial signs are then followed by an arrest and regression of the neurologic deficits in all except the fatal strokes, although worsening of edema (associated with the secondary injury phenomena) can result in progression of neurologic signs for a short period of 24–72 hours. In addition, intracranial hemorrhage can present with progression of signs for up to 24–72 hours before regression as a result of reorganization of the hemorrhage and edema resorption.

Neurologic deficits usually reflect a focal anatomic diagnosis and depend on the location of the vascular insult (telencephalon, thalamus, midbrain, pons, medulla, cerebellum). Infarction of an individual brain region is associated with specific clinical signs that reflect the loss of function of that specific region.

Diagnosis

Advanced imaging (CT, conventional and/or functional MRI) is a prerequisite for confirming a diagnosis of stroke, for defining both the vascular territory involved and the extent of the lesion, as well as distinguishing between ischemic and hemorrhagic disease. Imaging studies are also necessary to rule out other causes of neurologic deficit such as tumor, head trauma, and encephalitis.

Computed tomography images are frequently normal during the acute phase of ischemic stroke, making the diagnosis of ischemic stroke using CT an exercise in the exclusion of other differential diagnoses. In part, this is due to the relatively noisy CT images of the brain in animals with a large skull to brain ratio, compared with people. Early CT signs of ischemia can be subtle and difficult to detect even by very experienced readers and include parenchymal hypodensity, loss of gray–white matter differentiation, subtle effacement of the cortical sulci, and local mass effect. By way of contrast, CT is exquisitely sensitive for the detection of acute hemorrhage in hemorrhagic stroke. Acute hemorrhage is evident as a hyperdensity on CT due to hyperattenuation of X-rays by the globin portion of blood, particularly for the first eight days following onset. The attenuation decreases until the hematoma is isodense about one month after the event. The periphery of the hematoma contrast enhances from six days to six weeks after onset, due to revascularization.

Magnetic resonance imaging can be used to identify ischemic stroke within 12–24 hours of onset and to distinguish hemorrhagic lesions from infarction. T2-weighted and FLAIR images are particularly useful in imaging of ischemic stroke since they allow correlation of the lesion with anatomic structures and vascular territories. With these sequences, ischemic infarction appears as a hyperintense lesion. The conformity of an infarct to a vascular territory is an important element in the diagnosis that helps in distinguishing these lesions from other differentials. Ischemic infarcts are limited to the region of the brain vascularized by the affected vessel, and are often wedge-shaped in appearance with resultant sharply demarcated borders. There is minimal to no mass effect associated with these lesions. Changes are best appreciated in the gray matter and are well visualized in deep gray matter structures such as the thalamus and basal ganglia due to their selective vulnerability to ischemia. Contrast enhancement (associated with reperfusion) is not usually seen until at least 7–10 days but the inverse is a useful indicator – lack of contrast uptake in the ischemic region often results in a noticeably darker area on postcontrast T1-weighted scans.

In the case of hemorrhagic stroke, particular characteristics of hematoma evolution are useful in making the diagnosis with conventional sequences. As the hematoma ages, oxyhemoglobin sequentially breaks down into several paramagnetic products – first deoxyhemoglobin, followed by methemoglobin, and finally hemosiderin. The earliest possible detection of hemorrhage depends on the conversion of oxyhemoglobin to deoxyhemoglobin which occurs after 12–24 hours. Whilst oxyhemoglobin provides a signal similar to that of normal brain parenchyma, the iron exposed to surrounding water molecules in the form of deoxyhemoglobin creates a signal loss, making it easy to identify on T2-weighted and susceptibility-weighted sequences. Gradient echo (T2-weighted) sequences are exquisitely sensitive to the disruption of the local magnetic field that this creates and show hemorrhage as dense hypointense regions.

In addition to conventional MRI sequences, several functional MRI (fMRI) techniques have been developed for the early diagnosis of stroke. These include diffusion and perfusion imaging and magnetic resonance angiography (MRA). Diffusion-weighted imaging (DWI) is

used commonly in humans in the diagnosis of acute stroke. DWI sequences detect the random diffusion of water molecules through tissues. When brain parenchyma loses its blood supply, energy delivery to neurons fails and water becomes trapped within cells by cell membranes. This can be detected on DWI sequences as a hyperintense region within the brain representing brain parenchyma in which water diffusion is restricted as a result of this energy failure. In addition to DWI, perfusion-weighted imaging is employed to depict regions of hypoperfusion in the brain and can document the tissue "at risk" (i.e., penumbra) by comparing the results with the findings on DWI. In addition, MRA can noninvasively assess the intracranial vessels of stroke patients.

Cerebrospinal fluid analysis is unlikely to confirm a diagnosis of CVA but helps to rule out inflammatory CNS disease. CSF is variable in dogs and cats with CVA. In most cases, it is either normal or reflects a mild mononuclear or neutrophilic pleocytosis. CSF proteins are occasionally elevated.

Identification of Underlying Causes of Stroke

In the case of presumptive or confirmed ischemic stroke, ancillary diagnostic tests should focus on evaluating the animal for hypertension (and its potential underlying causes), endocrine disease (hyperadrenocorticism, hypothyroidism, hyperthyroidism, diabetes mellitus), kidney disease (especially protein-losing nephropathy), heart disease, and metastatic disease. Diagnostic tests in presumptive or confirmed cases of hemorrhagic stroke should focus on screening the animal for a coagulopathy, hypertension (and potential underlying causes), and metastatic disease (particularly hemangiosarcoma).

Treatment and Prognosis

Once the diagnosis of a stroke has been made, any potential underlying or associated disease should be identified and treated accordingly. Generally, treatment of these patients aims to provide supportive care, maintain adequate tissue oxygenation, and manage neurologic and nonneurologic complications. Nursing management of a recumbent dog will be vital to the success of more specific therapies. Such management includes attention to the prevention of decubital ulceration, aspiration pneumonia, and urine scald, in addition to physical therapy and enteral nutrition provision. More specific therapies are aimed at preventing further neurologic deterioration.

Most cases of ischemic stroke recover within several weeks with only supportive care. Potential underlying causes should be investigated and treated accordingly to limit the risk of recurrences. Definitive therapy in people involves thrombolytic therapy in an attempt to salvage the ischemic penumbra – tissue surrounding the ischemic core in which rapid restoration of the blood supply may reverse the initial damage. However, the window of opportunity for this to occur is approximately six hours, making it very rarely achievable in animals. Monitoring and correction of basic physiologic variables are important, as is maintaining normal blood pressure.

The most important consideration in hemorrhagic stroke is maintenance of cerebral perfusion by treatment of hypotension and elevated ICP, as well as treating the underlying cause if one has been identified. The medical management of dogs with intracranial hemorrhage commonly includes:

- stabilization of the patient (airway protection, monitoring and correction of vital signs)
- assessment and monitoring of the neurologic status
- determination and treatment of potential underlying causes of the hemorrhage
- assessment of the need for specific treatment measures, including management of increased ICP.

The risk of neurologic deterioration and cardiovascular instability is highest during the first 24 hours after the onset of an intracranial hemorrhage, as the space-occupying lesion slowly expands and cerebral vasogenic edema develops. During this phase, if the neurologic status deteriorates, aggressive therapy to control ICP with mannitol (0.25–1 g/kg administered IV over 20 min) or other agents may need to be considered, and in rare cases craniotomy to alleviate cerebral edema.

The prognosis for ischemic or hemorrhagic stroke depends overall on the initial severity of the neurologic deficit, the initial response to supportive care, and the severity of the underlying cause if one has been identified. Most cases of ischemic stroke recover within several weeks with only supportive care and there appears to be no association between the region of the brain involved, the type of infarction (territorial or lacunar), and outcome. However, dogs with a concurrent medical condition have a significantly shorter survival time than those with no identifiable medical condition. Dogs with a concurrent medical condition are also significantly more likely to suffer from recurrent neurologic signs due to subsequent infarcts.

Feline Ischemic Encephalopathy

Feline ischemic encephalopathy (FIE) represents a peculiar variant of cerebrovascular disease. FIE is an ischemic necrosis of cerebral tissue that has been reported sporadically in male and female cats of all ages, especially in summer months in the US. Clinical signs are usually acute in onset, nonprogressive, and variable, and typically suggest unilateral cerebral or brainstem involvement. Signs may include depression, head tilt, anisocoria, circling, seizures, and changes in attitude/

behavior. Clinical signs may be modified or disappear with time and, unlike other forms of cerebrovascular accident, multiple episodes may occur. Hematology, blood chemistries, and skull radiographs are usually normal while MRI reveals classic signs of a major ischemic infarct. CSF analysis may be normal or show mild to moderate elevations in cell numbers (usually monocytic) or protein levels. Lesions are usually unilateral and may involve up to 75% of one cerebral and/or cerebellar hemisphere. The major area of infarction is frequently in the distribution of the middle cerebral artery.

The cause of this enigmatic ischemic condition has been uncertain but clinical similarities between FIE and *Cuterebra* infection of the brain have historically been noted. Intriguingly, at postmortem some of these cats have been found to harbor *Cuterebra* larvae within the cranial vault (commonly within the olfactory bulbs and optic nerves following migration through the cribiform plate) – and some of the changes visualized are associated with the migration track of the parasite. However, much of the vascular compromise occurs in locations distant to the parasite, suggesting an elaborated toxic factor causing disseminated vasospasm and consequent ischemia. It should be noted that although this association has been noted in the US, some cats in other countries in which *Cuterebra* is not found can also be affected with similar ischemic lesions.

Treatment is largely supportive. Prognosis is often favorable since many of the signs seen initially will ameliorate; however, behavioral changes and uncontrollable seizures may persist.

72

Vestibular Disease

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The term *vestibular disease* is used to describe a neuroanatomic localization within the vestibular system of any cause, and therefore, is not a specific diagnosis.

The purpose of the vestibular system is to provide balance by adjusting limb extensor/flexor tone to accommodate for changing head and body positions. This results in controlled and coordinated eye-head-trunk-limb movement with proper postural support.

The structures of the vestibular portion of the inner ear include semicircular canals that are responsible for conveying information regarding acceleration in angular planes, and the utriculus and sacculus which convey information regarding linear acceleration and static head position (relative to gravity). Information from these receptor organs travels via the vestibular portion of the vestibulocochlear nerve (CN VIII) to the vestibular nuclei (four on each side of the brainstem – rostral, caudal, medial, and lateral), through the caudal cerebellar peduncle, to the flocculonodular lobes of the cerebellar hemisphere. The dorsal spinal nerves of C1–3 provide input to head position and balance and can also cause vestibular signs when dysfunctional.

Dysfunction of one or more parts of the vestibular system may result in the signs we classically recognize as "vestibular disease" – a head tilt, nystagmus, walking in circles, ataxia/falling or even rolling, abnormal limb extensor tone, and nausea/vomiting. These signs are due to the vestibular system's extensive connections with various parts of the central nervous system (CNS).

- Projections via the medial longitudinal fasciculus to the nuclei of CN III, IV, and VI which control the extraocular eye muscles. In homeostatic conditions, these connections result in normal physiologic nystagmus (oculocephalic reflex), and with dysfunction, pathological nystagmus.
- Projections via the vestibulospinal tract, to the neck, trunk, and limbs, resulting in appropriate head/neck position relative to gravity and with movement, and appropriate limb tone and position relative to gravity and head position. Dysfunction results in head tilt, and imbalance in extensor tone such that the animal leans or circles to the side with less tone.
- Projections to the vomiting center (in the reticular formation) leading to ptyalism, inappetence, and vomiting.
- Projections to the cerebral cortex to provide conscious awareness of the body's position in space via the thalamus (pathway not well identified), and awareness of dysfunction such that the patient may "feel bad."
- Projections to the cerebellum (via the caudal cerebellar peduncle, in the vestibulocerebellar tracts) which may result in decreased extensor tone on one side of the body and increased tone on the other (leaning).

As with all problems involving the CNS, the location of the lesion, not what caused the lesion(s), determines the signs you see. Therefore, a thorough neurological examination is critical to proper localization and an accurate differential list which, in turn, guides the diagnostic plan.

Peripheral versus Central Disease

For vestibular disease, the first step is differentiating peripheral from central disease. Peripheral vestibular disease is characterized by a head tilt and circling towards the side of the lesion, and pathological nystagmus with the fast phase away from the lesion. Unfortunately, central vestibular disease cannot be definitively ruled out on exam alone. However, any of the following abnormalities can lead to a confident central localization.

- Cranial nerve deficits other than VII or VIII. Deficits associated with VII or VIII alone can be seen with both peripheral and central disease, as can sympathetic dysfunction (Horner syndrome). Involvement of other

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cranial nerves is typically due to brainstem involvement where the cranial nerve nuclei are situated and there may also be concurrent mentation changes due to the diffuse projections of the reticular activating system (RAS) in this location.
- Cerebrothalamic dysfunction – mentation changes, seizures, head turn +/– wide circles, visual deficits, proprioceptive deficits, etc. Signs are due to multifocal/diffuse disease or increased intracranial pressure.
- Cerebellar signs – intention tremors, hypermetria, truncal sway, absent menace with intact vision. Cerebellar lesions produce ipsilateral signs (or bilateral if diffuse/multifocal cerebellar involvement).
- Proprioceptive deficits +/– paresis – proprioceptive deficits may come from a lesion interrupting the flow of information anywhere along the pathway from the cortex through the thalamus and brainstem (which may result in varying degrees of paresis) or from the cerebellum (no paresis).

The presence of one or more of the above signs, by definition, localizes the problem to the CNS. Central disease may be due to a multifocal problem (i.e., infections, inflammatory disease, lymphoma, multiple metastatic lesions), from increased ICP leading to compression of adjacent vestibular structures, or from direct involvement of the central vestibular system.

Examination of the vestibular patient can be challenging, making localization difficult. For example, patients that are profoundly affected by nausea and imbalance often feel/act mentally dull and lethargic. Supporting patients to assess proprioception can be futile when they are rolling and flailing. Finally, it is important to consider any preexisting disease that may suggest two localizations or multifocal disease, such as a history of cervical pain or seizures.

Nystagmus has been classically used to localize vestibular disease as peripheral versus central, but this should be undertaken with caution. Vertical nystagmus is strongly suggestive of, but not definitive for, central disease. Constant, unchanging horizontal nystagmus is associated with peripheral disease.

Paradoxical vestibular disease is associated with lesions in the rostral and medial vestibular nuclei, the caudal cerebellar peduncle, or the flocculonodular lobe of the cerebellum, and therefore it is always central in origin. Lesions associated with any of these neuroanatomic localizations should produce lateralizing signs. Once the side is determined (i.e., side of proprioceptive deficits, hypermetria), if the head tilt/circling is away from the lesion, +/– the fast phase of the nystagmus towards the lesion, then it is considered paradoxical vestibular disease.

Etiology

To ensure a complete list of differential diagnoses, breaking down differentials into larger categories and then fitting specific differentials into those categories will help limit oversights.

- Degenerative
- Anomalous/congenital
- Metabolic
- Neoplasia, nutritional
- Infectious, inflammatory, idiopathic, iatrogenic
- Toxic, traumatic
- Vascular – hemorrhagic or ischemic

In general, acute versus chronic history should help with ranking differentials. Acute histories are more commonly associated with idiopathic disease, vascular events (ischemic vs hemorrhagic), toxin exposure (metronidazole, ronidazole) +/– otitis interna (usually with an associated chronic otitis externa/media). Thiamine deficiency is often acute and can progress rapidly in cats. Of course, there are always exceptions.

Peripheral Vestibular Disease

Anomalous/Congenital

Some animals are born with signs of peripheral vestibular disease, either unilateral or bilateral. Bilaterally affected animals are commonly deaf as well. The exact cause is unknown, although both degeneration of the vestibular nerve and inflammation of the labyrinth have been described. Recent research suggests a possible genetic mutation in a doberman puppy. The signs are often noted when the animal first becomes mobile. Head tilt and ataxia, +/– circling are seen. Bilaterally affected animals may look more "cerebellar," swinging the head back and forth, and have a more generalized appearance to the ataxia. Often pathological nystagmus is not appreciated and physiological nystagmus is frequently decreased/absent in these bilaterally affected patients. Most animals will remain static or improve with time, but deafness is typically permanent. Congenital vestibular disease and deafness are possible in any breed, but reported breeds include Siamese, Burmese, and Tonkinese cats, Dobermans, cocker spaniels, akitas, German shepherds, beagles, and smooth fox terriers.

Primary secretory otitis media is a disease most commonly seen in Cavalier King Charles Spaniels and less commonly in other brachycephalic breeds, such as french bulldogs. It results in a collection of mucoid effusion in the tympanic bulla presumably due to these breeds extreme nasopharyngeal confirmation compromising normal drainage. It is rarely associated with vestibular signs.

Idiopathic

Canine idiopathic vestibular disease is common in older dogs. The history is often an acute onset of head tilt, nystagmus (fast phase away from the head tilt), ataxia/falling/rolling, drooling/nausea, inappetence, and vomiting. The severity can be quite variable, from mild to extreme. There is no specific treatment, but symptomatic therapy with antinausea/antiemetic medications for apparent nausea, fluid support to maintain hydration until they are eating, +/– diazepam (GABA modulator acting centrally to suppress vestibular responses) can help the patient feel better during recovery. Appropriate recumbent care is necessary in nonambulatory patients, especially since they will often lie only on one side. Improvement can be quick (hours) but more commonly takes 1–3 weeks and often there is a residual head tilt. Signs are exacerbated in the dark since visual compensation is the primary means for improved function. It is uncommon, but possible, for idiopathic vestibular disease to recur. However, repeated events should encourage diagnostic testing to exclude other causes.

Feline idiopathic vestibular syndrome can occur in cats of any age and affects outdoor cats more frequently. It appears to be more common in the summer and fall months in the northeastern United States, although this timing is not appreciated in other parts of the country. Clinical signs are similar to canine idiopathic disease, but vomiting is less common. Diagnosis is based on exclusion of other causes of peripheral vestibular disease. Cats also spontaneously recover within a few weeks.

Infectious

Otitis Media/Interna

Ascending infection via the auditory tube can result in otitis media/interna in the absence of otitis externa. Otoscopic exam may not be conclusive in these cases unless there are obvious changes to the tympanic membrane (bulging, rupture). Otitis externa is often present without concurrent otitis media/interna. Therefore, definitive diagnosis of otitis media/interna typically requires advanced imaging. This may not be practical in all cases. Cats with otitis media may also have evidence of Horner's syndrome as the sympathetic fibers pass through the bullae in this species. Since the facial nerve travels near the horizontal external ear canal and by the bulla, severe and chronic ear disease may also result in signs of facial paresis/paralysis if the periauricular tissues are involved. Depending on the severity of the problem, treatment may involve medical or surgical management. Typically, the outcome is better for surgical management with antibiotic/antifungal therapy based on culture and sensitivity results. Clinical signs may still be present after resolution of infection due to permanent nerve damage, including deafness.

Inflammatory

Nasopharyngeal Polyps

A polyp is a fleshy mass composed of granulation tissue covered with respiratory epithelium, that originates from the lining of either the auditory tube or the middle ear. The primary etiology is unknown, but viral and/or chronic inflammatory processes are suspected to play a role. They are most common in cats 1–5 years of age but have been documented in much older cats as well, with an equal distribution in males and females. Polyps can also lead to secondary infection or inflammation of the middle and inner ear, and therefore, patients may present with vestibular signs. Since the mass can also grow into the pharyngeal area, signs of sneezing and gagging may be the presenting clinical complaint. Polyp removal is typically via traction or surgical approach (ventral bullae osteotomy) but recurrence is possible. Rarely dogs are affected.

Cholesteatoma

A cholesteatoma is a nonneoplastic concretion of keratin debris, keratinizing epithelium, and epidermoid cystic structure(s) that is thought to be a rare sequela of chronic inflammation and is reported infrequently in dogs with otitis media. The cholesteatoma results in bullae expansion and secondary osteolysis. Patients often present for pain on opening the mouth, pain on palpation of the ear, +/– peripheral vestibular signs. Surgical intervention is necessary, so it should not be mistaken for primary infectious otitis and managed medically. There are imaging characteristics that can help differentiate it from primary infectious otitis which should prompt surgical intervention. Risk of recurrence after surgery is high. Monitoring with advanced imaging every 6–12 months should be considered.

Neoplasia

Any neoplastic process adjacent to the vestibular anatomy (such as squamous cell carcinoma, adenocarcinoma, osteosarcoma, fibrosarcoma, chondrosarcoma) can potentially result in peripheral vestibular signs. The mass may track along the skull base where cranial nerves exit their respective foramina, resulting in one or more of the following in addition to vestibular signs: facial paralysis, change in voice, stridor, difficulty swallowing, and tongue deviation or dimpling/contracture. If there are no changes in mentation and no proprioceptive deficits or paresis, localization to the peripheral vestibular system would still be suspected (i.e., the process has not yet invaded the cranial vault to any appreciable degree on exam). Advanced imaging and cytology/biopsy would be needed to determine the extent of the disease, treatment options, and prognosis.

Toxicity

Drug toxicity (topical, intravenous, and inhaled drugs) can result in both deafness and vestibular signs by damaging the hair cells or the vestibulocochlear nerve itself. Antibiotics (aminoglycosides, erythromycin, minocycline, topical choramphenicol, etc.), antiseptics (chlorhexidine), diuretics (furosemide), and miscellaneous other agents (salicylates, propylene glycol, ceruminolytic agents, lead, mercury, etc.) are all recognized as causes of ototoxicity in veterinary patients, with aminoglycoside being the most commonly reported cause. NSAIDs are a well-recognized cause of reversible toxicity in people. Early recognition and withdrawal of the medication may limit damage, but by the time signs are recognized, the damage may be permanent. Even when animals do not recover fully from peripheral disease due to ototoxicity, they usually compensate adequately to maintain a good quality of life.

Metabolic

Hypothyroidism is often linked to peripheral vestibular disease, although the association is tenuous. If hypothyroidism is detected in a patient with peripheral vestibular disease, treatment should be considered.

Trauma

Since the vestibular apparatus is housed in the hardest bone in the body, the petrous temporal bone, trauma is not a common cause of vestibular disease. However, blunt trauma, typically hit by car, can result in skull/bulla fractures, hemorrhage in the soft tissues of the middle and inner ear and lead to vestibular disease. Horner's syndrome and facial paralysis may also result from direct trauma or soft tissue swelling/hemorrhage involving the adjacent tissue as they are in close proximity to CN VIII. Treatment for the vestibular signs would be supportive care and time. Resolution of vestibular signs may be incomplete.

Central Vestibular Disease

Brain tumors, stroke-like events, drug toxicities (such as metronidazole and ronidazole), nutritional deficiencies (thiamine), infections (such as distemper, feline infectious peritonitis, *Toxoplasma gondii*, *Neospora caninum*, and fungal infections) or diseases that cause inflammation of the brain (such as granulomatous or necrotizing meningoencephalitis) may all lead to central vestibular disease in both the dog and the cat.

Anomalous/Congenital

Malformations resulting in central vestibular signs may be present at birth but can progress over time due to obstruction of CSF flow either within cystic structures (i.e., arachnoid cysts/diverticuli) or leading to progressive dilation of the fourth ventricle. Arachnoid diverticuli within the quadrigeminal cistern are more commonly associated with seizures if clinical signs are present at all, but vestibulocerebellar signs may be noted. Caudal occipital malformation syndrome (also called a Chiari-like malformation) that leads to a degree of obstructive hydrocephalus and dilation of the fourth ventricle or bulbomyelia may result in central vestibular signs. Severe generalized hydrocephalus can occasionally be associated with vestibular signs because of fourth ventricle involvement, but this would be an uncommon clinical sign. Malformations leading to high cervical instability (i.e., atlantooccipital or atlantoaxial subluxation/luxations) can rarely lead to secondary edema and inflammation extending cranial to involve the vestibular nuclei but caudal nuclei involvement would also be present.

Infection

Otitis can extend through the internal acoustic meatus and result in intracranial disease with compression of the brainstem from abscess formation or even active meningitis/encephalitis, although this is less common. Infectious agents are usually bacterial, but fungal disease is also possible.

Systemic infections involving the CNS or infections apparently isolated to the CNS are uncommon in dogs, with the exception of certain signalments and geographic locations: *Cryptococcus* on the west coast, coccidiodiomycosis in desert locales, histoplasmosis and blastomycosis in the Midwest, to name a few. Infections typically cause multifocal signs that may include the vestibular system.

Young dogs and cats are at higher risk for viral diseases, with distemper and FIP being the most commonly diagnosed.

Neospora and distemper appear to have a predilection for cerebellar involvement which may result in vestibular signs.

Vascular

Vascular events (ischemic vs hemorrhagic) typically have an acute onset, but may appear progressive over a 24-hour period. Causes of vascular events often do not have an underlying identifiable cause, but screening for causes of thromboembolic disease, +/− bleeding disorders, is warranted.

Hypertension, primary or secondary, can lead to vestibular episodes. Many of these cases mimic idiopathic vestibular disease in history and examination findings, but the events will often recur, similar to TIAs in people, and only resolve or improve once hypertension is controlled. In cases where there is an acute onset of vestibular signs that clearly localize to the central vestibular system, the cerebellum is most commonly involved, in

the author's experience. MRI may be normal or show evidence of ischemia within the vestibular system. A normal MRI cannot exclude an ischemic event as the area of compromised tissue may be smaller than the resolution of the MRI (especially in small patients and low field magnets), or sequencing that best highlights tissue ischemia may not be available (software limitations). MRI done in close temporal relationship to the onset of signs could miss lesions that may be evident if done a few hours to days later. Very small hemorrhages or ischemic areas may be missed if gradient echo or diffusion-weighted sequences are not pursued.

Hypothyroidism can result in the formation of atherosclerosis, leading to vascular thrombosis and signs mentioned earlier.

Hemorrhagic vascular events are less common and underlying causes such as thrombocytopenia, clotting deficiencies (rodenticide toxicity, liver disease, etc.), metastatic hemangiosarcoma, and hypertension should be investigated.

Inflammatory

Inflammatory CNS disease (i.e., granulomatous meningoencephalitis, necrotizing meningoencephalomyelitis, and breed-specific encephalitides) is one of the more common diseases neurologists diagnose. Young to middle-aged toy-breed dogs are typically affected, but any age and breed are susceptible. It usually presents as multifocal disease and the patient may have one or more of the following clinical signs: vestibular signs, cervical pain, paresis, cranial nerve deficits, circling, obtundation, seizures. The cause is unknown but may be a combination of genetic predisposition and an antigenic trigger (recent illness, vaccination/medication, environmental antigenic stimulation) resulting in an inappropriate immune system attack on nervous tissue. MRI and spinal fluid analysis are needed at a minimum to determine a diagnosis. Often ruling out infectious disease (i.e., PCR on CSF, serology, cultures, etc.) is necessary as the inflammation may be secondary to another cause. Biopsy would be needed for a definitive diagnosis and, given the invasiveness, risk and cost associated, is not often pursued. Therefore, treatment is based on the signalment, history, and collection of diagnostic results supporting a sterile inflammatory disease process.

As with other immune/inflammatory diseases, treatment involves immunosuppression with one or more medications (i.e., prednisone, cytosar, azathioprine, cyclosporine, etc.) for a prolonged period of time, often months, sometimes years. Response to treatment can be quite variable, but in the author's experience many patients can be weaned off drugs with the less severe forms of disease. Inflammatory granulomas can cause mass lesions that may be mistaken for neoplasia. These granulomas seem to have a predilection for the cerebellar pontine angle, leading to vestibulocerebellar signs, but can occur in other locations as well.

Neoplasia

Neoplastic processes that affect the central vestibular system include those that are commonly found at the cerebellar pontine angle (CPA), such as malignant peripheral nerve sheath tumors of the trigeminal nerve that extend intracranially, meningiomas, chorioid plexus tumors, or ependymomas. Meningiomas, gliomas, round cell tumors, and metastatic disease involving the cerebellum (flocculonodular lobe) or brainstem vestibular nuclei can also result in vestibular signs. Changes in intracranial pressure due to neoplastic mass lesions elsewhere can result in vestibular signs due to brainstem or cerebellar compression (including cerebral herniation under the tentorium cerebelli or cerebellar herniation from the foramen magnum). MRI, +/−CSF, and surgical or CT-guided biopsy are necessary to confirm an antemortom definitive diagnosis of neoplasia. However, most diagnoses of intracranial neoplasia are made on imaging characteristics and treated as such with radiation therapy, +/− chemotherapy with definitive diagnosis only confirmed after necropsy.

Nonneoplastic Mass Lesions

Epidermoid cysts, dermoid cysts, and teratomas are thought to arise from trapped ectodermal embryonic tissue as the neural tube is closing and therefore could be included in the anomalous category. When found intracranially, they appear to have a predilection for the caudal fossa and thus can produce vestibular signs. Other nonneoplastic mass lesions that could produce vestibular signs include arachnoid cysts/diverticuli, inflammatory granulomas, cholesterol granulomas, infectious abscesses/granulomas, parasitic cysts, and hematomas.

Nutritional

Thiamine deficiency (vitamin B1) in carnivores often includes signs of central vestibular disease in addition to cerebrothalamic signs (mental dullness, seizures) and postural changes, cervical ventroflexion (in cats in particular), and paraparesis in dogs. Cat are more commonly affected than dogs and signs can progress rapidly. Unconventional diets (raw fish diets, diets cooked at very high temperatures, diets with sulfur dioxide preservatives) are typically the cause, but even commercial diets can lead to thiamine deficiency. Bilaterally symmetric changes on MRI (most apparent on FLAIR and gradient echo sequences) within the brainstem nuclei (caudal colliculi are most affected) are classic for thiamine deficiency. Histologic changes include petechial hemorrhages, edema, and neuronal necrosis.

Ideally, patient thiamine levels +/– diet thiamine levels would be pursued. Often, supplementation with thiamine and resolution of signs may be the only option. The signs are completely reversible if treated in a timely manner and fatal if untreated.

Metronidazole and Ronidazole Toxicity

Toxicity associated with metronidazole is most often found with high doses (15–30 mg/kg BID) or prolonged therapy even at more conservative doses. Signs vary in severity and often appear more cerebellar than vestibular, but may include vertical nystagmus or ocular tremors, intact vision with absent menace, mild to severe generalized ataxia, possibly progressing to a nonambulatory state with decerebellate posturing, hypermetria in ambulatory patients (sometimes more severe in the PL), kyphosis, and proprioceptive deficits without loss of strength.

Discontinuation of the medication will result in resolution of signs over days to weeks, but treating with IV or oral diazepam (0.5 mg/kg TID 3–5 days) can expedite recovery.

Ronidazole is most commonly used for the treatment of tritrichomonas foetus in cats and toxicity results in similar signs as above.

The mechanism of toxicity is not known. In people, changes on MRI show bilaterally symmetric alterations in the cerebellar dentate nuclei signal intensity and often the vestibular nuclei as well. There is speculation that it may be mediated by thiamine deficiency due to similar MRI changes in patients diagnosed with Wernicke encephalopathy.

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73

Meningoencephalitis and Meningomyelitis

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Etiology/Pathophysiology

The meninges comprise three connective tissue layers that surround the brain and spinal cord: the pia mater, arachnoid mater (these collectively known as the leptomeninges), and the dura mater (or pachymeninx). Inflammation of the meninges, known as meningitis, may remain confined to these structures, or may also involve the underlying brain and/or spinal cord, termed *meningoencephalitis* and *meningomyelitis* respectively.

There are a whole host of infectious diseases that can cause inflammation of the meninges or underlying central nervous system (CNS) in small animals. These include viral, bacterial, fungal, rickettsial, protozoal, and parasitic organisms (Table 73.1). These organisms may infect the CNS as part of a systemic, multiorgan process (e.g, *Rickettsia rickettsia*, canine distemper, *Blastomyces dermatitidis*) although some agents display a notable neurotropism with CNS entry via the bloodstream or nasal passages (e.g., *Cryptococcus neoformans*, *Cladophialophora bantiana*). Within the CNS, these infectious agents may cause clinical signs through a variety of mechanisms. Their presence often results in an immune response with resulting inflammation. Such an inflammatory response can occasionally involve the vasculature supplying the CNS, leading to vascular injury and resulting ischemic or hemorrhagic disease. Inflammation of the ependymal surface and changes in the viscosity of the cerebrospinal fluid (CSF) can result in disruption of CSF flow and obstructive hydrocephalus (e.g., with feline infectious peritonitis [FIP]). Some organisms can infect neurons or glia, causing direct dysfunction or death of these cells (e.g., canine distemper virus).

Despite this large number of organisms that can cause CNS disease, documented infections comprise a very small proportion of small animal meningoencephalitis and meningomyelitis cases. Cats are generally considered more likely to develop infectious CNS disease than dogs, although documentation of infectious agents is still difficult in this species. In dogs, the vast majority of meningoencephalitis and meningomyelitis cases appear not to have a direct infectious cause, and are often termed "sterile" as a result. In these animals, invading immune cells lead to CNS inflammation and resulting clinical signs. Whether these represent a response to an as yet undetected infectious organism, an overactive immune-mediated response to an unknown environmental trigger or a true autoimmune process remains to be determined. However, broad screening studies aimed at detecting previously unknown infectious agents have thus far been relatively unrewarding, and an immune-mediated process appears more likely for the majority of canine cases.

There are several well-recognized syndromes that occur in dogs where infectious agents have not been identified (Table 73.2). Many of these conditions are highly breed associated and a genetic role in their pathophysiology has long been suspected. Such a role has been best investigated in pug dogs with necrotizing meningoencephalitis (NME). Several studies in this breed have shown a strong association of disease with a specific haplotype localized in the major histocompatibility complex (MHC) II region of chromosome 12. This finding resembles what is seen in many immune-mediated diseases in humans, including multiple sclerosis. However, this association probably does not identify a strictly causative mutation, but likely confers an increased risk of disease development, and it is suspected that other factors, such as the presence of a "trigger" to set the disease in motion, also play a role. Interestingly, other dog breeds with NME that develop a histologically identical lesion do not seem to share the same at-risk haplotypes as pugs and clearly more work to define these underlying susceptibilities needs to be done.

The pathophysiology of most canine and feline meningoencephalitides is relatively poorly understood,

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Table 73.1 Infectious agents causing meningoencephalomyelitis in small animals

Category of agent	Examples of specific organisms
Viral	Canine distemper virus, feline infectious peritonitis, feline immunodeficiency virus, rabies, pseudorabies, West Nile virus
Fungal	*Cryptococcus neoformans*, *Coccidioides immitis*, *Blastomyces dermatidis*, *Aspergillus* spp., *Cladophialophora bantiana*
Rickettsial	*Ehrlichia canis*, *Rickettsia rickettsia*, *Anaplasma phagocytophilum*
Bacterial	*Streptococcus* spp., *Bartonella* spp., *Borrellia burgdorferi*, *Leptospira* spp.
Protozoal	*Neospora caninum*, *Toxoplasma gondii*, *Entamoeba histolytica*
Parasitic	*Cuterebra* spp., *Dirofiliaria immitis*, *Baylisascaris procyonis*, *Angiostrongylus* spp., *Prototheca* spp.

and has been sparsely investigated. One exception is steroid-responsive meningitis-arteritis (SRMA), which is a systemic inflammatory condition with a focus of inflammation in the leptomeninges and its associated arteries.

Epidemiology

Environmental conditions and exposures play an important role in the transmission of many of the infectious organisms that cause meningoencephalitis or meningomyelitis. These include housing density and animal-to-animal transmission (e.g., canine distemper virus, FIP), transmission via wildlife bites (e.g., rabies, feline immunodeficiency virus [FIV]), exposure to soil or stagnant water sources (e.g., *Blastomyces dermatidis*, *Cryptococcus neoformans*, *Entamoeba histolytica*), or transmission from insect or arthropod vectors (e.g., *Dirofilaria immitis*, *Ehrlichia canis*, *Rickettsia rickettsia*). As mentioned above, most of the CNS inflammatory diseases seen in

Table 73.2 Presumed noninfectious inflammatory central nervous system (CNS) conditions in dogs

Condition	Breeds predisposed	Neuroanatomic distribution	Typical cerebrospinal fluid results	CNS imaging
Steroid-responsive meningitis-arteritis (SRMA)	Boxer, Bernese mountain dog, beagle, petit basset griffon Vendéen, Nova Scotia duck tolling retriever, Weimaraner	Meninges of cervical region, rarely involves underlying CNS	Marked neutrophilic pleocytosis	Possible meningeal enhancement, may be normal
Granulomatous meningoencephalitis (GME)	Terriers, miniature poodle	Preferentially affects medulla, cerebellum, and cervical spinal cord	Moderate-marked mononuclear or mixed pleocytosis	Meningeal enhancement, contrast-enhancing CNS parenchymal lesions, focal mass lesion possible
Necrotizing meningoencephalitis (NME)	Pug, Maltese, Chihuahua, shih tzu, papillon, Pekingese	Forebrain	Mild-marked mononuclear pleocytosis; occasionally normal	Meningeal enhancement, brain parenchymal lesions with or without enhancement, loss of gray-white matter distinction, mass effect possible
Necrotizing leukoencephalitis (NLE)	Yorkshire terrier, French bulldog	White matter of forebrain and brainstem	Mild-marked mononuclear pleocytosis; occasionally normal	Brain white matter parenchymal lesions with or without enhancement
Idiopathic eosinophilic meningoencephalitis	Rottweiler, golden retriever	Brain usually involved, occasionally spinal cord	Eosinophilic pleocytosis (>20% eosinophils)	Possible meningeal enhancement and parenchymal CNS lesions; poorly described and variable in literature
Generalized tremor syndrome ("little white shaker/shaky dog disease")	Often small white dogs	Likely diffuse CNS	Mild mononuclear pleocytosis or normal	Possible meningeal enhancement, often normal; poorly described in literature
Greyhound meningoencephalitis	Greyhounds	Forebrain (olfactory bulbs, frontal and temporal lobe gray matter, caudate nuclei)	Mild-moderate mononuclear pleocytosis, can be normal	Brain parenchymal lesions with minimal or absent contrast enhancement

dogs have no known infectious etiologies, and are likely immune-mediated processes that occur in individuals with a genetic predisposition after some sort of antigenic "trigger." Such triggers remain unknown at this time but might be related to exposure to environmental antigens or to antigens from infectious agents not involving the CNS (e.g., respiratory or gastrointestinal infection).

Signalment

Although dogs and cats of any age or breed can be affected by inflammatory CNS disease, certain populations are predisposed to its development. Infectious diseases occur more frequently in younger animals, which may be related in part to maturation of the immune system or vaccination failures. As mentioned above and detailed in Table 73.2, many of the apparent noninfectious canine meningoencephalitides have strong breed predispositions, and these diseases also have fairly consistent ages of onset. As a general rule, meningoencephalitis occurs more frequently in young to middle-aged animals. Gender seems to play a minor role in most of these diseases, although some early reports of GME and a more recent study of NME have described a female predominance. In contrast, most of the dogs reported to develop eosinophilic meningoencephalitis have been male.

History and Clinical Signs

The history may reveal important predisposing factors for some of the infectious diseases, including vaccination history, exposure to ticks or mosquitoes, animal bites, ingestion of raw food or carrion, and exposure to soil or stagnant water. Obtaining a thorough travel history may elucidate additional potential differential diagnoses as some of the tick-borne and fungal diseases have clear geographic distributions.

Clinical signs of meningoencephalitis and meningomyelitis typically have an acute onset with progression over time; chronic infection or inflammation of the CNS is unusual. The signs seen are dependent on the region of the nervous system that is involved. Animals with meningitis (including SRMA) typically present for pain, particularly cervical pain, and neurologic deficits are frequently absent or subtle. Patients with forebrain involvement may present with seizures, altered mentation, depressed consciousness, visual deficits, and compulsive pacing or circling. Brainstem disease can result in cranial nerve deficits such as vestibular dysfunction, facial nerve paralysis, pupillary abnormalities, strabismus, dysphagia, megaesophagus or tongue atrophy together with ataxia and paresis of all four limbs. Myelitis also results in ataxia and paresis, together with spinal pain and possibly deficits in segmental spinal reflexes. Postural reaction deficits may be seen with lesions in any of these regions. One hallmark of inflammatory disease of the CNS is that it frequently results in a multifocal distribution of signs (i.e., multifocal lesion localization), which is uncommonly seen with other disease processes.

Occasionally, signs that are very characteristic for a specific disease may be noted, such as distemper "myoclonus" or rigid limb extension due to muscle contractures in dogs with *Neospora caninum* infection. In addition, some infectious diseases may involve multiple organ systems, producing signs referable to the respiratory system (e.g., canine distemper, blastomycosis), bone (*Coccidioides immitis*), integument (canine distemper, blastomycosis), gastrointestinal tract (canine distemper, *Prototheca*) or other systems. Involvement of other systems is not typical for the "sterile" meningoencephalitides, although occasionally polyarthritis is seen in dogs with SRMA.

Diagnosis

A complete blood count may show abnormalities with certain infectious agents, such as thrombocytopenia with rickettsial infections or eosinophilia with some parasite or protozoal diseases. If CNS inflammation is part of a multisystemic infectious or inflammatory process, then a neutrophilic or monocytic leukocytosis may be evident. Serum chemistry may similarly show abnormalities in certain conditions such as hyperglobulinemia with FIP or *Ehrlichia canis* infections or changes indicative of renal or hepatic dysfunction in multisystemic infections. However, in most animals with inflammatory CNS disease, the complete blood count (CBC), serum chemistry, and urinalysis are relatively unremarkable. Although infrequently analyzed, acute phase proteins may show changes in some animals, such as elevations in serum C-reactive protein, fibrinogen or serum amyloid A protein.

A diagnosis of meningoencephalitis or meningomyelitis is most commonly made with advanced diagnostic imaging and analysis of CSF. Conventional imaging tests such as radiography or ultrasound have little role in the diagnostic process outside of screening other organs within the thoracic and abdominal cavities for disease. Myelography is a technique that involves the injection of contrast material into the subarachnoid space, followed by radiography of the vertebral column. Interruptions in the flow of contrast material can result in several imaging patterns indicating mass lesions in

extradural, intradural-extramedullary or intramedullary locations. Although myelography may be abnormal with meningomyelitis if a mass effect or spinal cord swelling is a component of the disease process, these abnormalities are nonspecific and rarely facilitate a definitive diagnosis. In addition, myelography itself results in inflammation of the meninges and spinal cord, which can worsen clinical signs, and so this intervention must be pursued with caution. Therefore, more advanced imaging modalities are preferred for patients with potential inflammatory CNS disease, if available.

Computed tomography (CT) is a technique that utilizes X-rays to produce cross-sectional images of desired anatomic structures. Software packages allow manipulation of images to highlight tissues of varying densities ("windowing") and images can be obtained both before and after the administration of intravenous contrast material, which can highlight areas within the CNS where normal vascular barriers are compromised (e.g., neoplastic tissue, areas of inflammation). Computed tomography can also be combined with myelography to improve visualization of contrast within the subarachnoid space, which increases the diagnostic utility of this latter technique. In animals with meningoencephalitis or meningomyelitis, CT may show areas of hypodensity within the brain or spinal cord parenchyma respectively, corresponding to inflammation and associated edema; these areas often show enhancement after contrast administration. Meningeal enhancement, either occurring alone or in conjunction with parenchymal enhancement, may also be noted. There are some limitations associated with CT imaging, including a relative lack of sensitivity for inflammatory lesions when compared with magnetic resonance imaging (MRI) and the occurrence of a phenomenon known as beam hardening artifact, which compromises imaging of the medulla oblongata due to the thick nature of the adjacent petrous temporal bone.

Magnetic resonance imaging is currently the gold standard for visual evaluation of CNS anatomy and associated disease states. Compared with CT, it has improved sensitivity for the detection of most CNS pathology, including inflammatory diseases. It utilizes a completely novel technology that does not rely on ionizing radiation but rather on placing the patient in a high magnetic field and delivering radiofrequency pulses, which change the movements and behavior of hydrogen atoms (protons) within the patient. As these protons move, they create a magnetic signal that is captured to generate images. As protons are primarily concentrated within water in biologic tissues, the differences in water content between different tissues and different pathologic processes are what determine the contrast within the images generated. The parameters controlling delivery of the radiofrequency pulse and capture of the resulting signal can be adjusted to create many different sequences, which can highlight or remove signals associated with certain tissues or pathologies. Inflammatory lesions generally appear as hypointense on T1-weighted images and hyperintense on T2-weighted images, with some degree of enhancement after contrast administration. Enhancement of both parenchymal lesions and meninges can be seen after intravenous contrast administration. This enhancement varies in intensity and uniformity, and may be influenced by a variety of factors including the degree of inflammatory cell infiltrate, associated tissue edema and the presence of necrotic tissue within the lesion.

The analysis of CSF is an integral part of the diagnostic process for patients with inflammatory CNS disease. Cerebrospinal fluid can be collected from the cerebellomedullary cistern or the lumbar subarachnoid space. Normal CSF has very few leukocytes (0–5/μL), an absence of erythrocytes, and a low protein concentration (0–20 mg/dL). Meningeal, brain or spinal cord inflammation usually leads to increases in leukocytes (pleocytosis) and protein concentration within the CSF. Occasionally, an infectious (e.g., canine distemper) or noninfectious meningoencephalitis or meningomyelitis will lead to an increased protein without a corresponding increase in white blood cell numbers, which is known as albuminocytologic dissociation. Cytologic evaluation of the CSF can also provide valuable information to the clinician. The composition of leukocytes within the CSF can provide clues to an infectious etiology in some cases (e.g., eosinophilic pleocytosis with parasitic and some fungal infections, lymphocytic pleocytosis with viral infections) or can be associated with presumed immune-mediated conditions in others (e.g., neutrophilic pleocytosis with SRMA, mononuclear pleocytosis with NME). In rare cases, infectious organisms can be visualized on CSF cytology (e.g., *Cryptococcus neoformans*).

It must be noted that CSF pleocytosis is not exclusive to inflammatory disease, as such a pattern can also be seen with other conditions, including neoplasia or acute trauma. In addition, albuminocytologic dissociation is a common and relatively nonspecific change seen with compressive, vascular, neoplastic, and degenerative CNS diseases. As a result, CSF evaluation is ideally performed in conjunction with advanced diagnostic imaging (preferably MRI) in order to rule out these other conditions.

Despite utilizing both CNS imaging and CSF analysis, the diagnosis can remain elusive in some cases. The most common scenario is difficulty in distinguishing inflammatory from neoplastic disease. In these situations, obtaining meningeal and/or brain tissue for histologic evaluation may be the best way to arrive at a definitive diagnosis. Brain biopsy is rarely performed for suspected

meningoencephalitis, although advances in stereotactic biopsy systems and minimally invasive methods may help in making such an option more acceptable to both clinicians and the owners of affected animals. As GME, NME, and NLE are diagnoses that can only be made with histopathology, many clinicians will refer to cases of inflammatory CNS disease diagnosed with imaging and CSF analysis as meningoencephalitis of unknown etiology (MUE) or unknown origin (MUO). This designation typically does not include dogs with SRMA, eosinophilic meningoencephalitis, or greyhound meningoencephalitis as these patients have distinctive signalments, clinical syndromes, imaging findings, and/or CSF abnormalities (see Table 73.2).

A variety of assays are available to identify infectious agents within the blood, CSF or other body fluids. These include assays for organism antigens (e.g., *Cryptococcus neoformans*), antibodies generated against the organism (e.g., IgG and IgM for canine distemper or *Toxoplasma gondii*), and polymerase chain reaction (PCR) for organism DNA or RNA. Cytologic findings associated with other body systems (e.g., inclusion bodies in cells from a conjunctival swab in animals with canine distemper) may also aid in the diagnosis of certain infectious diseases and prompt additional testing for suspected organisms.

Therapy

Therapy for meningoencephalitis and meningomyelitis depends on the underlying etiology causing the inflammation, but typically involves antimicrobial, antiinflammatory or immunosuppressive medications. There are no antiviral medications known to be effective or currently recommended for use in small animals with CNS viral infections, and treatment for these patients remains largely supportive. Animals with a documented or suspected bacterial meningoencephalitis are ideally treated with an antibiotic that shows good penetration of the blood–brain and blood–CSF barriers (Table 73.3). Antifungal medications are indicated in some patients, and these also vary in their ability to penetrate the CNS. Doxycycline not only has antibacterial activity with good CNS penetration, but also is the drug of choice for animals with rickettsial infections. Animals with *T. gondii* or *N. caninum* infections may respond to sulfa antibiotics, clindamycin and/or pyrimethamine. Animals with infectious meningoencephalitis often benefit from short-term, antiinflammatory doses of glucocorticoids, although immunosuppressive doses and prolonged administration of these medications should be avoided as they can impair clearance of the infecting organisms and substantially worsen clinical signs.

Table 73.3 Antimicrobial medications for meningoencephalitis and meningomyelitis

Medication	Dosing	Indications	Additional considerations
Potentiated sulfonamides (e.g., trimethoprim/sulfa)	15 mg/kg q12h	Bacterial meningitis, protozoal disease of central nervous system (CNS)	Consider concurrent folate supplementation
Clindamycin	5–25 mg/kg q12h	Bacterial meningitis, protozoal disease of CNS	Penetration of CNS controversial
Doxycycline	5–10 mg/kg q12–24h	Bacterial or rickettsial disease of CNS	
Third-generation cephalosporins	Variable	Bacterial meningitis	
Chloramphenicol	25–50 mg/kg q8h (dog) or 12–25 mg/kg q12h (cat)	Bacterial meningitis	Concurrent use with phenobarbital not recommended
Fluoroquinolones (enrofloxacin, ciprofloxacin)	5–15 mg/kg q12h (ciprofloxacin) 2.5–10 mg/kg q12h (enrofloxacin)	Bacterial meningitis	Penetration of CNS controversial Avoid higher doses in cats due to retinal toxicity
Metronidazole	10–15 mg/kg q12h	Bacterial meningitis (anaerobic)	CNS toxicity possible at higher doses
Meropenem	25 mg/kg IV q8h	Bacterial meningitis	Doses up to 40 mg/kg q8h have been suggested but not tested in veterinary patients
Fluconazole	2.5–10 mg/kg q12–24h	Fungal infections	
Pyrimethamine	0.5–1 mg/kg q24h	Protozoal infections	

Treatment of the "sterile" meningoencephalitides focuses on the control of inflammation and suppression of the immune system with glucocorticoids and in some cases additional immunosuppressive medications. Prednisone or dexamethasone is often started at antiinflammatory doses after imaging studies and CSF collection, pending the results of infectious disease testing. Antimicrobial drugs are usually indicated while awaiting these results. When the clinician has ruled out infectious causes, the patient is reassessed and their response to therapy is evaluated. Some animals will respond fully to antiinflammatory glucocorticoids. However, those with an absent or partial response will often benefit from escalation to an immunosuppressive dose (Table 73.4). If remission is achieved, this dose is continued for an extended period and then the dose is slowly reduced over a period of weeks to months. Some animals are eventually able to have their glucocorticoid therapy discontinued, although they must be monitored closely for relapse of clinical signs. Conversely, many patients require long-term and often life-long therapy.

Some conditions, such as SRMA, generalized tremor syndrome and idiopathic eosinophilic meningoencephalitis, can typically be managed with glucocorticoids alone. This strategy can also work for patients with GME, NME or NLE although anecdotal evidence suggests that these dogs do not respond as well, and may benefit from additional immunosuppressive therapy. This benefit may occur due to additional mechanisms of immunosuppression (typically interference with lymphocyte proliferation) or by allowing a decreased glucocorticoid dose, which reduces adverse effects and improves overall management. Several different immunosuppressive drugs have been utilized in this scenario (see Table 73.4), and choice is based primarily on clinician preference, as rigorous studies demonstrating a

Table 73.4 Antiinflammatory and immunosuppressive medications for meningoencephalitis and meningomyelitis

Medication	Dosing	Mechanism of action	Adverse effects	Additional considerations
Prednisone or prednisolone	0.5–1.0 mg/kg q12–24h (antiinflammatory); 2.2–6.6 mg/kg/day (immunosuppressive)	Regulation of inflammatory gene expression, impaired leukocyte migration, interference with arachidonic acid cascade and cytokine production	Polyuria, polydipsia, polyphagia, gastrointestinal ulceration, hypercoagulability, hepatopathy	Prednisolone preferred in cats
Dexamethasone	0.07–0.15 mg/kg q12–24h (antiinflammatory); 0.3–1.0 mg/kg/day (immunosuppressive)	As for prednisone	As for prednisone	
Cytosine arabinoside	200 mg/m^2 IV over 8–24 hours or 50 mg/m^2 SC twice daily for 2 days	Interferes with pyrimidine (DNA) synthesis	Nausea, vomiting, bone marrow suppression, hepatic toxicosis	
Leflunomide	3–4 mg/kg/day	Interferes with pyrimidine (DNA) synthesis	Nausea, diarrhea, lethargy, bone marrow suppression (rare)	
Azathioprine	2 mg/kg q24h initially (5–14 days) then 0.5–1.0 mg/kg q48h	Interferes with purine (DNA) synthesis	Vomiting, diarrhea, bone marrow suppression, hepatic toxicosis	Clinical effect may be delayed up to 4–6 weeks
Mycophenolate mofetil	10 mg/kg q8h or 20 mg/kg q12h (dogs)	Interferes with purine (DNA) synthesis	Vomiting, diarrhea	
Ciclosporin A	5 mg/kg q12–24h	Calcineurin inhibitor (inhibits T cell proliferation)	Inappetence, vomiting, diarrhea, gingival hyperplasia, papillomatosis, hepatic or renal toxicosis (rare)	May adjust according to response or blood concentrations; concurrent ketoconazole administration may allow lower dose
Lomustine (CCNU)	60–90 mg/m^2 q4 weeks	Alkylating agent	Bone marrow suppression, hepatic toxicosis	
Procarbazine	25–50 mg/m^2 q24h	Alkylating agent (suspected)	Nausea, vomiting, bone marrow suppression, hepatic toxicosis	

clear benefit of these medications have not yet been published. The use of other immunomodulatory interventions, such as intravenous immunoglobulin and plasmapheresis, is an intriguing possibility that has yet to be investigated in small animal patients. Anticonvulsant therapy is utilized in animals with seizures. Dogs with generalized tremor syndrome may also benefit from concurrent diazepam therapy. Although the pain associated with meningoencephalitis or meningomyelitis usually improves dramatically with glucocorticoid therapy, additional analgesics such as gabapentin or opioid medications may prove beneficial until the inflammation subsides.

The primary means of monitoring response to therapy in animals with inflammatory CNS disease is assessment of clinical signs based on examination and questioning of the owners. Although complete normalization is ideal and achievable in many patients, some animals are left with residual deficits. A significant challenge for the clinician is to determine if such deficits are the result of active inflammation or permanent damage (i.e., loss of cells or tissue) to the CNS. Periodic monitoring with a CBC and serum biochemistry is indicated in patients receiving glucocorticoids or other immunosuppressive drugs to detect adverse effects associated with therapy (e.g., myelosuppression, hepatic failure) as well as infections occurring secondary to immunosuppression. Monitoring of serum drug concentrations is not routinely performed, although some clinicians will utilize this for ciclosporin A. Similarly, repeat CNS imaging and/or CSF evaluation can be helpful in some patients to assess the degree of ongoing inflammation and other pathology, although this is not routinely performed by all clinicians and is obviously dependent on the owner's financial means. Serial monitoring of antibody or antigen titers can be useful in the monitoring of some infectious diseases.

Prognosis

The prognosis for animals with inflammatory CNS disease is highly variable, and depends on both the underlying etiology as well as an individual's response to therapy. Some animals with viral disease may clear the virus, and the prognosis depends on the amount of damage that occurred to the CNS while infected (e.g., canine distemper). These animals may survive, although often with residual deficits (e.g., distemper "myoclonus"). Conversely, some viral diseases such as rabies, pseudorabies, and FIP are invariably fatal. Fungal disease typically requires long-term and often life-long therapy. Animals with bacterial or protozoal diseases can be treated successfully although they may be left with residual deficits and the prognosis is typically guarded.

Dogs with SRMA, generalized tremor syndrome, and idiopathic eosinophilic meningoencephalitis, usually have a good prognosis, with full resolution of clinical signs and long-term remission after therapy, although relapses are possible. The prognosis for dogs with GME, NME, and NLE is much more variable. Although some of these patients may respond fully to treatment, life-long therapy is typical, and many dogs will have an incomplete response. In addition, some dogs progress and die in spite of aggressive treatment. However, the prognosis for cases cited in the literature is likely to be overly pessimistic, as there is a bias towards dogs that have had disease confirmation via histopathology. Finally, the prognosis for animals with greyhound meningoencephalitis has been suggested to be poor, although aggressive therapeutic intervention has not yet been described in the literature.

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74

Diseases of the Neuromuscular Junction

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The neuromuscular junction (NMJ) consists of the efferent nerve terminals, the neuromuscular cleft, and the postsynaptic membrane. As an action potential reaches the presynaptic nerve terminal, voltage-gated calcium channels open, allowing Ca^{2+} ion efflux into the presynaptic nerve terminal. This Ca^{2+} influx allows synaptic vesicles containing neurotransmitter to dock and fuse with the sarcolemma in the process of exocytosis, thereby releasing the neurotransmitter acetylcholine (ACh) into the synaptic cleft. Fusion of the vesicular and plasma membranes is mediated by SNARE (soluble N-ethylmaleimide-sensitive fusion) proteins. Some of the SNARE proteins that are used for synaptic vesicle exocytosis include synaptobrevin (VAMP1), syntaxin 1a, and synaptosome-associated protein 25 (SNAP-25). These SNARE proteins may be the target of many disease processes and toxins.

The ACh released from these vesicles then diffuses through the synaptic cleft and binds to the nicotinic acetylcholine receptors (nAChRs) located on the specially folded postsynaptic muscle fiber sarcolemma. The adult nACHR has been shown to have four different protein subunits (α, β, δ, ε). The receptor is arranged in the fashion of five subunits: 2 α1, β1, δ, ε. These subunits span the lipid bilayer, creating a water-filled pore which forms a "hydrophobic girdle" that acts as a barrier to ion permeation. When ACh binds to the receptor, it undergoes conformational change that allows a preferential influx of Na+ > Ca++ and an efflux of potassium. This region is also closely associated with a high density of sodium channels in order to promote and amplify the signal to assure the propagation of an action potential to generate muscle contraction. As the sodium ions move into the muscle membrane, local depolarization occurs in what is termed an endplate potential (EPP) which spreads across the surface of the sarcolemma, with the ensuing excitation-contraction coupling allowing the muscle fiber to contract. The magnitude of the EPP is dependent on the amount of ACh released and the amount of nAChRs but there is normally an abundance of both, resulting in a large safety factor for neuromuscular transmission. Acetylcholinesterase then breaks down the ACh (producing choline and esterase) and the ACh diffuses away from the synapse, allowing the sodium channels to close. New ACh molecules are synthesized when the choline is transported, through reuptake into the presynaptic terminal.

The clinical presentation in animals with neuromuscular transmission disease is very similar regardless of whether the disorder is presynaptic (i.e., botulism) or postsynaptic (i.e., myasthenia gravis). There is usually a symmetric progressive generalized weakness in all limbs. Exercise intolerance is often seen as well. Tendon reflexes may or may not be intact. There is often facial muscle, laryngeal, pharyngeal or esophageal weakness associated with these disorders. Sensory function is unaffected, as would be expected.

Myasthenia Gravis

Myasthenia gravis (MG) is a neuromuscular transmission disorder caused by a reduction in the number of functional nAChRs on the postsynaptic membrane. It is usually the result of an acquired autoimmune disease and much less commonly a congenital disorder.

Clinical Presentation

Myasthenia gravis should be a consideration in any animal being examined for focal or generalized neuromuscular weakness. The clinical signs may be focal in nature and limited to esophageal dilation leading to regurgitation, pharyngeal dysfunction causing dysphagia and laryngeal paresis/paralysis causing dysphonia (voice change). Multiple cranial nerve abnormalities may also occur in

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the absence of generalized muscle weakness. One study demonstrated that 43% of dogs with a confirmed diagnosis of MG (positive AChR antibody titer) did not have clinically detectable limb muscle weakness. The remaining 57% of dogs had generalized weakness, with 13% of these having no esophageal or pharyngeal dysfunction.

The classic presentation of a dog with MG is generalized muscle weakness that worsens with activity but not all animals display this exercise intolerance. Dogs are more likely than humans or cats to develop megaesophagus because the canine esophagus contains more skeletal muscle than smooth muscle. If megaesophagus is present there is a higher risk of aspiration pneumonia. An acute fulminating form of MG (<5% of cases) has been described. These dogs present with acute onset of rapidly developing signs. They are usually tetraparetic/plegic with marked respiratory distress due to a combination of aspiration pneumonia and respiratory muscle weakness. These animals require intensive care and may need ventilatory support. For this reason, acute fulminating MG has a higher mortality rate. This form has also been associated with a higher rate of thymoma. Thirty to 50% of dogs with thymoma may develop MG. In order for these cases to resolve, thymectomy is recommended.

The clinical signs of MG in cats are also variable, with the two most common clinical signs being generalized weakness without megaesophagus and generalized weakness associated with a cranial mediastinal mass. The incidence of megaesophagus and dysphagia was lower compared to dogs. Myasthenia gravis was also documented in five hyperthyroid cats. These cats developed weakness 2–4 months after treatment with methimazole and were seropositive (AChR antibodies). It was postulated that the drug caused a reversible lack of tolerance to self-AChRs

Acquired Myasthenia Gravis

Acquired MG is an immune-mediated disorder in which autoantibodies (typically IgG) against postsynaptic nicotinic AChRs of skeletal muscle are produced, resulting in impaired neuromuscular transmission.

In acquired MG, there is a T lymphocyte-dependent production of specific autoantibodies directed against the main immunogenic region (MIR) of the nicotinic ACHR, which is located at the extracellular tip of the α1-subunits, allowing antibodies to cross-link AChRs and induce antigenic modulation. These antibody complexes result in immune-mediated destruction of the postsynaptic receptor via three main mechanisms:

- there is complement-dependent lysis of the postsynaptic membrane caused by antibodies bound to AChRs
- antibody cross-linked AChRs result in increased internalization of AChRs, a decreased receptor lifespan and a decrease in the total number of AChRs
- direct inhibition of AChR function.

A familial acquired MG has been reported in the Newfoundland and Great Dane.

Diagnosis of Acquired Myasthenia Gravis

The diagnosis of MG cannot be made on clinical signs alone and should be considered in any animal with signs of neuromuscular disease. Other diseases that may have similar clinical presenting signs include inflammatory and noninflammatory myopathies, polyneuropathy, especially acute ones such as polyradiculoneuritis, endocrine disorders such as hypoadrenocorticism or other diseases of neuromuscular transmission such as tick paralysis, botulism, and organophosphate toxicity. A minimum database including a complete blood count (CBC), chemistry profile with creatine kinase (CK), urinalysis and potentially a thyroid panel should be done to rule out other conditions resulting in or contributing to weakness. Thoracic radiographs may identify megaesophagus, aspiration pneumonia, or a cranial mediastinal mass.

The use of the short-acting anticholinesterase drug edrophonium chloride (Tensilon®) (dogs 0.1–0.2 mg/kg IV and cats 0.25–0.5 mg total dose) may provide a presumptive diagnosis of MG but there are both false-positive and false-negative results. An overdose of edrophonium or its use in a nonmyasthenic patient may cause parasympathetic overstimulation and necessitate the use of atropine sulfate. Cats should be pretreated with atropine as they appear to be more sensitive to edrophonium. Dramatic improvement in muscle strength after edrophonium administration provides a presumptive diagnosis of MG but other myopathic or neuropathic disorders may also show an improvement. Dogs with fulminant MG may not have enough AChRs available to elicit a noticeable response. In dogs with focal MG, there may not be a positive response to the edrophonium chloride test or it may be hard to judge the improvement, for instance in a dog with megaesophagus alone. Unfortunately edrophonium chloride is no longer clinically available therefore this type of testing would be limited to clinicians who have any remaining supply of edrophonium. It is the authors clinical experience that injectable neostigmine can be used as a diagnostic challenge as well. Standard dosing (dogs 0.04 mg/kg IM) is used and the time to respond skin may be up to 30 minutes.

Electrodiagnostic testing may also be useful to add supportive evidence to the diagnosis and exclude other neuromuscular disorders. Electromyography (EMG) and

nerve conduction studies are normal in MG. Repetitive nerve stimulation may show a decremental response of the compound muscle action potential but does lack sensitivity and specificity. More than one muscle group should be tested, especially in patients with focal MG. Single-fiber EMG (SFEMG) is a sensitive test of neuromuscular transmission and techniques for recording SFEMG have been described in both the cat and the dog. SFEMG records the variability of consecutive discharges of the interpotential interval between two muscle fiber action potentials belonging to the same motor unit (jitter). In MG, the jitter values are increased. SFEMG is technically difficult to perform and not widely available. All these electrodiagnostic tests need to be performed under general anesthesia so may not be suitable for all cases of neuromuscular weakness based on their anesthetic risk assessment.

The gold standard for the diagnosis of MG is the demonstration of serum autoantibodies directed against muscle AChRs. The test is extremely sensitive and specific but cannot predict the degree of weakness or severity of the disease. Immunosuppressive drugs may lower the antibody titers and serum should ideally be submitted before the use of corticosteroids or other immunosuppressive drugs. An AChR antibody titer of greater than 0.6 nmol/L in the dog and 0.3 nmol/L in the cat is diagnostic for MG, with rare false-positive results. Seronegative MG occurs in approximately 2% of dogs with generalized MG but the incidence of seronegative focal MG is unknown. The AChR assay is species specific and while there is cross-reactivity, canine or feline assay systems should be used. Low-positive titers may be missed if a human AChR is used as an antigen.

Congenital Myasthenia Gravis

Congenital MG is characterized as a postsynaptic deficiency of ACh receptors with no evidence of autoimmune destruction, with a congenital familial form (autosomal recessive trait) having been described in Jack Russell terriers, springer spaniels, and smooth fox terriers. A congenital MG was described in three 8-week-old miniature smooth-haired dachshunds. These dogs had decreased density of ACh receptors in intercostal muscle biopsy samples with no demonstrable AChR antibodies or antibody complexes demonstrated against the AChR in muscle biopsies. Interestingly, their clinical signs resolved spontaneously at six months of age which is not typical but is similar to a familial infantile myasthenia described in humans. There are a few cats reported with congenital MG.

Diagnosis of Congenital MG

The diagnosis of congenital MG should be considered in any young animal with the typical clinical presentation of acquired MG (see later). Regurgitation associated with megaesophagus has been reported in congenital MG but not as commonly as in acquired MG. As expected based on the pathology, serologic tests for AChR antibodies would be negative. A positive edrophonium (Tensilon) response test (0.1–0.2 mg/kg IV) can be consistent with the diagnosis of congenital MG but does not allow for differentiation of the acquired form of the disease and a negative test does not exclude the diagnosis of congenital MG. Other neuromuscular disorders may be excluded by routine serologic and electrophysiologic testing and muscle and nerve biopsy. Fresh-frozen muscle biopsy samples may also be evaluated for localization of AChE, AChR, AChR subunits, IgG, and complement components at the neuromuscular junction. Quantification of muscle AChR may be done but requires a fresh muscle specimen intact from origin to insertion, such as external intercostal or anconeus muscle.

Anticholinesterase drugs should be of benefit in animals with AChR deficiency. Congenital cases of MG do not seem to respond as completely as the acquired disease with full return of strength being unusual. The weakness can often progress to death within the first year but with proper care and anticholinesterase therapy, some affected Jack Russell terriers have survived several years. Both cats reported with congenital MG survived several years.

Seronegative Myasthenia Gravis

Seronegative MG does occur and the patients may have the same clinical presentation as a seropositive case. Seronegative MG in dogs is defined as a patient with clinical signs suggestive of MG, a positive edrophonium response, supportive electrodiagnostic testing (decremental response on repetitive nerve stimulation, increased jitter on SFEMG), improvement of muscle weakness after anticholinesterase therapy, and at least two negative serum AChR antibody titers. The antibody titers should be repeated 1–2 months apart as seroconversion may occur.

Seronegative MG may occur because there are antibodies directed against non-ACHR end plate proteins, the antibodies are all bound to the endplates with little to no circulating antibodies, or the antibodies may be lost during the AChR extraction procedure.

In humans, autoantibodies have been detected against a receptor tyrosine kinase, MuSK, in about 70% of AChR seronegative patients. The MuSK enzyme is located on the postsynaptic membrane and induces acetylcholine accumulation. A dog with a negative AChR antibody titer and positive MuSK autoantibodies has been identified. The ryanodine receptor (RyR) may also play a role in MG. This channel receptor is responsible for the release of calcium necessary for muscle contraction. Autoantibodies

against RyR have been detected in both humans and dogs and in conjunction with AChR antibodies can cause a severe form of thymoma-associated MG.

In people with MG, autoantibodies directed at striational muscle proteins (myosin, actin, alpha-actinin, titin, sarcoplasmic reticulum) have been described. They have also been described in the dog. Since these proteins are normally not exposed to circulating antibodies they are thought to be nonpathogenic but may reflect muscle damage in cases where the AChR antibody titer is negative, thereby supporting a diagnosis of MG. Eighty percent of human patients with thymoma and MG, 24% of thymoma patients without MG, and 30% of MG patients without thymoma have antistriational antibodies. The incidence in dogs is not known.

Treatment

There are many reported treatments of MG but well-controlled prospective studies are not available. Many canine patients will undergo spontaneous remission. In one study, 47/53 (88.7%) AChR antibody-positive patients treated with anticholinesterase drugs alone went into remission over an average of 6.4 months. This included focal, generalized, and fulminating forms. The presence of spontaneous remission needs to be considered when evaluating any treatment modality. Good clinical judgment should be used when determining the therapeutic options in a case of MG. The presence or absence of dysphagia, esophageal weakness or megaesophagus may necessitate alternate feeding procedures such as elevated feedings, a "Bailey Chair" (www.baileychairs4dogs.com) or a gastrotomy tube.

Anticholinesterase inhibitor (AChEI) drugs are the key therapy for MG and work by prolonging the action of acetylcholine at the neuromuscular junction. The dose may need to be titrated to effect as these drugs have both muscarinic and nicotinic effects. A return to full muscle strength is the goal. Animals can develop a cholinergic crisis (weakness, abdominal pain, salivation, and diarrhea) and need treatment with atropine and a decrease in dosage or discontinuation of the AChEI. The most commonly used drugs are pyridostigmine bromide (Mestinon® 1–3 mg/kg PO BID-TID) and neostigmine bromide (Prostigmin® 2 mg/kg/day divided to effect). Pyridostigmine is most commonly used because it has a longer duration and fewer muscarinc effects. It is available as a tablet, syrup, and timed-release formulation. In critically ill patients or those with regurgitation that cannot take oral medication, a constant rate infusion (CRI) of pyridostigmine bromide (0.01–0.03 mg/kg/h) may be used. The author has used neostigmine as a CRI at the same dosage but found that it had many more adverse GI signs.

Corticosteroids may be used to treat MG if the patient is not adequately responding to anticholinesterase therapy alone. The optimal dosing regimen has not been determined prospectively in the dog, but large immunosuppressive doses are not recommended, especially in the face of aspiration pneumonia. In mild to moderately affected myasthenic dogs, a dose of 0.5 mg/kg daily to every other day has been recommended. There are reports of high-dose methylprednisolone therapy benefiting people but this must be used with caution in dogs. Other immunosuppressants and immunomodulators that have been described in case studies/series in the veterinary literature are azathioprine, ciclosporin A, and mycophenelate mofetil. These are uncontrolled retrospective case series and although success was noted in many of these cases, the use of these drugs should be tailored to each individual case at this time. As an example, a retrospective study of 27 dogs with AChR-positive antibody titers reported that there was no beneficial effect in dogs treated with pyridostigmine in combination with mycophenelate mofetil compared to pyridostigmine alone. Plasmapheresis has been described as a successful treatment in a single case report and more recently has been described in several dogs that had therapeutic plasma exhange. These were serologically confirmed patients with marked generalized weakness, megaesophagus, and aspiration pneumonia that were not adequately responding to traditional treatment. These dogs responded well to the therapy. Although promising, this may have limited value due to cost and the need for specialized equipment.

The management of severely compromised respiratory patients due to aspiration pneumonia and intercostal or diaphragm weakness usually needs to be done at facilities with intensive care facilities and the ability to ventilate patients if needed. Respiratory failure is the most common cause of death in these patients. Antibiotics with the potential for neuromuscular blockade such as aminoglycosides and ampicillin should be avoided.

Serial monitoring of the AChR antibody titer should be done in all patients and treatment should continue until the antibody titer is negative. This would need to be interpreted in light of any concurrent immunosuppression.

Treating acquired feline MG is very similar to the dog but since there is a higher incidence of thymoma in cats, all patients should have thoracic radiographs whether or not signs of megaesophagus or respiratory distress are present. The natural course of the disease in cats is also not known so we do not know if they also have spontaneous remission. Cats can be treated with anticholinesterase drugs but may also handle the adverse effects of corticosteroids better than dogs and therefore these may be more beneficial.

Other Disorders of Neuromuscular Transmission

Presynaptic Disorders

Tick Paralysis

A salivary neurotoxin secreted by certain tick species can interfere with ACh release, resulting in impaired neuromuscular transmission and clinical weakness. The signs are usually that of an acute progressive lower motor neuron (LMN) disease. The North American common wood ticks, *Dermacentor variabilis* and *Dermacentor andersoni* (Rocky Mountain wood tick), are most often responsible for the disease. In Australia, *Ixodes holocyclus* is the most important species. Less commonly associated ticks are *Ixodes cornuatus*, *I. hirsti*, *I. pacificus*, and *I. scapularis*.

The clinical signs are commonly seen as pelvic limb ataxia that then progresses to involve the thoracic limbs, leading to recumbency in 24–72 hours. Dysphonia and dysphagia can be early signs, and masticatory muscle weakness and facial paresis may also be present. Death may occur within several days from respiratory paralysis. The diagnosis is made by clinical signs and resolution of signs following tick removal. Prognosis is usually good, with recovery occurring in 1–3 days following complete tick removal.

In Australia, the clinical signs with *Ixodes* spp tend to be more severe and include autonomic disturbances that include peripheral vasoconstriction, arterial hypertension, increased pulmonary capillary hydrostatic pressure, pulmonary congestion and edema, tachyarrhythmias, and pupillary dilation. In addition to the previously described clinical presentation, other signs may include voice change, depressed gag reflex, megaesophagus, salivation, regurgitation and/or vomiting, dyspnea, and cyanosis. Death may occur within 1–2 days in untreated patients. In addition to tick removal and supportive care, neutralization of circulating toxins can be attempted with tick antitoxin serum. The antitoxin serum adverse effects are anaphylaxis and autonomic disturbance. The antiserum treatment needs to be given in the early stages of the disease and is expensive. Alpha-adrenergic blocking agents such as phenoxybenzamine hydrochloride and prazosin may help with the hypertension. Severely affected animals with respiratory compromise may require ventilator support.

The prognosis can be guarded even with appropriate treatment. The prognosis seems to be inversely related to the severity of clinical signs, as dogs with mild disease recovered more quickly than those with severe paresis/paralysis and respiratory compromise.

Botulism

Botulism occurs by ingesting the preformed neurotoxin (exotoxin) of *Clostridium botulinum* which is contained in carrion or spoiled food. In rare cases, botulism may occur as a result of colonization of the gastrointestinal (GI) tract (toxico-infectious) or wound infection. There are eight botulinum toxins but type C1 is the most common in dogs although there have been infrequent reports of type C2 and D. Botulism has not been reported in the cat.

Botulinum neurotoxins inhibit neurotransmitter release from the presynaptic nerve terminals by cleaving proteins required for synaptic vesicle fusion with the plasma membrane. They may affect either the synaptic vesicles (synaptobrevin) or the plasma membrane (SNAP-25 and syntaxin), depending on the neurotoxin serotype. The neurotoxins enter the nerve terminal by specifically interacting with the luminal domain of synaptic vesicle proteins (synaptotagmin or SV2, depending on serotype) which are briefly exposed during exocytotic membrane fusion. This leads to a presynaptic blockade of ACH release and resulting muscle weakness. There may be some disturbance in autonomic function as well.

The clinical signs may occur within hours to days and are typically an acute onset of symmetric diffuse LMN dysfunction starting in the pelvic limbs and progressing forward. The severity of dysfunction may range from mild weakness to complete tetraplegia with respiratory paralysis. The spinal reflexes are not intact and there is often paresis associated with cranial nerve functions such as the facial musculature, laryngeal, pharyngeal and esophageal musculature.

The diagnosis can be made by detection of the toxin in ingested material, serum, vomit, and feces and by a neutralization test in small mice. Samples should be collected as early as possible in the course of the disease. ELISA tests have been used in the detection of botulinum toxin in people but not for type C (reportedly used in cattle) so obtaining a diagnosis by this method would be difficult. Electrodiagnostic studies may be useful to differentiate botulism from other acute disorders such as polyradiculoneuritis. There may be a slight decrease in motor nerve conduction velocity and decreased amplitude of the compound muscle action potential (CMAP). Repetitive nerve stimulation may reveal a decremental response at low (>5 Hz) rate or incremental response at high (>50 Hz) rate. EMG may show some spontaneous activity such as fibrillation potentials and positive sharp waves but it is often normal.

Treatment of botulism consists of supportive care, with mildly or moderately affected dogs recovering over a period of several days. Intensive management may be required for dogs needing ventilatory support or having megaesophagus and dysphagia as they are at high risk for

aspiration pneumonia. Recumbent nursing care, which includes frequent turning, good padding to prevent decubital ulcers and bladder care, is essential for a good recovery and to avoid secondary complications. Oral antibiotics are of no benefit, unless toxico-infectious botulism is suspected and in that case penicillins or metronidazole would be indicated. Administration of *C. botulinum* antitoxin needs to be type specific and would not be beneficial unless a specific type C-antitoxin were available. The antitoxin administration only helps to inactivate circulating unbound toxin and not toxin already fixed at the site of neuromuscular junction damage so, depending on the timing of administration, it could be too late in the course of the disease to use. Complete recovery is possible with proper care and should occur within 1–3 weeks. Dogs with aspiration pneumonia and respiratory paralysis may have a more guarded prognosis depending on severity and the ability to obtain respiratory support.

Postsynaptic Disorders

Organophosphate and Carbamate Toxicity

Organophosphates (OP) and carbamates are commonly used compounds found in many pesticides and insecticides. They are long-acting anticholinesterases that irreversibly bind acetylcholinesterase (AChE) in nervous tissue and muscle, allowing accumulation of ACh to cause continuous cholinergic stimulation. This occurs in central, muscarinic, and nicotinic cholinergic synapses, resulting in clinical signs that include autonomic overstimulation (salivation, lacrimation, urination, defecation) and neuromuscular dysfunction. A delayed OP-induced polyneuropathy has also been described. Clinical toxicity in veterinary medicine is usually associated with inappropriate or accidental dosing, with cats being more susceptible to these compounds than dogs. Historical information is imperative to reaching the diagnosis.

Although serum cholinesterase concentrations can be measured, the results are usually not available in a timely fashion so a presumptive diagnosis based on history and clinical signs is enough to begin treatment.

Clinical signs of OP intoxication are usually dominated by the autonomic effects, but neuromuscular signs include a stiff rigid gait, muscle tremors, and fasciculation (except for fenthion).

Treatment for these toxicities consists of reducing further exposure or absorption by bathing or gastric lavage as appropriate. Atropine sulfate can be titrated to effect to counteract the parasympathetic signs. Pralidoxime chloride (2-PAM or protopam chloride) and pralidoxime mesylate (P2S) can be used in OP toxicity but not in carbamate toxicity (except for aldicarb). These oxime reactivators cause release the bound AChE from the OP compound.

Drug-Induced Neuromuscular Blockade

Certain drugs have been shown to induce NMJ blockade in veterinary medicine although most reports are experimental, with very few documented clinical cases. The most commonly associated antibiotics are aminoglycosides, lincomycin, penicillamine, polymyxins, and tetracyclines. The mechanism of action in aminoglycoside NMJ blockage is presynaptic inhibition of ACh release as a result of blocked calcium influx. There is also blockage of calcium influx on the postsynaptic membrane. The degree of transmission impairment with aminoglycosides depends on the specific drug and the balance between the pre- and postsynaptic effects. The most potent effects, in descending order, are from neomycin, kanamycin, amikacin, gentamicin, and tobramycin. Penicillamine has been documented to cause an immune-mediated MG in people. Polymyxins have their most profound effect on the postsynaptic membrane by acting as a noncompetitive nondepolarizing agent. Tetracyclines have the proposed effect of chelating calcium ions and thereby depressing the effect of ACh on the postsynaptic muscle fiber.

It is important to remember that these drugs can potentiate neuromuscular blocking agents used during surgical procedures or may worsen or unmask preexisting disorders of neuromuscular transmission. The use of these agents should be avoided in the treatment of other neuromuscular disorders such as MG patients. Other drugs that have a reported effect on neuromuscular transmission are antiarrhythmic agents, phenothiazines, methoxyflurane, magnesium, and the antiprotozoals chloroquine and quinine. Methimazole has been documented to cause a reversible drug-induced autoimmune MG in hyperthyroid cats.

Black Widow Spider Envenomation

The black widow spider (*Lactrodectus* spp.) has a worldwide distribution. The most potent component of its venom is the purified fraction B known as alpha-latrotoxin. The toxin causes a massive release of neurotransmitter and loss of synaptic vesicles. The synaptic vesicle loss is caused by increased fusion and docking of the synaptic vesicles with the plasma membrane and inhibition of new vesicle formation.

The cat appears to be more susceptible to envenomation and the clinical signs usually occur within the first eight hours. There are fine muscle tremors, muscle spasticity, abdominal rigidity, pain, and profound flaccid muscle weakness. Hypertension and electrolyte abnormalities may also occur.

Treatment consists of administering the appropriate antivenin and supportive care. A rapid response to the antivenin is reported in people.

Snake Envenomation

There are four families of snakes that produce venom which causes neuromuscular blockade: Atractaspididae (African mole viper), Colubridae (bloomsang, twig snake), Elapidae, and Viperidae. The Elapidae have three major subfamilies: Elapidae (cobras, mambas, coral snakes), Hydrophiinae (sea snakes), and Laticaudinae (sea kraits). The Viperidae have two major subfamilies: Crotalinae (pit vipers, copperheads, cotton mouths, and rattle snakes) and Viperinae, the "Old World" vipers (carpet vipers, adders, desert vipers).

The pit viper toxin that causes neuromuscular weakness is the Mojave toxin. It causes a presynaptic block of ACh release which can then lead to complete neuromuscular blockade when there is a facilitatory release of neurotransmitter leading to complete cessation of neurotransmitter release. The Elapidae family, such as the coral snake, produce at least three neurotoxins (taipoxin, beta-bungarotoxin, and notexin). These toxins have phospholipase A_2 activity and damage synaptic vesicles. There is also a change in the morphologic structure of the motor axon terminal, including a decreased number of synaptic vesicles. The clinical signs of snake envenomation are of a progressive neuromuscular weakness with cranial nerve involvement, with death usually resulting from respiratory paralysis. If the snake can be identified then the use of antivenin has a positive effect on outcome, especially the coral snake.

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75

Myopathies

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Etiology/Pathophysiology

Myocytes are specialized cells, with contractile elements (actin and myosin) comprising the majority of the intracellular space, along with the other organelles (mitochondria, lysosomes, etc.) Disruption of myocytes (myofibers) will result in decreased ability to contract the muscle with appropriate strength. Myopathies occur secondary to either intrinsic pathology within the myofiber itself (noninflammatory myopathy) or infiltration and damage by inflammatory cells (myositis) from infectious or immune-mediated disease. Any disruption of the muscle membrane or intracellular structures results in myofiber dysfunction, whether through accumulation of storage products, through cellular infiltration, or dysfunction of the sarcolemma, other cytoskeletal proteins, or membrane ion channels.

Epidemiology

The wide range of etiologies for myopathies makes delineating epidemiology difficult for each specific disease. About one-third of canine generalized inflammatory myopathies (myositides) are associated with infectious agents, although a causal relationship will be difficult to determine unless histopathologically confirmed. There is also an association with canine polymyositis and skeletal muscle lymphoma, whether through malignant transformation of infiltrating lymphocytes, a paraneoplastic syndrome, or as primary skeletal muscle lymphoma.

Signalment

Inherited myopathic processes (Box 75.1) typically exhibit clinical signs in young animals (<6 months old) and may be static or progressive. Acquired myopathies (Box 75.2) may develop at any age, and are often progressive unless the underlying cause is addressed.

Some myopathies have (to date) only been described in certain breeds (Box 75.3), and presentation by one of these breeds with appropriate clinical signs should raise suspicion for one of these breed-associated myopathies.

History and Clinical Signs

Functional manifestations of myopathies may include gait abnormalities (lameness, stiff or stilted gait), exercise intolerance, focal or generalized weakness, dysphonia, dysphagia, regurgitation, possibly megaesophagus, muscle tremors and/or fasciculations, and postural alterations (e.g., cervical ventroflexion, especially in cats). The history and clinical signs of patients with myopathies are often the same as with other neuromuscular diseases (neuropathies and junctionopathies), so noting these signs in the patient's history often just localizes a problem to the neuromuscular system, and not necessarily specifically to a nerve, muscle, or junction problem.

Specific physical manifestations of myopathies may include decreased muscle mass (atrophy or hypotrophy) or even hypertrophied muscles in some diseases (myotonia congenita, some muscular dystrophies). Very young patients with muscle diseases may have limb deformities

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Box 75.1 Inherited myopathies (all non-inflammatory)

Muscular dystrophies
- Myotonias and other channelopathies (myotonia congenita, hyperkalemic periodic paralysis)
- Congenital myopathies (nemaline rod myopathy, centronuclear myopathy, others)
- Metabolic myopathies (glycogen or lipid storage diseases)
- Mitochondrial myopathies

Box 75.2 Acquired myopathies

Inflammatory myopathies
- Infectious – bacterial, protozoal, etc.
- Immune mediated
  - Masticatory muscle myositis (MMM)
  - Polymyositis
  - Dermatomyositis
  - Inclusion body myositis
  - Lymphoma-associated polymyositis

Endocrine myopathies
- Hypothyroidism
- Hyperadrenocorticism

Electrolyte imbalance, especially potassium, calcium, magnesium

Cachexia

Box 75.3 Breed-associated myopathies

Familial polymyositis
Hungarian Vizsla dogs, Newfoundland, boxer

Dermatomyositis
- Collie, Shetland sheepdog

X-linked myotubular myopathy
- Labrador retriever

Centronuclear myopathy
- Labrador retriever, border collie

Muscular dystrophies
- Golden retriever, Japanese spitz, Labrador retriever, cats, German short-haired pointer, Cavalier King Charles spaniel, miniature schnauzer, among others

Inherited myopathy of Great Danes

Glycogen storage diseases
- Curly-coated retrievers (type IIIa)
- Lapland dog (type II)
- English springer spaniel (phosphofructokinase deficiency – type VII glycogen storage disease)

or orthopedic abnormalities secondary to the effects of abnormal muscle forces on the bones.

Patients with myositis (inflammatory myopathies) may exhibit apparent myalgia or pain on muscle palpation. Dogs with masticatory muscle myositis often present with apparent pain on opening the mouth or chewing.

Diagnosis

History, physical, and neurologic examinations permit the clinician to localize a problem to the neuromuscular system. Further isolating the problem to a myopathic process typically requires a combination of serologic, functional, and histologic evaluation of the muscle.

Hematology/Serology

In certain myopathic diseases with prominent myonecrosis or rhabdomyolysis, serum creatine kinase (CK) level may be elevated (normal 55–260 IU/L), and in some myopathies (e.g., muscular dystrophy), serum CK can be markedly elevated (>50 000 IU/L). CK is specifically released secondary to damage to the myofiber sarcolemma. Not all myopathies have elevations in CK, so a normal CK does not rule out a myopathic process; however, with appropriate clinical signs, elevated serum CK will raise the suspicion of a myopathy.

Canine masticatory muscle myositis (MMM) is an immune-mediated disease against the 2M myofibers, exclusively located in the muscles of mastication (temporalis, masseter, pterygoids, rostral digastricus). A serologic assay for 2M antibodies is available through the Comparative Neuromuscular Laboratory (http://vetneuromuscular.ucsd.edu/), and is highly sensitive and specific.

Functional

Electromyography (EMG) performed on the anesthetized patient assesses the stability of the muscle membrane. Normal muscle maintains electrical silence on EMG, while myofibers with membrane instability will depolarize spontaneously, resulting in abnormal spontaneous activity (fibrillation potentials, positive sharp waves, complex repetitive discharges). One EMG abnormality specific for myotonia is the presence of myotonic discharges which spontaneously wax and wane, but more often than not, EMG alone is not sufficient to diagnose a myopathy. Abnormal spontaneous activity on EMG indicates either a myopathic process or denervation of that muscle, so motor nerve conduction velocities should be done to assess nerve function, as well as muscle and nerve biopsies to assess muscle histology.

Electromyography is useful to confirm that the motor unit is affected and helps the clinician determine the extent of the disease process (focal, generalized). EMG may be especially helpful to screen for subclinical disease; a common recommendation for EMG examination is to assess a minimum of two limbs, usually the thoracic and pelvic limbs on one side of the patient. Often, only one side is examined with EMG to maintain the opposite limbs free of iatrogenic mechanical injury from the exploring needle so biopsies can be obtained. Sometimes an additional limb is examined (e.g., both pelvic limbs and a thoracic limb), especially if the clinician wants to assess the contralateral limb for comparison.

Histology

A definitive diagnosis of a myopathy is based on histologic abnormalities of the muscle. For the clinician, biopsy selection, handling, and processing are extremely important. Prior to biopsy, clinicians must decide whether they will submit fresh muscle to a specialized laboratory for processing, or will take samples to submit in formalin for routine histopathologic evaluation. Fresh muscle must be packed appropriately and shipped overnight to the lab, so the clinician must schedule sampling and shipping so that the muscle arrives in good condition.

For generalized disease processes, biopsies of the triceps, biceps femoris/quadriceps, and cranial tibial muscles permit evaluation of both proximal and distal muscles, as well as the thoracic and pelvic limbs. Temporalis muscle, if affected, is another muscle frequently sampled, particularly if there is a clinical suspicion of MMM (although measuring serum 2M antibody titer is less invasive – see Hematology/Serology earlier). If a different, specific muscle is the only one affected, then the clinician should consider sampling that as well. By sampling multiple muscles, the clinician increases the likelihood of obtaining a biopsy with pathologic changes, since only a small portion (about 1 cm^3) of any muscle is taken, and focal or multifocal processes may be missed. Two laboratories process international veterinary fresh muscle samples, and information on shipping is available on their websites (see Resources below).

Muscle histopathology is broadly categorized into inflammatory (true myositides) or noninflammatory (dystrophic) myopathies (see Boxes 75.1 and 75.2). Macrophages are present for myofiber phagocytosis from any cause, but true myositis is characterized by excessive cellular infiltration in the endo- and perimysium, with lymphocytes, neutrophils, and eosinophils, as well as macrophages. If the myositis is secondary to an infection, the causative agent may be apparent in the biopsy, but again, the small sample makes it highly likely that microorganisms may be missed.

Noninflammatory myopathies may have vacuoles, abnormal accumulations within the myofibers, loss of normal cytoskeletal architecture (cores), necrosis and phagocytosis with macrophages only, may have nonspecific abnormalities, or may be completely normal on histopathology.

Therapy

For inflammatory myopathies, specific treatment for the infectious process or immunosuppression is indicated, but for most noninflammatory myopathies, unless an underlying or concurrent treatable disease is identified that could cause the myopathy (e.g., electrolyte imbalance, endocrine disease, etc.), there are no definitive treatments.

Nonspecific Therapy

Nutritional supplementation with L-carnitine (50 mg/kg PO q12h), co-enzyme Q10 (100 mg PO q24h), and vitamin B complex for "muscle support" has been recommended for many noninflammatory myopathies, and there are only anecdotal reports of clinical improvement with these medications.

Inflammatory Myopathies

If an infectious etiology (parasitic, bacterial, protozoal, etc.) is identified on biopsy or suspected clinically, appropriate antimicrobial therapy should be instituted. In small animal medicine, immune-mediated myositides are likely more common than infectious, and immunosuppressive therapy is required. In some cases, immune-mediated myositis may be secondary to a chronic infection. Clinicians may choose from several different immunomodulatory drugs, including glucocorticoids, azathioprine, and cyclosporine.

Prognosis

Prognosis will depend on the specific underlying myopathy, and can range from grave to excellent. Some inherited myopathies may have tolerable clinical signs and function throughout the life of the patient (e.g., some myotonias), while others progress relentlessly to markedly impair quality of life (e.g., muscular dystrophies).

For most acquired myopathies, if the underlying cause is identified and appropriately treated, patients may have an excellent outcome.

Resources

http://vetneuromuscular.ucsd.edu/ – 2M antibody titers; accepts fresh muscle (and nerve) biopsies from canine and feline patients.

https://neurology.vetmed.ucdavis.edu/ndl – accepts fresh muscle (and nerve) biopsies from canine, feline, equine, and food animal patients.

Further Reading

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76

Myelopathy

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Myelopathy is a nonspecific term representing pathologies that result in signs of spinal cord dysfunction. It is important for the clinician to recognize the neurologic signs of myelopathy and to differentiate from or avoid misdiagnosis of other mimicking orthopedic and neuromuscular (nerve, muscle, neuromuscular junction) disorders. Signalment, history, and physical and neurologic examination findings will establish presence of a myelopathy, provide neuroanatomic localization and consideration of differentials. Ultimately, with neurodiagnostics to narrow the differential diagnosis, appropriate therapies can be selected for treatment or management of patients with spinal cord disease.

History

An accurate clinical history is important in defining the cause of the myelopathy. Time of onset (sudden or insidious), rate of progression (static, gradual or rapid), and temporal relation (intermittent/episodic, stable or chronic) can be established. Acute disorders such as fibrocartilaginous embolism (FCE), aortic thromboemboli, trauma, discospondylitis, and Hansen type I intervertebral disc herniation and meningomyelitis often present with sudden onset and can be rapidly progressive (Table 76.1).

Chronic disorders such as spinal canal/spinal cord neoplasia, degenerative lumbosacral syndrome, cervical spondylomyelopathy, degenerative myelopathy, and Hansen type II intervertebral disc herniation cause insidious signs of myelopathy (Table 76.2).

Pathophysiology

The spinal cord serves as a conduit for the upper motor neuronal fibers, sensory pathways and the origin of the motor units of the cervical, thoracic, lumbar, sacral, and caudal segments. The severity of motor and sensory deficits from spinal cord disease is dependent upon the rapidity of disease onset, extent of lesion involvement, and the area within the vertebral column.

Spinal cord injury occurs through primary mechanical and secondary injury mechanisms. Primary injury results from extrinsic or intrinsic injury processes causing laceration, compression, contusion, ischemia, and inflammation of the tissue. The acute stage consists of primary tissue effects after injury such as central hemorrhage after a severe compression/concussive injury. Typically, myelopathic changes initially involve the gray matter with centrifugal spread to the white matter. Sequential hemorrhage, edema, and neuronal necrosis depend on severity and type of injury. The primary injury initiates a cascade of vascular, ionic, and biochemical events, associated with ischemia that contributes to secondary spinal cord injury processes and irreversible neuronal damage. Physical attributes of the chronic stage subsequent to secondary injury mechanisms include cavitation, presence of apoptosis, and Wallerian degeneration. Neurodegenerative diseases related to underlying inherited, metabolic or toxic causes result in intrinsic neuronal degeneration involving the cell body, axon, and/or myelin.

Clinical Signs

The primary objective of the neurologic examination in spinal cord disease is to determine an accurate neuroanatomic localization (C1–5, C6–T2, T3–L3, L4–S3, and caudal segments) (Table 76.3) and lesion distribution (focal, multifocal, diffuse). Careful interpretation of the neurologic examination is essential to avoid diagnostic procedures that are inappropriate for lesion determination and potentially harmful to the patient.

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Table 76.1 Differential diagnosis for acute-onset myelopathy

Differential category	Differentials	Comments
Degenerative	*Hansen type I intervertebral disc herniation*	Asymmetric or symmetric
Anomalous	*Atlantoaxial instability*	Usually symmetric
Neoplastic	*Metastatic, vertebral body tumors, pathologic fracture, histiocytosis, lymphoma, other hematopoietic neoplasia*	Often asymmetric
Inflammatory (infectious)	*Bacterial, protozoal, and fungal meningomyelitis, canine distemper virus, feline infectious peritonitis, discospondylitis, spinal cord epidural empyema*	Asymmetric or symmetric
Inflammatory (noninfectious)	*Steroid-responsive meningitis-arteritis, granulomatous meningoencephalomyelitis*	Usually symmetric
Trauma	*Fracture/subluxation*, acute noncompressive intervertebral disc herniation	Asymmetric or symmetric; nonprogressive
Vascular	Fibrocartilaginous embolism, *aortic thromboembolism*	Usually asymmetric; nonprogressive

Italicized differentials indicate diseases associated with hyperesthesia on spinal palpation.

Table 76.2 Differential diagnosis for chronic myelopathy

Differential category	Differentials	Comments
Degenerative (spinal cord)	Degenerative myelopathy, myelinopathy, neuronopathy, axonopathy, subarachnoid diverticulum, storage disorders	Symmetric
Degenerative (vertebral column)	Hansen type II intervertebral disc herniation, *cervical spondylomyelopathy (wobbler syndrome)*, *degenerative lumbosacral syndrome*, spinal synovial cyst, diffuse idiopathic skeletal hyperostosis, spondylosis deformans, mucopolysaccharidosis, osteochondromatosis	Symmetric or asymmetric
Anomalous	Chiari-like malformation (*syringohydromyelia*), *atlantoaxial instability*, vertebral malformation, myelodysplasia, spinal stenosis, dermoid sinus	Usually symmetric
Neoplastic	*Meningioma, primary spinal cord (oligodendroglioma, astrocytoma, ependymoma), nephroblastoma*	Often asymmetric
Inflammatory (infectious)	Bacterial meningomyelitis, canine distemper virus, feline infectious peritonitis, protozoal, fungal	Asymmetric or symmetric

Italicized differentials indicate diseases associated with hyperesthesia on spinal palpation.

General Proprioceptive Ataxia

General proprioceptive (GP) ataxia reflects the lack of information reaching the central nervous system (CNS) responsible for the awareness of movement and position of neck, trunk, and limbs in space. Due to anatomic proximity within the spinal cord of the proprioceptive pathways and motor tracts, proprioceptive abnormalities often overlap with those caused by upper motor neuron (UMN) weakness. A deficit of GP appears as misplacement or knuckling of the foot, which may not occur with every step, and poorly controlled swaying of the body. The feet may be crossed or placed too far apart. Overall movement of the limbs lacks coordination.

Paresis/Plegia

Paresis/plegia is a deficit/loss of ability to carry out voluntary motor function. The terms lower motor neuron (LMN) and UMN are applied to differentiate two basic types of neurologic weakness. Clinical signs of UMN weakness are characterized by spasticity with normal to increased spinal reflexes and muscular hypertonia. LMN weakness manifests as flaccidity, hyporeflexia to areflexia and muscle atrophy that is severe and rapid in onset. Neuroanatomic localization to a specific spinal cord region is upon UMN or LMN signs (see Table 76.3). In addition, the affected limbs have inadequate or absent voluntary motion, which may be described as monoparesis/plegia (involvement of one limb), paraparesis/

Table 76.3 Neurologic signs associated with spinal cord regions

	Clinical signs			
Evaluations	**C1 to C5**	**C6 to T2**	**T3 to L3**	**L4 to S3 and caudal segments**
Mental status	Normal	Normal	Normal	Normal
Posture	Normal; wide-based stance all limbs; +/- recumbency; horizontal neck carriage	Normal; wide-based stance all limbs, recumbent; +/– horizontal neck carriage	Normal; falling; acute – Schiff–Sherrington posture,	Normal; falling; tail tone decreased or flaccid
Gait	Normal, GP/UMN ataxia (PL > TL), spasticity all limbs, tetraparesis/ plegia, hemiparesis/ plegia	Normal, spastic PL, GP/ UMN ataxia (PL > TL), shorten stride TL, tetraparesis/plegia, hemiparesis/ plegia	GP/UMN PL ataxia, symmetric or asymmetric spastic paraparesis/plegia	GP PL ataxia, weakness may vary; symmetric or asymmetric (more often with cauda equina) paraparesis/ plegia
Cranial nerves	Normal; bilateral or ipsilateral Horner syndrome	Normal; bilateral or ipsilateral Horner syndrome	Normal	Normal
Postural reactions	Normal, mild-severe deficits (PL > TL); absent	Normal, mild-severe deficits (PL > TL); absent	Mild-severe deficits; absent	No deficits; mild-severe deficits; absent
Spinal reflexes	Normal, hyperreflexia all limbs	Normal, hyporeflexia or absent reflexes TL; normal to hyperreflexia PL	Normal to hyperreflexia PL	Hypo- to areflexia; pseudohyperreflexic patellar reflex with sciatic nerve dysfunction
Spinal hyperesthesia	None; mild-severe on palpation; resists neck movements	None; usually mild; may resist neck movement	None; mild-severe on palpation	None; mild-severe on palpation; accentuate on tail extension
Sensation (nociception)	Usually normal; severe lesions may show mild-severe sensory loss	Usually normal; severe lesions may show mild-severe sensory loss	Mild-severe sensory loss; absent	None; mild-severe (more common with intumescence lesion) sensory loss
Micturition	Usually intact; may have detrusor areflexia; sphincter hypertonia	Usually intact; may have detrusor areflexia; sphincter hypertonia	Usually affected with loss of motor function, detrusor areflexia-sphincter hypertonia	None; mild-severe detrusor areflexia; sphincter hypotonia

C, cervical; GP, general proprioceptive; L, lumbar; LMN, lower motor neuron; PL, pelvic limb; S, sacral; T, thoracic; TL, thoracic limb; UMN, upper motor neuron.

plegia (involvement of pelvic limbs), tetraparesis (involvement of all limbs) or hemiparesis (involvement of the ipsilateral thoracic and pelvic limbs).

Gait is assessed with regard to coordination, voluntary motor functions, and direction. The action of gait is characterized by swing (flexion) and stance (extension) phases. The voluntary motor system involves recruitment of the flexor muscles to initiate the swing phase and the postural system recruits extensor muscles for the stance and propulsive phases. Animals with UMN weakness will often have a gait of long stride length, whereas with LMN weakness the stride length is shortened. The gait in animals with spinal pain may have a shortened stride length. Animals with joint, muscle, or meningeal pain often appear to be "walking on eggshells." Thoracic or pelvic limb lameness may represent radicular pain (nerve root signature).

Postural Abnormalities

Abnormal postures can be specific for vertebral column abnormalities and spinal cord dysfunction. Ventroflexion of the neck is a common phenomenon in animals with disorders of neuromuscular weakness (especially cats) or pain. Animals with spinal malformations can show kyphosis (dorsal deviation), scoliosis (lateral deviation), and lordosis (ventral deviation). A stiff neck or an arched back is often reflective of cervical or generalized spinal pain. Neck pain may manifest with horizontal neck carriage, increased muscle tone, and intermittent spasms/ jerks. The animal tends to move by turning the entire body when changing directions. When the arched back is centered to the thoracolumbar region, this may indicate pain localized to the caudal thoracic and lumbar regions. Arching of the back with low head carriage also

can be observed in animals with neck pain. An animal with pain localized to the lumbosacral area will have its pelvic limbs tucked under the caudal abdomen.

Postural Reaction Deficits

Various postural reactions (paw replacement, hopping, hemiwalking, wheelbarrow, extensor postural thrust) can further define the location and symmetry of the weakness. Asymmetric weakness is common with vascular, inflammatory, and compressive myelopathies.

Spinal Reflex Abnormalities

Spinal, myotatic, and withdrawal reflexes can assist with neuroanatomic localization to specific spinal regions (see Table 76.1). Presence of hypo- to areflexia of limb reflexes can localize the lesion to within an intumescence. The cutaneous trunci reflex can further assist with localization of a thoracolumbar spinal cord lesion.

Hyperesthesia

Hyperesthesia denotes an unpleasant behavioral response to a nonnoxious stimulus. As part of a routine neurologic examination, spinal hyperesthesia is evaluated by deep palpation of the spinal epaxial musculature and by detecting resistance with flexion-extension and lateral movements. Testing for spinal hyperesthesia should be performed near the end of the neurologic examination. Spinal palpation should begin distal to the suspected lesion localization. Cervical spinal hyperesthesia can be elicited by deep palpation of the cervical spinal musculature near the vertebral transverse processes. Clinical signs include caudal flinching of the ears, twitching spinal musculature, and behavioral signs of discomfort. The neck is manipulated by flexion, extension, and lateral movements. Normal animals have full range of movement with no resistance. Resistance or behavioral reluctance to move is evidence of spinal pain. Meningeal pain often is diffuse but will commonly localize to the cervical spine. Joint and muscle pain are assessed during palpation and evaluating range of motion of the limbs.

Differentials associated with spinal hyperesthesia include those associated with inflammation or compression (e.g., intervertebral disc herniation, neoplasia). Anatomic structures with nociceptors include the meninges, nerve roots, outer one-third of the disc, joints, periosteum, and muscle. Tissue damage or inflammation produces pain through stimulation of nociceptors that are sensitive to mechanical, thermal, and chemical stimuli. Neuropathic pain occurs with injury to neural tissue and represents abnormalities in transmission and somatosensory processing in the peripheral and central nervous systems. Some disease processes encompass both nociceptive/inflammatory and neuropathic pain mechanisms.

Loss of Nociception

Nociception (pain sensation) is considered the most important prognostic indicator for functional recovery of myelopathy. In dogs with thoracolumbar Hansen type I intervertebral disc herniation, the majority of those with intact nociception have an excellent prognosis. Dogs with loss of nociception longer than 24–48 hours prior to surgery have a poorer prognosis for return of ambulatory function. If surgery is performed within 12–36 hours, the prognosis is better for more rapid and complete recovery. In spinal fractures, however, animals with loss of nociception are assumed to have complete injury of neural tissues and have a poor prognosis for recovery.

Acute Spinal Cord Dysfunction

It is important to recognize specific physical and neurologic examination findings associated with acute spinal cord injury. Neurogenic shock is a systemic complication associated with severe cervical or cranial thoracic injury to the spinal cord. This syndrome results from sympathetic loss (decreased blood pressure and heart rate resulting from unopposed vagal tone) and continual vagal tone. This phenomenon results in loss of spinal cord blood flow regulation and subsequent ischemia. Neurogenic shock resolves with fluid therapy and pressor agents.

Spinal shock usually manifests as flaccidity of the limbs distal to the lesion. The spinal reflexes are depressed to absent. The bladder may be flaccid with urine retention and the sphincter hypotonic. This phenomenon may mislead a neuroanatomic localization if neurologic examination is not reassessed. The duration of spinal shock is proportional to the degree of species encephalization and thus may last only a few hours in quadrupeds. Cause may be cessation of tonic input of spinal neurons by excitatory impulses in descending pathways.

The Schiff–Sherrington posture is characterized by increased extensor tone of the thoracic limbs and flaccid paralysis of the pelvic limbs after acute T3–L3 spinal cord lesions. "Border cells," which exert inhibitory influences on extensor motor neurons of the thoracic limbs via the fasciculus proprius, are predominantly located in the L2–4 spinal cord segments. Damage to these cells or interruption of the fasciculus proprius as it ascends through the thoracolumbar spinal cord causes release of thoracic limb extensor motor neurons and hypertonia. Despite the increase in extensor tone, the thoracic limbs are neurologically normal. Schiff–Sherrington posture does not indicate that the spinal cord lesion is irreversible.

A *traction injury* of the spinal cord involving tethering of nerves often is traumatic in origin. This injury commonly involves the nerves associated with the sacrococcygeal and cervicothoracic spinal cord segments. Traction of nerves/nerve roots causes injury of associated spinal cord segments such as tail-pull and brachial plexus avulsion. For example, in cats with tail-pull injury, injury to the sacral segments affects the pelvic nerve and its innervation of the bladder, resulting in loss of bladder contraction.

Ascending and descending hemorrhagic myelomalacia should be suspected in dogs with thoracolumbar intervertebral disc disease (IVDD) that have an ascending loss of the cutaneous trunci reflex. Other neurologic signs of myelomalacia include loss of nociception caudal to the lesion, ascending and descending flaccidity, weakness and areflexia, which can lead to tetraplegia, hyperthermia, and respiratory distress. Death results from asphyxia from intercostal and diaphragmatic muscle paralysis. Clinical signs of ascending and descending myelomalacia may manifest in hours to several days from onset of paraplegia.

Diagnostic Approach

Diagnostic evaluation of an animal with spinal cord disease begins with bloodwork (complete blood count, serum biochemistry), urinalysis, and survey spinal radiographs. Thoracic radiography is recommended in animals older than 5 years or when neoplasia is considered a disease differential. If a diagnosis cannot be determined through these routine procedures, referral to a specialty practice is recommended.

Conventional radiography of the vertebral column can assist with recognition of obvious abnormalities such as congenital malformation, discospondylitis, fracture/luxation, and bone neoplasia. Meticulous technique, collimation, and proper patient positioning, usually under anesthesia or heavy sedation, are essential to detection of subtle changes that are often the key to a diagnosis. Although many lesions are obvious with cursory inspection, subtle changes may be difficult to appreciate.

However, in the majority of instances, the diagnostic capability of plain radiography of the vertebral column is limited. The diagnostic capabilities are improved with myelography, injection of iodinated contrast media into the subarachnoid space. Myelography is accurate and sensitive for identifying compressive lesions. Dynamic studies (traction, extension, flexion) also can be performed. Masses that occupy space in the vertebral canal (e.g., tumors, abscesses, disc herniations) cause alterations in the myelographic contrast column. The extradural, intradural/extramedullary, or intramedullary location can be determined by the type of distortion occurring in the contrast column.

Cross-sectional imaging includes computed tomography (CT) and magnetic resonance imaging (MRI) and is more likely to provide a definitive diagnosis. These imaging modalities are now available at many specialty practices. Lesion descriptions affecting the spinal cord are similar to those described for myelography. Administration of contrast media can improve visualization of pathology on MRI and CT. Intravenous administration of contrast media can increase the conspicuity of a lesion due to breakdown in the blood–brain barrier and better define its borders by creating greater contrast between the lesions and surrounding tissue.

Computed tomography is a cross-sectional imaging modality in which images are constructed based on the attenuation of X-rays through tissue. The main benefit of CT over conventional radiography is that with CT, there is greater soft tissue differentiation and lack of superimposition of overlying structures which greatly improves the evaluation of the vertebral column. CT also can assist with determining lesion extent after myelography. CT images should be evaluated for alterations in attenuation of tissues. Dark or relatively black areas are hypodense or hypoattenuating while light or relatively white areas are hyperdense or hyperattenuating. CT may provide more useful information than MRI in cases of vertebral fractures or subluxation where bony detail is important. Taking advantage of the density of dystrophic mineralized intervertebral disc material, CT can be used in the evaluation of chondrodystrophic dogs with suspected IVDD. Due to the inferior soft tissue contrast, assessment of soft tissues within spinal cord tissue is limited.

Magnetic resonance imaging is the preferred imaging modality for assessment of the spinal cord. The primary reason for this is the superior soft tissue contrast that MRI provides, allowing differentiation of anatomic structures. No other imaging procedure provides conspicuity of soft tissue discrimination along with exceptional resolution. Imaging can be performed in different planes (transverse, sagittal, dorsal) without loss of resolution, enabling examination of complex anatomic regions. MRI is based on the magnetic properties of hydrogen atoms, which are extremely abundant in tissues containing water, protein, and fat. Lesions are characterized based on number (single or multiple), intensity (hypo-, hyper-, isointense in relationship to an adjacent normal area), distribution of the intensity (homogeneous or heterogeneous), lesion borders (well or poorly defined), anatomic location of the lesion as well as lesion location in reference to the spinal cord and meninges. Similarly, lesions are characterized based on pattern of contrast enhancement.

Cerebrospinal fluid (CSF) is contained within the subarachnoid space, which lies between the arachnoid and pia mater. Cerebrospinal fluid analysis will assist with determining the presence of inflammatory disease. Abnormalities in CSF cytology and protein are sensitive indicators of CNS disease but rarely specific for a disease process. On occasion, infectious organisms or neoplastic cells may be identified. The CSF profile, including protein content, cell counts and cytology, will assist the clinician to narrow the differential diagnosis.

Additional diagnostic procedures include electrodiagnostic evaluation (electromyography and nerve conduction studies), CSF protein electrophoresis, serology, and exploratory surgery.

Differential Diagnosis

Myelopathies can be classified according to the DAMNIT V scheme (degenerative, anomalous, metabolic, neoplastic, nutritional, inflammatory-infectious/noninfectious, traumatic, toxic, vascular) (see Tables 76.1 and 76.2).

Degenerative

Degenerative conditions of the spinal cord can occur in both young and adult animals. Myelinopathies, axonopathies, and neuronopathies present initially with progressive signs of paraparesis and eventual tetraparesis. Many of these conditions are breed specific and inherited. Recent identification of gene mutations has enhanced our understanding of the underlying pathogenesis for many degenerative conditions associated with ion channel defects, abnormalities in protein aggregation, loss of enzyme function (storage disease), and dysfunction in protein metabolism and growth factors.

Canine degenerative myelopathy (DM) is an adult-onset neurodegenerative disease. Most dogs are at least 8 years old before onset of clinical signs. The initial signs of degenerative myelopathy typically include asymmetric GP ataxia and spastic paresis in the pelvic limbs. At this stage, segmental spinal reflexes are indicative of UMN loss. Dogs become nonambulatory paraparetic within one year after onset. When euthanasia is delayed, weakness can ascend to the thoracic limbs with emergence of LMN signs, dysphagia, and widespread muscle atrophy. Recently, a missense mutation in the gene superoxide dismutase 1 (*SOD1*) was established as a genetic "risk factor" for dogs developing DM. Dogs that are homozygous (two copies of the mutant allele) for the *SOD1* mutation are considered at risk for developing degenerative myelopathy. Because a variety of common acquired compressive spinal cord diseases can mimic early DM, a presumptive diagnosis is made by ruling out other spinal cord disorders by cross-sectional imaging and CSF analysis combined with results for the *SOD1* mutation analysis. A dog with progressive T3–L3 myelopathy that has normal neurodiagnostics and is homozygous for the *SOD1* mutation is likely to have degenerative myelopathy.

Degenerative conditions of the vertebral column such as intervertebral disc herniation, cervical spondylomyelopathy, and degenerative lumbosacral stenosis secondarily cause myelopathy by spinal cord compression. Other less common degenerative conditions of the vertebral column include synovial cysts, canal stenosis, and diffuse idiopathic skeletal hyperostosis (DISH).

Anomalies

Dogs and cats with congenital spinal malformations often have abnormalities involving multiple segments of the vertebral column and spinal cord. Malformations associated with the spinal cord are often referred to as spinal dysraphism that involve defects in closure of the neural tube. Such defects may also involve the vertebral column. Spinal dysraphism is a result of abnormal midline fusion and disrupts the normal pattern of spinal cord circuits. Other defects include syringomyelia, dermoid sinus, spina bifida, and caudal vertebral hypoplasia. Genetic mutations and exposure to toxic and infectious agents at certain stages of development can lead to these malformations. Abnormal formation of vertebral bodies by itself does not cause spinal cord dysfunction but some conditions can cause myelopathy from spinal cord compression or spinal canal stenosis.

Congenital anomalies affecting the craniocervical junction include atlantoaxial instability and atlantooccipital overlapping, which also can occur simultaneously. The subsequent spinal cord compression results in signs of C1–5 myelopathy or manifests as cervical spinal pain.

Metabolic

Endocrocrine-related peripheral neuropathies such as diabetes mellitus, hypothyroidism, and insulinoma paraneoplastic neuropathy reflect as sciatic nerve disease. Clinical signs appear in the pelvic limbs first and may mimic myelopathy.

Neoplastic

Tumors affecting the spinal cord are described as extradural, intradural-extramedullary, and intramedullary based on location with respect to the spinal cord. Intramedullary tumors include gliomas (astrocytoma, oligodendroglioma, and ependymoma) and neuronal-derived tumors. Common intradural-extramedullary

tumors include meningiomas, neuroepitheliomas, and nerve sheath tumors. Extradural tumors include primary bone tumors, metastatic tumors, and hematopoietic tumors (e.g., histiocytic disease, lymphoma, plasma cell tumors). Tumors that involve the vertebral body cause secondary spinal cord compression. Metastatic disease of the spinal cord can occur from spread within the CNS (drop metastasis) or from extraneural tissues via direct extension or hematogenously. Hemangiosarcoma, melanomas, and carcinomas are the most common tumors to metastasize to the spinal cord and vertebral column.

Inflammatory (Infectious, Noninfectious)

Meningitis (inflammation of the meninges) and meningomyelitis (inflammation of the meninges and spinal cord) cause focal or diffuse signs of myelopathy and severe spinal pain. Onset is acute, peracute or insidious. Signs typically progress but can wax and wane. Neurologic signs are variable and related to the area of spinal cord affected. Common clinical signs include GP ataxia, limb paresis, and paraspinal hyperesthesia. Lesion distribution can be focal or multifocal, causing asymmetric neurologic deficits. Animals with meningomyelitis could also have signs of encephalitis. Spinal cord MRI combined with CSF analysis is the most reliable diagnostic approach for identifying the presence and extent of CNS inflammation. Some infectious agents affect other organ systems in addition to the CNS. Serology and molecular techniques screen for infectious etiologies. Disease confirmation often requires biopsy or necropsy examination.

Common infectious diseases causing myelopathy include viral (e.g., feline coronavirus, feline infectious peritonitis, canine distemper virus, feline immunodeficiency virus, feline leukemia virus), protozoal, rickettsial, algal, and fungal diseases. In the dog, canine distemper virus and protozoa are the most frequently identified agents. Infectious meningomyelitis seems to be the most common cause underlying myelopathy in the cat. Granulomatous meningoencephalomyelitis (GME) and steroid-responsive meningitis-arteritis are noninfectious inflammatory diseases that predominate in the dog.

Inflammation/infections of the vertebral column can involve the vertebra (osteomyelitis, physitis) or intervertebral disc space (discospondylitis). Spinal cord epidural empyema is defined as an extensive accumulation of purulent material in the epidural space of the vertebral column related to direct extension of osteomyelitis or discospondylitis. Discospondylitis is associated with bacterial or fungal infection of the intervertebral disc and contiguous vertebrae. Hyperesthesia of the vertebral column is the primary clinical sign. Radiographic features of discospondylitis include lysis and sclerosis of the vertebral endplates. Pathologic changes and lesion extent can be more conspicuous with CT and MRI. Due to its zoonotic potential, *Brucella canis* screening is indicated. Antimicrobial selection should be based on susceptibility testing of bacteria isolated from urine or blood or from infected tissue.

Trauma

Animals with spinal fractures and luxations are assessed with minimal manipulation to prevent further injury and displacement of the spine. Nociception is assessed in plegic animals to assist with determining prognosis. Spinal fracture/luxation in dogs and cats is most commonly associated with severe external trauma and results in spinal cord dysfunction. Diagnosis is based on radiography or cross-sectional imaging of the entire spine. Nonsurgical or surgical management depends upon presence of instability. The prognosis for recovery from a spinal fracture/luxation with loss of nociception is considered poor.

Vascular Occlusive Disorders

Fibrocartilaginous embolic myelopathy is the most common cause of vascular occlusion of the spinal cord in dogs and infrequently can occur in cats. FCE most commonly affects the younger, larger dog breeds but also occurs in small dog breeds, with the miniature schnauzer overrepresented. Onset of signs is often peracute or acute with little progression. Key neurologic signs include asymmetric paresis with lack of paraspinal hyperesthesia. Localization frequently reflects the segments of the cervicothoracic and lumbosacral intumescences; however, segments within L4–S3 and T3–L3 are most commonly reported. The pathogenesis still remains enigmatic. Spinal cord arteries become occluded with fibrocartilage that originates from the nucleus pulposus of the intervertebral disc. The clinical presentation is sometimes difficult to distinguish from the concussive, noncompressive extrusions of the intervertebral disc. Prognosis is dependent on the severity of neurologic deficits, lesion location and extent, and owner's commitment to nursing care. The prognosis is favorable in patients that show improvement within two weeks of onset.

In cats with acute onset of asymmetric paresis/paralysis, aortic thrombosis is a primary differential. The pelvic limbs are commonly affected, with signs of loss of femoral pulse, pain and firmness in the muscles, and loss of nociception distally. Hypertrophic cardiomyopathy is the most frequent underlying disease. Diagnosis is suspected based upon clinical signs, elevated creatine kinase concentration, and evidence of cardiac disease. Initial therapy involves management of the cardiac disease, preventing further clot

formation and supportive care. Long-term prognosis is guarded during the early recovery phase.

Treatment

Treatment of myelopathy is determined based on the underlying disease diagnosis. Specific treatment approaches focus on surgical decompression of compressive lesions, excision/debulking of compressive masses (neoplasia, cyst), stabilization procedures and appropriate therapy of infectious and inflammatory diseases. Principles of appropriate supportive care and physical rehabilitation assist with expediting recovery and prevention of secondary complications of a recumbent patient.

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77

Neuroophthalmology

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Neuroophthalmology is a complex discipline involving the intricate relationship between the eye and the central nervous system (CNS). A thorough understanding of afferent and efferent pathways is crucial in the localization and diagnosis of neuroophthalmic disorders. A review of normal anatomy and physiology is beyond the scope of this chapter and can be found elsewhere. Abnormalities in the afferent or efferent arm may present as changes in vision, eye position, tear production, eyelid carriage, function, sensation, and pupil shape, size or response. This chapter will focus on common neuroophthalmic diseases.

Amaurosis

Amaurosis is defined as partial or complete vision loss without observable ophthalmic pathology. Clinical signs of vision loss include a reduced or absent menace response, inability to track a cotton ball, failure to navigate around stationary objects, and possibly an absent dazzle reflex or pupillary light reflex (PLR). Amaurosis may be caused by primary retinal disease, such as sudden acquired retinal degeneration syndrome (SARDS), retrobulbar optic nerve disease, or any lesion along the optic chiasm, optic tract, lateral geniculate nucleus, optic radiation, or visual cortex. Electroretinography (ERG) is essential in differentiating retinal disease from CNS disease as ERG will identify a retina that appears normal on examination but fails to function properly. Frequently, magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis are instrumental in diagnosing a primary CNS cause of vision loss. Neoplasia is the most common CNS cause of vision loss in dogs and cats. Prognosis for return of vision is grave with SARDS and poor with CNS disease, depending on the underlying etiology.

Optic Neuritis

Inflammation of the optic nerve is usually bilateral and results in complete vision loss with the absence of pupillary light reflexes. On ophthalmic exam, the optic disc is enlarged and hyperemic with focal hemorrhages and peripapillary retinal detachment (Figure 77.1). If only the retrobulbar optic nerve is affected, the ophthalmic exam will be normal and diagnosis is confirmed through a normal ERG and abnormal MRI. T2-weighted MRI may reveal an enlarged, moderately hyperintense optic nerve. CSF analysis in dogs with optic neuritis is variable and may reveal a marginal to marked increase in protein or cellularity.

Optic neuritis can be secondary to infectious, inflammatory, and neoplastic disease. In dogs, infectious causes include viral (distemper and tick-borne encephalitis virus), fungal (cryptococcosis, blastomycosis, histoplasmosis), protozoal (toxoplasmosis), and bacterial (ehrlichiosis). Granulomatous meningoencephalitis is the most common inflammatory disorder, although idiopathic and necrotizing meningoencephalitides have also been reported. Primary optic nerve tumors and space-occupying retrobulbar masses may trigger secondary nerve inflammation. In cats, optic neuritis is often secondary to feline infectious peritonitis, but may be due to other infectious diseases, including cryptococcosis and toxoplasmosis. Most cases of optic neuritis are considered idiopathic due to lack of an apparent cause even with a thorough systemic medical work-up.

Treatment of optic neuritis is directed at the underlying cause when feasible. If no underlying cause is identified, immunosuppressive doses of corticosteroids are used to reduce inflammation. Even with appropriate therapy, prognosis for return of vision is poor and optic nerve atrophy is an unfortunate common end-result.

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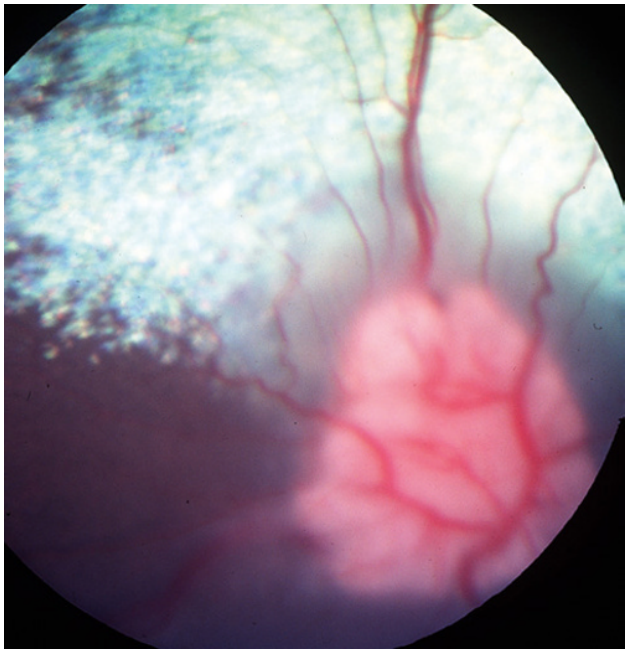


Figure 77.1 Idiopathic optic neuritis in a dog. Note the optic disc is edematous and hyperemic with peripapillary retinal detachment.

Anisocoria

Pupil diameter is regulated by autonomic control of the iris sphincter and iris dilator muscles. Anisocoria is defined as unequal pupils. Physiologic anisocoria may occur with heterochromia iridis or age-related iris atrophy with the affected pupil dilated. When not physiologic, determination of which pupil is abnormal can be challenging. Examination of the patient in bright, ambient, and dim light conditions facilitates diagnosis. An abnormal mydriatic pupil will not constrict completely in bright light compared to the normal pupil. In contrast, an abnormal miotic pupil will not dilate completely in dim light compared to the normal pupil.

Unilateral mydriasis in dogs and cats can have primary ocular or neurogenic causes. Ocular causes include iris atrophy, glaucoma, end-stage retinal degeneration, optic nerve atrophy, and pharmacologic dilation with agents such as tropicamide or atropine. Neurogenic causes include a lesion in the parasympathetic nerve, oculomotor nerve, or brainstem. Due to the unique innervation of the cat sphincter muscle by two short ciliary nerves controlling either side of the iris, parasympathetic denervation may result in hemiplegia and a "D" shaped or reverse "D" shaped pupil. Iris sphincter hemiplegia has been associated with trauma and iris stromal infiltration by lymphoma. Mydriasis alternating between eyes is secondary to feline spastic pupil syndrome. Cats affected with feline spastic pupil syndrome tend to be feline leukemia positive with C-type virus particles present within the ciliary nerves or ganglia.

Unilateral miosis in dogs and cats can be secondary to anterior uveitis, Horner's syndrome (discussed later), or pharmacologic agents such as pilocarpine or topical prostaglandin analogs. Anterior uveitis is differentiated from Horner's syndrome based on concurrent ophthalmic clinical signs including conjunctival hyperemia, episcleral congestion, corneal edema, blepharospasm, aqueous flare, keratic precipitates, and ocular hypotony.

Internal and External Ophthalmoplegia

Unilateral mydriasis may be secondary to an afferent or efferent defect. Afferent defects involve the retina, optic nerve, or optic tract. Efferent defects involve the oculomotor nucleus, oculomotor nerve, or iris sphincter muscle. Vision and PLR testing are vital in distinguishing afferent from efferent defects. Animals with afferent lesions are nonvisual, have an absent direct PLR, and an absent consensual (affected to nonaffected eye) PLR. Animals with efferent lesions are visual, have an absent direct PLR, and a normal consensual (affected to nonaffected eye) PLR. The presence of a normal consensual PLR from the nonaffected eye to the affected eye rules out an efferent arm lesion.

Efferent lesions may involve the oculomotor nucleus, oculomotor nerve, or iris sphincter muscle. Peripheral parasympathetic fibers along the medial aspect of the oculomotor nerve are responsible for pupillary constriction. The oculomotor nerve also innervates extraocular muscles (superior, medial, and inferior rectus, inferior oblique) and the levator palpebrae superioris muscle. Lesions affecting just the peripheral aspect of the nerve will result in mydriasis only, termed *internal ophthalmoplegia* (Figure 77.2). Lesions affecting the entire nerve will result in lateral strabismus and ptosis, adding the diagnosis of external ophthalmoplegia. External ophthalmoplegia is defined as paralysis of one or more of the extraocular muscles and may only involve the oculomotor nerve or may also involve the trochlear and abducens nerves.

When evaluating mydriasis, it is important to distinguish ophthalmoplegia from a pupillomotor defect. Pupillomotor defects are usually secondary to iris atrophy or previous topical anticholinergic medication administration. Animals with iris atrophy may have a slight direct PLR or may have a characteristic scalloped appearance to the pupillary margin. When these signs are absent, pharmacologic testing is useful in differentiating a pupillomotor defect from ophthalmoplegia.



Figure 77.2 Internal ophthalmoplegia in a dog. The right pupil is normal. The left pupil is mydriatic with an absent direct and consensual (right to left) PLR. Topical application of 2% pilocarpine resulted in pupil constriction within five minutes, confirming an efferent pathway deficit.

Pharmacologic testing has classically involved the use of both indirect- and direct-acting parasympathomimetics. Indirect acting agents, such as topical 0.5% physostigmine, will cause rapid pupillary constriction in cases of a preganglionic (proximal to the cilary ganglion) lesion due to release of acetylcholine stores at the postganglionic axon terminals. Direct-acting agents, specifically 1% to 2% pilocarpine, are more commonly used. One drop of pilocarpine acts directly on the iris sphincter muscle by binding to and activating acetylcholine receptors, inducing pupil constriction within 30 minutes. Use of a direct-acting agent will allow pupil constriction with both pre- and postganglionic lesions and therefore is useful in differentiating ophthalmoplegia from a pupillomotor defect but does not differentiate a preganglionic from a postganglionic site. Lack of pupillary constriction following administration of a topical parasympathomimetic confirms a pupillomotor defect. In a young dog or one without clinical evidence of iris atrophy, pharmacologic mydriasis is commonly the cause. A thorough history will aid in diagnosis.

Internal and external ophthalmoplegia occur as a result of oculomotor nerve, ganglion, or nucleus compression. They are a result of neoplasia, trauma, or inflammation at the level of the midbrain, brainstem, or cavernous sinus. Other CNS signs may be evident depending on the specific localization of the lesion.

The presence of concurrent internal and external ophthalmoplegia should prompt the clinician to evaluate for intracranial disease to explain involvement of multiple cranial nerves. Imaging (MRI) is the diagnostic tool of choice. Treatment is limited unless the underlying cause is found. Prognosis is poor as most cases progress to involve adjacent CNS sites.

Trigeminal Nerve Deficit

Two of the three branches of the trigeminal nerve provide sensory innervation to the eye, adnexa, and periocular skin. Lateral sensation is primarily via the maxillary branch and medial sensation via the ophthalmic branch. Corneal sensation is derived through afferent fibers within the long ciliary nerves that originate in the ophthalmic branch. Decreased or absent function is diagnosed through an absent palpebral reflex (i.e., blink response) and an absent corneal reflex. Lack of sensation must be distinguished from lack of motor function (facial nerve deficit) where the patient is unable to blink. Differentiation is accomplished by attempting to elicit a menace response or dazzle reflex while avoiding contact with the skin. A patient with trigeminal nerve dysfunction will blink in response whereas animals with a facial nerve defect will not have a palpebral reflex or normal menace response.

The long ciliary nerves derive from the nasociliary nerve, a branch of the ophthalmic branch of the trigeminal nerve. Inadequate function of the long ciliary nerves results in corneal anesthesia or hypoesthesia. With loss of these neurons, there is a loss of normal regulatory neuromediators such as acetylcholine, substance P, calcitonin gene-related peptide, and neuropeptide Y which are instrumental in maintaining normal corneal integrity. Neurotrophic keratitis describes pathology resulting from a trigeminal nerve defect. The decrease in corneal sensation leads to reduced corneal epithelial cell proliferation and delayed healing with corneal ulceration. Neurotrophic keratitis is likely secondary to trigeminal nerve trauma, but as in humans, diabetes mellitus and herpes virus may be predisposing factors.

The mandibular branch of the trigeminal nerve has both motor and sensory components. It is responsible for motor innervation to the masticatory muscles and sensation to the mouth, lower face, and ear. Bilateral disruption of the mandibular branch results in the inability to close the mouth. Ninety percent of cases are idiopathic and clinical signs typically resolve over three weeks. Prolonged cases may develop atrophy of the muscles of mastication. When the pterygoid muscles are affected,



Figure 77.3 Neurotrophic and neuroparalytic keratitis in a dog. Note the left eye is enophthalmic, the third eyelid is elevated, the ocular surface is dry, and a deep, infected stromal corneal ulcer is present. Also note the severe masseter and temporalis muscle atrophy. Neuroophthalmic localization of the lesion is at the petrosal temporal bone.

secondary enophthalmos and passive third eyelid elevation may occur (Figure 77.3).

Treatment for trigeminal nerve defects is supportive. Topical lubricating agents are recommended to support surface ocular health and symptomatic treatment for secondary corneal ulceration is indicated when necessary. As most cases are secondary to trauma or are idiopathic, prognosis for return of function is fair. Other reported causes of trigeminal dysfunction include neoplasia and polyneuritis of unknown origin.

Facial Nerve Paralysis

The efferent arm of the palpebral, menace, corneal, and dazzle reflex are all mediated by the facial nerve. The facial nerve arises at the facial nucleus in the brainstem and courses with the vestibulocochlear nerve through the petrosal bone before branching. Ultimately, the zygomatic branch innervates the orbicularis oculi and retractor anguli oculi muscles and controls the blinking response. Clinical signs associated with facial nerve paralysis may be restricted to the eye or may also involve other structures, depending on the site affected. Nonocular clinical signs associated with facial nerve paralysis may include deviation of the nasal septum toward the unaffected side, drooping of the ipsilateral lip or pinna, and lack of sensation to the inner pinna. Ocular signs of facial nerve paralysis include an absent palpebral reflex, neuroparalytic keratitis, and, potentially, neurogenic dry eye.

Differentiation of facial nerve paralysis from trigeminal nerve dysfunction can be difficult. Animals with facial nerve paralysis still have normal sensation and may retract their eye and elevate the third eyelid in response to a menacing gesture or painful stimulus applied to the adnexa. Animals with a trigeminal nerve defect have a normal menace response.

Without the ability to close the eyelids completely, neuroparalytic keratitis may arise due to chronic corneal exposure and tear film evaporation. With progression, corneal vascularization, scarring, and ulceration ensue (see Figure 77.3). Corneal protection is the treatment of choice and involves the use of topical lubricants, topical antibiotics, and possibly placement of a temporary tarsorrhaphy. If the parasympathetic fibers that run with the facial nerve to the lacrimal gland are affected, neurogenic dry eye will occur. Approximately 20% of dogs with facial nerve paralysis develop neurogenic dry eye that can be diagnosed by a routine Schirmer tear test. Concurrent neurogenic dry eye hastens corneal deterioration. Treatment with oral or topical parasympathomimetics will aid in return of tear production due to denervation hypersensitivity and upregulation of acetylcholine receptors at the lacrimal gland.

Facial nerve paralysis is reported to be idiopathic in 75% of dogs and 25% of cats. Other causes include surgery, trauma, neoplasia, hypothyroidism, and otitis media. Total ear canal ablation and bulla osteotomy surgery results in facial nerve paralysis or paresis in 49% of dogs and cats. Median time to restoration of function is 2–4 weeks. Neoplasia is an uncommon cause in dogs, but the most common in cats. Inflammation of the middle or inner ear is often present with facial nerve paralysis. With primary or secondary petrosal bone inflammation, other neuropathies may become apparent. The trigeminal, vestibulocochlear, glossopharyngeal, and oculosympathetic and parasympathetic nerves course through the petrosal bone. Therefore, additional clinical signs may include ocular and facial anesthesia or hypoesthesia, neurotrophic keratitis, masticatory muscle atrophy, vestibular disease, loss of taste sensation, and Horner's syndrome. Fifty to sixty percent of dogs and cats with facial nerve paralysis will have additional signs, with vestibular disease most common in cats and hypothyroidism or vestibular disease most common in dogs.

Treatment of facial nerve paralysis involves addressing the underlying cause when present. All patients with facial nerve paralysis should have a thorough otic exam and a thyroid level completed. If an underlying cause is not found, and true idiopathic facial nerve paralysis exists, supportive care to involve ocular lubrication and protection is indicated. Prognosis for return to function is guarded, with some cases improving in several weeks and others never.

Horner's Syndrome

Sympathetic fibers to the eye originate in the paraventricular nucleus of the hypothalamus, course within the spinal cord and exit between T1 and T3 into the thoracic cavity, forming the sympathetic trunk. These fibers travel through the mediastinum and join the vagosympathetic trunk in the neck before synapsing at the cranial cervical ganglion located adjacent to the tympanic bulla. All fibers prior to this synapse are considered preganglionic and those that course from the cranial cervical ganglion to the eye are considered postganglionic. Any disruption of nerve conduction along this circuitous route will lead to the classic clinical signs of Horner's syndrome.

Clinical signs include ptosis secondary to loss of tone in Müller's muscle of the upper and lower eyelid, miosis due to loss of sympathetic tone in the iris dilator muscle, and enophthalmos with secondary third eyelid elevation due to loss of smooth muscle tone of the periorbita (Figure 77.4). These four clinical signs are diagnostic for Horner's syndrome. Depending on where nerve conduction is disrupted, these may be the only clinical signs, or additional clinical signs may be present, including altered behavior/mentation, altered gait or paresis, spinal or neck pain, dysphagia, coughing, regurgitation, otitis media, vestibular disease, keratoconjunctivitis sicca, or facial nerve paralysis. Localization of the lesion is important for both prognosis and potential treatment.

Pharmacologic testing along with identifying clinical signs are useful in differentiating preganglionic from postganglionic Horner's syndrome. Topical application of indirect-acting sympathomimetic drugs such as 1% hydroxyamphetamine will induce norepinephrine release from postganglionic neurons, allowing immediate pupil dilation. This positive test confirms preganglionic Horner's syndrome. There is no effect of an indirect-acting sympathomimetic with cases of postganglionic Horner's syndrome. With the difficulty in obtaining these agents and abuse potential, this testing is rarely completed. Direct-acting sympathomimetic agents such as 0.001% epinephrine or dilute (1%) phenylephrine can be used to confirm a postganglionic lesion due to denervation hypersensitivity of smooth muscle. With a postganglionic defect, application of these agents will allow improvement of the clinical signs within 5–20 minutes. Lack of a response is suggestive, but not diagnostic, of a preganglionic lesion.



Figure 77.4 Horner's syndrome in a cat, demonstrating ptosis of the left upper eyelid, enophthalmos, third eyelid elevation, and miosis.

Preganglionic lesions carry a worse prognosis than postganglionic. The majority of preganglionic cases are secondary to neoplasia, vascular events, or significant head, neck, brachial plexus, or chest trauma. A diagnosis of preganglionic Horner's requires further diagnostics to localize the lesion and should include a complete blood count, serum biochemistry, thyroid level, thoracic radiography, MRI of brain and spinal cord, and CSF analysis. Treatment is directed toward the underlying cause. Prognosis for return of function is guarded.

Postganglionic lesions tend to be idiopathic or secondary to otitis media, but can be secondary to retrobulbar disease or trauma. If there is no evidence of ear disease, an idiopathic cause is assumed. Golden retrievers and Labrador retrievers between the ages of 10 and 12 years are overrepresented. Most cases of idiopathic, postganglionic Horner's syndrome resolve without treatment within two months.

Cavernous Sinus Syndrome

The cavernous sinus incorporates two venous sinuses located at the base of the cranial vault extending from the orbital fissure to the petrooccipital canal. The sinuses are joined by several anastomoses across the midline. Structures of clinical significance that pass through or are in close proximity to the cavernous sinus include the oculomotor nerve, trochlear nerve, ophthalmic and maxillary branches of the trigeminal nerve, abducens nerve, and postganglionic sympathetic axons.

Dogs and cats with cavernous sinus syndrome present with a multitude of clinical signs related to the affected cranial nerves, including internal and external ophthalmoplegia (mydriasis, ptosis, lateral or ventrolateral strabismus), corneal anesthesia, periorbital and facial anesthesia, and enophthalmos. Most cases are unilateral, with rare bilateral cases reported. Mean age of affected dogs and cats is 9 and 10 years of age, respectively.

Diagnosis is obtained through observation of the clinical signs. Advanced imaging, preferably MRI, is necessary to confirm the diagnosis. Most reported cases in dogs occur secondary to primary or metastatic neoplasia. In cats, intracranial neoplasia and infectious disease

have been reported. Long-term prognosis is poor even with treatment aimed at the underlying cause.

Dysautonomia (Key–Gaskell or Dilated Pupil Syndrome)

Dysautonomia is a rare, idiopathic condition in which there is generalized loss of autonomic nervous system function secondary to degeneration of parasympathetic and sympathetic neuronal ganglia. Ophthalmic clinical signs may be the first observed and include bilateral mydriasis with absent PLR, elevated third eyelids, ptosis, and decreased tear production. Dysautonomia can be readily differentiated from Horner's syndrome by the presence of mydriasis rather than miosis. Nonocular clinical signs may include xeromycteria, xerostomia, dysphagia, vomiting, regurgitation, gastric distension, anorexia, diarrhea, bradycardia, constipation, and urinary bladder distension.

Both cats and dogs can be affected, although the disease is much more prevalent in cats. A geographic distribution has been suggested, with most affected cats living in the United Kingdom and most affected dogs living in the American Midwest. Animals tend to be young and have a rapid onset (two days to two weeks). Although there is no known cause, 50% of cats in one study did test positive for *Clostridium botulinum* type C.

Diagnosis of dysautonomia is generally accomplished through the overt clinical signs. Pharmacologic testing as described previously for internal ophthalmoplegia and Horner's syndrome can be completed. In cases of dysautonomia, application of dilute pilocarpine will induce pupillary constriction and application of dilute epinephrine or phenylephrine will allow third eyelid retraction.

Treatment for dysautonomia is supportive. Prognosis for survival is poor, with 75–85% of animals succumbing to the disease or being euthanized due to the difficulty in maintenance of supportive care. Some cats have spontaneously recovered, although this is rare and should not be expected.

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Dedication

To CB Chastain, Dick Nelson and Ed Feldman for trying their best to make me a better clinician. For someone interested in internal medicine and endocrinology I could not have had better mentors.

To all of my former students, interns and residents, thanks so much for always keeping me honest and forcing me to try to stay ahead of those I was supposed to be teaching.

To all the wonderful folks at Wiley (Erica Judisch, Gillian Whitley, Purvi Patel, Holly Regan-Jones, and Katrina Maceda) that made this book possible and tried their best to keep me on track. You turned the idea into reality and improved the book at every step in the process.

To my amazing children McKenna, Taylor, Ivy and Cole, thanks for letting me be a part of your lives. Being your Dad is the best job in the world.

To my amazing wife and best friend Maya. You make my life complete and I look forward to sharing every day with you.

Contents

Preface *xix*
List of Contributors *xxi*
About the Companion Website *xxix*

VOLUME I

Section 1 Evaluation and Management of the Patient *1*

1 **The Concept of One Medicine** *3*
Lonnie J. King

2 **Statistical Interpretation for Practitioners** *7*
Philip H. Kass

3 **Using Data for Clinical Decision Making** *17*
Philip H. Kass

Section 2 Endocrine Disease *27*

4 **Principles of Endocrinology** *29*
Robert Kemppainen

5 **Neuroendocrinology** *35*
Maya Lottati

6 **Feline Acromegaly** *43*
David S. Bruyette

7 **Pituitary-Dependent Hyperadrenocorticism in Dogs and Cats** *49*
David S. Bruyette

8 **Polyuria and Polydipsia** *65*
Jennifer L. Garcia

9 **Canine Hypothyroidism** *71*
David S. Bruyette

10 **Feline Hyperthyroidism** *75*
David S. Bruyette

11 Hypoadrenocorticism in Dogs and Cats 81
Patty Lathan

12 Diabetes Mellitus in Dogs and Cats 93
Jacquie S. Rand

13 Hypoglycemia in Patients without Diabetes Mellitus: Evaluation and Management 103
Rhett Nichols

14 Canine Autoimmune Polyglandular Syndromes 113
Deborah Greco

Section 3 Cardiovascular Disease 117

15 Approach to the Patient with Suspected Cardiovascular Disease 119
Ingrid Ljungvall and Jens Häggström

16 Imaging in Cardiovascular Disease 127
Valérie Chetboul

17 Electrocardiography 165
Anna R.M. Gelzer and Marc S. Kraus

18 Pathophysiology of Heart Failure 175
Barret J. Bulmer

19 Management of Heart Failure 185
Steven Rosenthal and Mark A. Oyama

20 Ventricular Arrhythmias 199
Amara H. Estrada and Romain Pariaut

21 Supraventricular Arrhythmias 205
Romain Pariaut and Amara H. Estrada

22 Systemic Hypertension 219
Rebecca L. Stepien

23 Pulmonary Hypertension 225
Heidi B. Kellihan

24 Congenital Heart Disease 231
Brian A. Scansen

25 Valvular Heart Disease 245
Michele Borgarelli

26 Canine Myocardial Disease 253
M. Lynne O'Sullivan

27 Feline Myocardial Disease 267
Virginia Luis Fuentes

28 Pericardial Disease 275
Ashley B. Saunders and Sonya G. Gordon

Section 4 Respiratory Disease 287

29 A Respiratory Pattern-Based Approach to Dyspnea 289
Christopher G. Byers

30 Feline Bronchial Asthma 297
Christine M. Serafin

31 Canine Chronic Bronchitis 305
Kevin Kumrow

32 Pulmonary Thromboembolism 313
Robert Goggs

33 Surgical Approaches to Thoracic Disease 325
Raegan Wells

34 Pleural Effusion 333
Ashley Allen and Gareth Buckley

Section 5 Critical Care Medicine 345

35 Approach to the Patient in the Critical Care Setting 347
Sarah Allen

36 Fluid Therapy 355
Teresa Rieser

37 Cardiopulmonary Resuscitation 365
Nathan Peterson

38 Respiratory Monitoring in Critical Care 373
Mathew Mellema

39 Acute Respiratory Failure 381
Matthew Mellema

40 Mechanical Ventilation 393
Kate Hopper and Mathew Mellema

41 Approach to the Patient with Shock 403
James W. Barr

42 Cardiogenic Shock 413
Nathan Peterson and James W. Barr

43 Septic Shock 421
James W. Barr

44 Disorders of Heat and Cold 431
Sarah Allen

45 Acute Poisoning 437
Ben O'Kelley

46 Medical Management of Trauma and Burns 445
Nathan Peterson

47 Venomous Snake Bites 459
Nathan Peterson

Section 6 Gastrointestinal Disease 467

48 Gastrointestinal Imaging 469
Susanne M. Stieger-Vanegas

49 Gastrointestinal Endoscopy 507
Craig Ruaux

50 Diseases of the Oral Cavity and Salivary Glands 533
Maria M. Soltero-Rivera and Alexander M. Reiter

51 Gastritis and Gastric Ulceration in Dogs and Cats 547
Katie Tolbert and Emily Gould

52 Disorders of the Esophagus 557
Silvia Funes and Craig Ruaux

53 Motility Disorders of the Alimentary Tract 563
Reto Neiger and Silke Salavati

54 Exocrine Pancreatic Insufficiency in Dogs and Cats 583
Panagiotis G. Xenoulis

55 Pancreatitis in the Dog 591
Caroline Mansfield

56 Pancreatitis in the Cat 601
Craig Ruaux

57 Rectoanal Diseases – Medical and Surgical Management 609
Craig Ruaux and Milan Milovancev

58 Dysbiosis and the Use of Pre-, Pro- and Synbiotics 621
Jan S. Suchodolski

59 Diagnosis and Management of Chronic Enteropathies 627
Karin Allenspach

Section 7 Diseases of the Liver, Gallbladder, and Bile Ducts 639

60 Approach to the Patient with Liver Disease 641
Emma O'Neill

61 Imaging in Hepatobiliary Disease 659
Esther Barrett

62 Metabolic, Toxic, and Neoplastic Diseases of the Liver 677
Jan Rothuizen

63 Feline Inflammatory Liver Disease 687
Nicki Reed

64 Canine Inflammatory Liver Disease 695
Nick Bexfield

65 Cirrhosis and its Consequences 705
Katherine Scott

66 Portosystemic Shunts and Microvascular Dysplasia 713
Geraldine Hunt

67 Diseases of the Gallbladder and Extrahepatic Biliary Ducts 721
Ben Harris

Section 8 Neurologic Disease 727

68 The Neurologic Examination 729
Alexander de Lahunta

69 Central Nervous System Trauma 741
Simon R. Platt

70 Seizures and Movement Disorders 759
Michael Podell

71 Disorders of the Forebrain 773
Sam N. Long

72 Vestibular Disease 789
Tammy Stevenson

73 Meningoencephalitis and Meningomyelitis 795
Christopher L. Mariani

74 Diseases of the Neuromuscular Junction 803
David Lipsitz

75 Myopathies 811
Marguerite F. Knipe

76 Myelopathy 815
Joan R. Coates

77 Neuroophthalmology 823
Bradford J. Holmberg

VOLUME II

Section 9 Infectious Disease 829

Part 1 Diagnostic Considerations 831

78 Epidemiology of Infectious Disease 833
Peggy L. Schmidt and Helen T. Engelke

79 Laboratory Diagnosis of Infectious Diseases 839
Laia Solano-Gallego and Gad Baneth

Part 2 Select Infectious Diseases and Disease Agents 849

80 Canine Distemper 851
David S. Bruyette

81 Canine Herpesvirus 855
Yvonne Drechsler

82 Canine Viral Enteritis 857
Margaret C. Barr

83 Viral Papillomatosis 861
Margaret C. Barr

84 Canine Influenza Virus 865
Ellen Collisson

85 Feline Parvovirus 869
Margaret C. Barr

86 Feline Coronavirus 873
Yvonne Drechsler

87 Feline Leukemia Virus 877
David S. Bruyette

88 Feline Immunodeficiency Virus 883
Tom Phillips

89 Feline Viral Upper Respiratory Tract Disease 887
Yvonne Drechsler

90 Rabies in Dogs and Cats 891
Emily Beeler and Karen Ehnert

91 West Nile Virus 899
Tracey McNamara

92 Ebola Virus 901
Linda Kidd

93 **Ehrlichiosis and Anaplasmosis** *903*
Pedro P. Vissotto de Paiva Diniz

94 **Salmon Poisoning Disease** *913*
Pedro P. Vissotto de Paiva Diniz

95 ***Wolbachia pipientis* Infection** *917*
Pedro P. Vissotto de Paiva Diniz

96 **Bartonellosis** *919*
Pedro P. Vissotto de Paiva Diniz

97 **Hemotropic *Mycoplasma*** *927*
Séverine Tasker

98 **Nonhemotropic *Mycoplasma*, *Ureaplasma*, and L-Form Bacteria** *931*
Joachim Spergser

99 **Spotted Fever and Typhus Group Rickettsia** *937*
Linda Kidd

100 **Lyme Borreliosis** *941*
Meryl P. Littman

101 **Leptospirosis** *945*
Katharine F. Lunn

102 **Yersiniosis** *951*
Maria Grazia Pennisi

103 **Tularemia** *955*
Linda Kidd

104 **Q Fever** *959*
Linda Kidd

105 **Brucellosis** *963*
Erin E. Runcan and Marco A. Coutinho da Silva

106 **Tetanus and Botulism** *967*
Andrea Fischer

107 **Anthrax** *971*
Wayne E. Wingfield and Jerry J. Upp

108 **Actinomycosis, Nocardiosis, and Mycobacterial Infections** *977*
Joanna Whitney and Vanessa R. Barrs

109 **Fungal Infections** *985*
Jane E. Sykes

110 **Protozoal and Protozoa-Like Infections** *1003*
Gad Baneth and Laia Solano-Gallego

111 Coccidia 1023
Chris Adolph

112 Surgical, Traumatic, and Bite Wound Infections 1029
Laura L. Nelson

113 Canine Infectious Respiratory Disease Complex 1035
Jonathan Dear

Part 3 Therapeutic Considerations 1039

114 Antimicrobial Therapy in Dogs and Cats 1041
Katrina R. Viviano

115 Antifungal Therapy 1049
Daniel S. Foy

Part 4 Special Topics 1055

116 Nosocomial and Multidrug-Resistant Infections 1057
Jason W. Stull and J. Scott Weese

117 Management of Infectious Disease in Kennels and Multicat Environments: Creating a Culture of Compliance 1063
Frank Bossong

Section 10 Renal and Genitourinary Disease 1067

118 Disorders of Sodium and Water Homeostasis 1069
Julien Guillaumin and Stephen DiBartola

119 Disorders of Phosphorus and Magnesium 1079
Rosanne Jepson

120 Acute Kidney Injury 1089
Adam E. Eatroff

121 Glomerular Disease 1101
Shelly L. Vaden

122 Obstructive Uropathy 1109
Edward Cooper and Brian A. Scansen

123 Urolithiasis in Small Animals 1123
Alice Defarges, Michelle Evason, Marilyn Dunn, and Allyson Berent

124 Prostatic Diseases 1157
Serge Chalhoub

125 Management of Chronic Kidney Disease 1165
Jessica Quimby

126 The Role of Dialysis 1175
Adam E. Eatroff

127 Micturition and Associated Disorders 1181
Julie K. Byron

128 Urinary Tract Infections 1189
Nicole Smee

Section 11 Oncologic Disease 1197

129 Approach to the Cancer Patient 1199
Lisa DiBernardi

130 Biology of Cancer and Cancer Genetics 1205
Mary-Keara Boss

131 Endocrine Manifestations of Cancer: Ectopic Hormone Production 1213
Cory Brown

132 Paraneoplastic Syndromes 1217
Cory Brown

133 Lymphoid Leukemias, Myeloid Neoplasia, and Myelodysplastic Syndrome 1223
Angela R. Kozicki

134 Lymphomas 1231
Kristine Elaine Burgess

135 Plasma Cell Disorders 1241
Orna Kristal

136 Central Nervous System Tumors in Dogs and Cats 1247
David Ruslander

137 Cancer of the Nose and Mouth 1253
Lauren Askin Quarterman

138 Tumors of the Eye and Ocular Adnexa 1261
Erin M. Scott and Paul E. Miller

139 Cancer of the Heart 1271
Nick A. Schroeder and Lisa DiBernardi

140 Cancer of the Airway and Lung 1277
Joanne L. Intile

141 Cancer of the Esophagus and Stomach 1283
Avenelle I. Turner

142 Cancer of the Small and Large Intestine 1287
Edwin Brodsky

143 Exocrine Pancreatic Cancer 1293
Avenelle I. Turner

144 Pancreatic Endocrine Tumors 1297
Karen Eiler

145 Liver and Biliary Tract Tumors 1303
Amanda K. Elpiner

146 Tumors of the Urinary Tract 1307
Pedro A. Boria

147 Tumors of the Male Reproductive System 1311
Trina Hazzah

148 Gynecologic Cancers 1317
Trina Hazzah

149 Mammary Cancer 1321
Julie Bulman-Fleming

150 Tumors of Bone and Joint 1327
Stephanie L. Shaver, William T.N. Culp, and Robert B. Rebhun

151 Soft Tissue Sarcomas 1333
Lauren Askin Quarterman

152 Hemangiosarcoma 1339
Christine B. Oakley and John D. Chretin

153 Melanoma 1347
Philip J. Bergman

154 Nonmelanoma Skin Cancers 1353
Barbara E. Kitchell

155 Mast Cell Neoplasia 1359
Zachary M. Wright

156 Apheresis in Companion Animals 1369
Steven Suter

Section 12 Skin and Ear Diseases 1373

157 Approach to the Patient with Dermatologic Disease 1375
Lisa V. Reiter

158 Principles of Therapy of Dermatologic Diseases 1397
Sandra N. Koch

159 Atopic Dermatitis 1403
Alison Diesel

160 Allergic Skin Diseases 1413
Patrick Hensel

161 Cutaneous Adverse Food Reactions 1419
Ralf S. Mueller

162 Autoimmune and Immune-Mediated Skin Diseases 1423
Nicole A. Heinrich

163 Approach to Alopecia 1433
Linda A. Frank

164 Canine Sterile Papular and Nodular Skin Diseases 1441
Sandra Diaz

165 Parasitic Skin Diseases 1449
Elizabeth E. Toops

166 Bacterial Pyodermas 1461
Jennifer R. Schissler

167 Otitis 1471
Sue Paterson

168 Cutaneous Manifestations of Systemic Disease 1481
Kinga Gortel

169 Superficial Necrolytic Dermatitis 1491
Mitchell D. Song

170 Miscellaneous Skin Diseases 1495
Lisa V. Reiter and Sheila M.F. Torres

Section 13 Diseases of Bone and Joint 1507

171 Skeletal Development and Homeostasis 1509
Matthew J. Allen and Gert J. Breur

172 Metabolic Bone Diseases 1521
Keren E. Dittmer

173 Osteoarthritis in Small Animals 1529
Steven A. Martinez

174 Developmental Orthopedic Diseases 1537
Gert J. Breur, Nicolaas E. Lambrechts, and Heather A. Towle Millard

Section 14 Social and Ethical Issues in Veterinary Medicine 1553

175 Canine and Feline End of Life Care 1555
Robin Downing

Section 15 Preventive Care *1565*

176 Role of Immunization *1567*
Melissa Kennedy

177 Behavior Triage for Internists and the General Practitioner *1571*
Karen Lynn C. Sueda

Section 16 Laboratory Support *1581*

Index *1583*

Preface

Internal medicine is hard. Progress in science and technology makes it almost impossible to keep abreast of recent advances and on top of that, all of us want to balance our life both at work and home. Is there enough time in the day for everything?

There are a variety of ways in which we learn and the path is not the same for everyone. For those of us with an interest in internal medicine, and I'm assuming that includes the reader of this book, we rely on a number of resources. Our colleagues, continuing education seminars, the literature, professional educational networks, and reference textbooks. A concern of mine over the past few years has been the increasing reliance on technology to arrive at a clinical diagnosis rather than emphasizing the need to understand physiology and the value of a complete history and a thorough physical examination. We feel increasing pressure to arrive at a specific and definitive diagnosis and, more importantly, to arrive at that diagnosis almost immediately.

Your goal in internal medicine is not to arrive at a diagnosis. I would much prefer to see a pet respond to my treatment and recover without a definitive diagnosis than to arrive at a definitive diagnosis at necropsy. If you are successful in achieving a diagnosis, that can be very rewarding. However, your goal should be to accurately identify problems and address those problems in a logical, timely, and cost-effective manner, always weighing the risk/benefit of running myriad diagnostics versus improving the quality of life of your patient and the pet owner. While not every pet owner will be able to afford or desire to follow each and every one of our recommendations, it is our job to make sure that whatever decision the owner makes is based on being fully informed.

Illness is really physiology gone awry. If you have an understanding of what is normal, it makes your job of identifying the abnormal much easier. The body has a limited repertoire of responses to an insult so often many diseases will have very similar clinical presentations. While we all like to make lists of the 20 differential diagnoses for a given patient's abnormalities, it's important to recognize that in clinical practice, common things occur commonly and those differentials should be at the top of your rule-out list.

There are numerous excellent textbooks on the market and I use many of them on a daily/weekly basis. Some serve as definitive reference works for the topic under discussion. Some are brief, bullet point, clinically oriented texts that one can use to find something quickly. What I thought was currently lacking was a text that would be continually updated, provide enough background physiology to help the reader understand normal versus abnormal, and provide useful and, more importantly, clinically relevant material to help you with your patients.

The goal of this text was to first identify section editors who were recognized experts in their field both academically and clinically. The section editors then identified topics they felt were of greatest clinical importance and selected authors who could translate this information into a text that would be used every day. I hope we have achieved that goal. We will be updating the text online with new information and updated references on a quarterly basis, adding additional sections and chapters with future editions, and uploading podcasts consisting of interviews with the authors to highlight and emphasize the material in the text and any recent advances in the field.

We hope that you will find the text helpful and all credit for that success goes to the authors. Any omissions or errors lie with me so please let me know both the good and the bad so we can improve things going forward.

As my favorite philosopher once said "It's a magical world, Hobbes, ol' buddy, let's go exploring."

All the best and enjoy exploring the mysteries of medicine.

Dave

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Section 9

Infectious Disease

Part 1

Diagnostic Considerations

78

Epidemiology of Infectious Disease

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Infectious diseases pose many challenges for veterinarians. How was my patient exposed to the pathogen? When did exposure occur? Where did the disease originate? Are there others infected? Does my patient pose a risk to other pets or people? How can I determine if things are getting better or getting worse? Understanding the epidemiology of infectious disease can help veterinarians answer these and other questions which can lead to better informed decisions which then improve patient outcomes and mitigate further spread of disease. Two essential areas of infectious disease epidemiology for the practicing veterinarian to understand are performing disease monitoring and surveillance activities and outbreak investigations.

Disease Monitoring and Surveillance

Disease monitoring and surveillance are important activities designed to assess the health and disease status of a population of animals. Monitoring and surveillance, while sounding similar to the lay person, are considered epidemiologically distinct terms. Specific diseases, described syndromes, or general health status are monitored by veterinarians through the systematic collection and recording of data. Disease monitoring activities provide information which can inform treatment and prognosis of affected animals, but does not typically elicit an intervention at the population level.

Disease surveillance activities may include collection of the same data used for disease monitoring, but activities are more intensive and purposeful. Surveillance is an ongoing, somewhat cyclic event which to be effective occurs over a considerable period of time. Surveillance methods can include testing programs for new additions to populations, such as FeLV testing of new cats entering an animal shelter or cattery, or annual testing for infectious disease, such as annual heartworm testing for dogs. In surveillance, when a specified threshold disease level is reached, prevention, control, or eradication measures are triggered and applied at the population level.

Although most small animal clinical practices deal with individual animals rather than owned populations, disease monitoring and surveillance activities are no less important to the clinic population. For example, veterinarians may erroneously assume low disease prevalence in their area because of historic patterns of disease, thereby preventing early detection of disease in that area. As people, animals, and vectors move more freely and establish new areas of residence, previously rare diseases may incrementally increase in incidence.

Small animal veterinarians also have a responsibility to participate in population surveillance programs established for public health. Public health agencies at both the state and federal level maintain a list of reportable diseases which include zoonotic diseases that affect companion animals. While maintaining a focus on human cases of disease, an increasing number of agencies now include reporting of zoonotic disease cases in companion animals. For example, the California Code of Regulations requires veterinarians to report cases of category A bioterrorism agents, such as anthrax, plague, and tularemia, as well as zoonotic diseases such as brucellosis (other than *B. canis*) and rabies to local health officials. Veterinarians should check routinely with their state veterinarian and local health departments to keep current on reporting regulations related to zoonotic disease and potential bioterrorism agents.

Small animal veterinarians may serve on the front line for preventing incursions of foreign animal diseases. In 2007, an astute small animal veterinarian in Mississippi found fly larvae on a 16-year-old dog imported from Trinidad and reported the findings to the Mississippi state veterinarian. Further diagnostics identified the fly

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larva as *Cochliomyia hominivorax*, the New World screwworm, which had been successfully eradicated from the US in the 1960s.

Disease monitoring and surveillance activities can be formal or informal and help to identify increases in incidence of specific diseases or disease syndromes. Taking the time to formalize a hunch, collect and analyze data, and report findings to veterinary or public health officials may be the key to early identification of disease outbreaks within a practice population.

Outbreak Investigations

Outbreak investigations are parallel to a diagnostic workup of an individual patient. A series of steps, performed in a specific order, provide information which helps describe and diagnose the problem at hand, plus allows insight into measures to mitigate disease and prevent future spread. Sources will vary slightly on the number of steps involved in an outbreak investigation but this chapter will focus on a six-step process for outbreak investigation.

The outbreak investigation process mimics the clinical investigation process for individual animals with disease: recognize there is a problem, define the problem, gather subjective and objective information to better describe the problem, formulate a list of likely differentials, perform diagnostics to rule in or rule out differentials, design a treatment plan, and communicate findings with the client. Goals of an outbreak investigation are to verify the pathogen responsible for the disease, identify the source of disease in the population, determine methods of transmission, and define means to prevent further spread and future occurrences.

Pre-step (or Step Zero): Establish an Investigation Team

With outbreaks of food-borne or infectious disease affecting people, a team of physicians and epidemiologists is established prior to beginning an investigation. In small animal medicine, resources to assist in an investigation may be available through local departments of public health, especially if the outbreak has zoonotic potential or may significantly impact the mental well-being of owners or the community. Assistance may also be available from county or state veterinarians or local colleges of veterinary medicine.

Step 1: Confirm Presence of Disease Outbreak

Before moving forward with an investigation, confirmation of the presence of disease above normal levels must occur. Ideally, this would involve comparing current disease levels with historic endemic levels of disease in the area. Published prevalence studies from the literature may provide insight into endemic disease levels in specific geographic areas or populations. If endemic disease levels are unavailable, levels could be estimated by extracting diagnosis information from electronic medical records in previous years.

Step 2: Establish a Case Definition

Commonly seen diseases with available accurate diagnostic tests allow for easy establishment of a working case definition. For example, outbreaks of canine parvovirus are not uncommon and are reliably diagnosed by a combination of clinical signs and diagnostic test results. The disease under investigation may only present as a collection of clinical signs rather than through isolation and identification of a specific pathogen. In this situation, the case definition would include significant or unique clinical signs, signalment information, animal location (area of residence), and time of onset of disease.

Additional data from animals who meet the case definition should be collected to further inform the investigation. Data should include pertinent information from the patient history, physical exam, and diagnostic procedures. Patient outcomes or response to treatments should also be collected and recorded. As the investigation moves forward, the case definition will be continually refined in response to new information.

Step 3: Descriptive Epidemiology

Once the working case definition has been established, investigators should review available historical medical records to identify previous animals meeting the case definition. This allows for identification of the time point for the start of the outbreak. Data from previous cases, including species, breed, age, and sex, should be used to calculate prevalence of disease in various populations and further describe the disease epidemiology. Generating hypotheses for risk factors for disease will depend on this information.

Key descriptors for the outbreak investigation include temporal and geographic spread of disease. One of the easiest ways to describe these data is through epidemic curves (Figure 78.1). Epidemic curves inform hypotheses for disease introduction and transmission, estimate incubation periods, recognize possible pathogens, and identify possible interventions.

Point source epidemic curves are indicative of a common pathogen exposure in a group of animals in a single or relatively brief time point. They are characterized by a sharp slope at the beginning of the outbreak and a more gradual slope at the end. For infectious diseases, spread of the disease is limited to a single incubation period and further spread into naive populations does not occur.

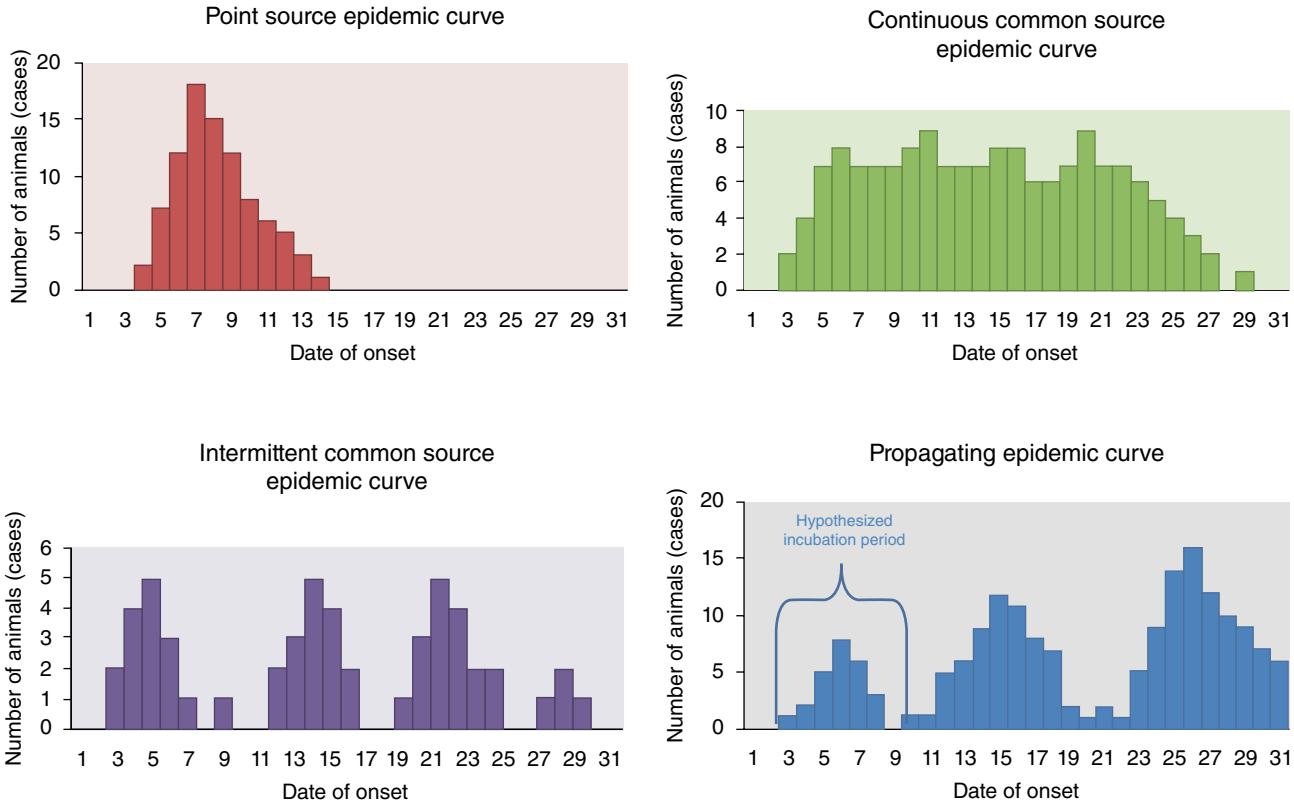


Figure 78.1 Epidemic curves.

Continuous common source epidemic curves also indicate a common pathogen exposure in a group of animals. Sharp onset and more gradual ending to the outbreak are similar to point source epidemics with the overall duration of the outbreak extending across a longer period of time which overlaps into multiple incubation periods.

Intermittent common source epidemic curves look like a series of point source epidemics across the measured time period. These epidemics may be misclassified as point source in nature when the studied time period is too brief to detect the sequential pathogen exposures. Periods between onset of case clusters can be used to estimate the incubation period of a suspected infectious pathogen.

Propagating epidemic curves resemble intermittent common source epidemics, but subsequent waves of infection peak at progressively higher levels of infection. These waves of infection represent secondary and tertiary cases of disease as a result of animal-to-animal spread of the pathogen. As with intermittent common source epidemic curves, periods of time between the onset of waves of infection can be used to estimate incubation period of a suspected infectious pathogen. If the pathogen responsible for the outbreak is yet undetermined, incubation period information can be used to narrow the list of potential pathogens.

Separate epidemic curves can be created for subpopulations of animals based on breed, age, or sex. Differences in the shapes of the curves may indicate potential risk factors for disease, helping to identify potential pathogens or intervention measures with a greater likelihood of success. Combining the temporal spread of a disease with the geographic spread can also provide further insight into potential pathogens and mechanisms for spread of disease between susceptible populations. For example, the CDC has published annual maps of the incidence of West Nile virus in people and animals from 2003 to 2019. These maps provide a visual reference for the spread of the disease from New York to California (wwwn.cdc.gov/arbonet/maps/ADB_Diseases_Map/index.html). Patterns of spread mapped against topographic information may support theories of vector-borne or water-borne disease and again may help with designing successful intervention strategies.

Step 4: Formulate and Test Hypotheses

Hypotheses related to disease introduction, spread, cause, and intervention will be formulated based on data gathered from animals meeting the case definition. If considered in isolation, the data can be informative but potentially deceptive. Without a nonaffected comparison population, false assumptions about prevalence

and risk factors can prevent implementation of successful interventions. This may lead to treatment failure and continued spread of the disease.

Observational studies facilitate comparisons between affected and nonaffected populations (cases and controls) with measures of association. Retrospective case–control studies are relatively quick and easy to perform, but may be hampered by incomplete or imperfect data collection or availability in medical records. Odds ratios can be calculated to identify risk factors for disease and support hypothesized control or prevention interventions.

Prospective cohort studies are more expensive and time consuming compared to case–control studies, but provide incidence data which lead to more accurate estimates of risk through relative risk calculations. Their prospective nature provides an opportunity for more complete data collection in both affected and nonaffected populations which would not be available in historical medical records. As with case–control studies, cohort studies also identify potential risk factors for disease and support interventions to reduce or prevent further disease spread.

Step 5: Implement Control and Prevention Measures

Descriptive epidemiologic data from epidemic curves and risk factors determined from observational studies must be carefully analyzed to determine what interventions will provide the greatest benefit and likelihood of success. Measures must be directed at controlling the current outbreak through treatment, if possible, and preventing continued spread of the disease into naive animals in the population.

In small animal clinical practice, these actions can provide significant challenges not encountered in populations under ownership or control of relatively few parties. When a population of animals has a single owner, the potential loss of a few animals is mitigated by the benefits of disease prevention in the larger population. Sacrificing a few animals for diagnostic procedures or to prevent further disease spread often makes economic sense. With companion animals, the value of individual animals does not lie just in dollars and cents, but also in an unquantifiable emotional value as a member of the family. The good of the population does not necessarily override the value of the individual, creating difficult choices for mitigating disease at a population level.

Recommendations for treating individual animals are likely to be accepted and, depending on the cause of the outbreak, individuals may have a good chance to recover from infection. Treatment options may be cost-prohibitive for some owners or treatment may be refused for various reasons. This may have little effect on spread of disease if owners follow strict isolation and quarantine protocols. Unfortunately, some owners may refuse quarantine and isolation procedures designed to stop the spread to naive animals and veterinarians have few options to mandate such procedures without a risk to public health or safety. In these situations, effective and compassionate communication of risk may help increase compliance and mitigate risk of further spread of disease.

Step 6: Communicate Findings

For public health outbreak investigations, communication of findings includes informing the healthcare community of the "who, what, where, when, why, and how" of the outbreak. This can increase awareness of the potential for continued spread of the disease and allow implementation of preventive measures and early detection of the disease in new populations.

If the disease outbreak under investigation has a public health implication, and local public health officials were not part of the investigation process, it is important to communicate relevant findings to the local public health department. Findings should include date of onset and conclusion (if outbreak has ended), case definition/diagnosis, populations affected, epidemic curves, and outcomes of control and prevention measures. This information should also be shared with other veterinarians in the practice area so results of the investigation can be used to control and prevent disease in the larger population of animals in the community.

Findings from new or novel disease outbreaks should also be communicated to the larger veterinary audience through publication in journals or presentations at continuing education functions. Increased awareness may prevent further outbreaks or mitigate the effects of outbreaks if they spread to new companion animal populations.

Conclusion

Epidemiology is an integral part of the daily practice of veterinary medicine whether veterinarians realize it or not. Tools and techniques for disease monitoring and surveillance and outbreak investigations are readily available and can add to a veterinarian's epidemiology

toolbox. Just as epidemiology is a science focused on populations, veterinarians should not work in isolation when investigating the incidence of disease in their practice populations. Local, regional, state, and federal veterinarians and health professionals should be part of the companion animal healthcare team responsible for rapid identification and resolution of diseases in the clinic and community populations.

Further Reading

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79

Laboratory Diagnosis of Infectious Diseases

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Veterinarians use diagnostic testing for infectious diseases for two main reasons:

- to confirm acute or chronic infection in a dog or cat with clinical signs or clinicopathologic abnormalities compatible with infectious diseases
- to detect subclinical infection or certify that animals are free of infection.

Detection of infection may be pursued to screen clinically healthy animals living in endemic regions, to prevent transmission by blood transfusion, to avoid importation of infected dogs and cats to nonendemic countries, to avoid transmission of disease to people in contact with the animal, including immune-suppressed owners, to monitor response to treatment, and for research. Different diagnostic procedures can be used depending on the purpose of the diagnostic investigation and the pathogen most likely affecting the dog or cat based on the differential diagnosis list. Test results might also be interpreted according to the aim of the diagnosis, type of pathogen, and clinical status of animals.

Accurate diagnosis of infectious diseases requires an integrated routine approach consisting of thorough clinical history, physical examination, pertinent routine laboratory tests such as complete blood count (CBC), complete biochemical profile and urinalysis, diagnostic imaging and additional diagnostic testing, depending on the differential diagnoses list for each individual patient. In addition, specific pathogen diagnostic assays should be carried out when infectious diseases are at the top of the differential diagnoses list.

This chapter describes general concepts of diagnosis of viral, bacterial, protozoal, and fungal infectious diseases with an overview of the most common diagnostic methods employed for these infections. Specific diagnostic features of common infectious diseases in dogs and cats, geographic distribution, main transmission modes, chief clinical signs, clinicopathologic abnormalities, treatment, prognosis, and prevention will be described in detail in other chapters in this section.

The most commonly employed techniques for the diagnosis of infectious diseases in small animals include microscopic examination of microorganisms in cytologic preparations or histopathologic specimens, serology, polymerase chain reaction (PCR), and culture of the organism in appropriate medium, as described in the following subsections of this chapter. The advantages and disadvantages of these diagnostic techniques are listed in Table 79.1. Sample collection, transport, and preservation of specimens for the different diagnostic tests and pathogens are described in Table 79.2.

Protozoal and Arthropod-Borne Infections

Microscopic Examination

Diagnosis can be based on cytologic or histologic detection of pathogens, either contained inside cells or free in routinely stained smears. Detection by light microscopy of pathogens in cytologic preparations or histopathologic specimens might be difficult, depending on the type of microorganisms causing infection. However, cytology is a more rapid and simple technique for the detection of some microorganisms compared with histopathology. Histopathology commonly requires special staining to detect bacterial, mycobacterial, fungal or protozoal infections. Standard Romanowsky stains such as Giemsa are used for cytologic detection of the majority of organisms (Figure 79.1). Special stains can also be used in cytology for enhancing the visualization of microorganisms but are less frequently needed.

Although the specificity of these methods is high, it is important to highlight that identification of species

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Table 79.1 Advantages and disadvantages of common diagnostic methods for the detection of infectious diseases in dogs and cats

Diagnostic techniques	Advantages	Disadvantages
Microscopic examination (cytology /histopathology)	• Permits direct detection of the pathogen and nature of the host response. • Findings could be suspicious of infection or allow exclusion of other differential diagnoses • Cytology is rapid and less invasive than obtaining tissues for histopathology by biopsy • Cytology usually permits easier visualization of pathogens when compared with histopathology	• Relatively low sensitivity for the detection of pathogens in tissues or body fluids • Requires the performance of other diagnostic tests such as immunohistochemistry and/or PCR when pathogens are not visualized • Does not distinguish between morphologically similar organisms • Requires expertise
Serologic testing (antibody detection)	• Detection of specific antibodies against the pathogen causing infection • Permits evaluation of seroconversion to confirm recent infection	• Does not detect the pathogen itself • Typically does not discriminate between vaccinated and naturally infected dogs or cats • Serologic cross-reactivity between related organisms is possible
– Qualitative	• Rapid in-clinic test	• Provides only positive or negative results • Variable sensitivities and performance with risk of false-negative results due to conservative cut-off level and use of recombinant proteins • A positive result will benefit from additional validation by quantitative serology
– Quantitative (IFA, ELISA)	• Determines the antibody level which is of major importance in some diseases such as leishmaniasis where high antibody levels in the presence of compatible clinical signs and/or clinicopathologic abnormalities are conclusive of clinical leishmaniasis	• Performance and accuracy of cut-off vary between laboratories • Frequent lack of sufficient standardization of techniques between laboratories • Low antibody levels frequently require further testing
Serologic testing (antigen detection)	• Allows the detection of pathogen	• May not be sensitive when low numbers of pathogens are present
Molecular testing	• Allows the detection of pathogen DNA and RNA • High sensitivity and specificity for target loci • Allows determination of pathogen load (by real-time PCR)	• False-positive results possible due to DNA contamination or to amplification of erroneous targets including host DNA • Different techniques used by diagnostic laboratories and lack of standardization
Culture	• Permits the isolation of pathogens and their maintenance for further comparisons and analysis • Facilitates in-depth identification of pathogens	• Time-consuming and laborious • Requires special equipment and biohazard conditions and therefore restricted to specialized laboratories • May require up to one month to provide a result

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ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescence assay; PCR, polymerase chain reaction.

based solely on morphology is often not possible and molecular analysis is required for speciation. Sensitivity will depend on the time spent searching for microorganisms, type of pathogen, tissue sampled, amount of organism in the tissue (parasite load), and clinical status of the patient. Generally speaking, higher diagnostic sensitivity is found in sick animals compared with subclinically infected dogs or cats. The diagnosis of chronically infected and carrier animals remains a diagnostic challenge due to low and often intermittent parasitemia, or low tissue pathogen load, which frequently make pathogen observation by microscopic evaluation difficult. Therefore, the use of molecular diagnostic assays is strongly recommended in those cases. In addition, identification of protozoa in formalin-fixed, paraffin-embedded sections of different tissues may be facilitated by immunohistochemical methods such as immunoperoxidase staining or *in situ* hybridization techniques.

The optimal tissue or body fluid for sampling will depend on types of pathogen involved and lesions found

Table 79.2 Collection, processing, and transport recommendations for different diagnostic tests in small animal infectious diseases. Follow all governmental guidelines relevant to a given infectious disease agent and clinical specimen

Diagnostic test	Specimen type	Collection and processing	Shipment
Histology	Any tissue specimen	Samples collected for histology should never be >1 cm thick (preferably 5–7 mm thick). Fix in 10% buffered formalin (10× volume)	Double bag and leak-proof container with adequate fixative
Cytology	Any tissue specimen or fluid analysis	Air-dried smear should be prepared immediately after the sample has been collected to minimize cell deterioration. Alcohol fixation is not needed. Analysis of various effusions and fluids usually includes determination of protein content, total cell concentration, and cytologic examination. A sample of effusion/fluid should be collected into an EDTA tube for routine analysis. A second sample should be collected into a serum tube if any biochemical analyses are to be performed or if a bacterial culture is desired	Blood or cytologic smears should never be mailed to the laboratory in the same package with formalin-fixed tissues because formalin vapors will produce artifacts in the specimen. Cytologic preparation should be transported at room temperature in a plastic container. Fluid samples should be shipped chilled but not frozen
Antibody or antigen testing	Blood, plasma, serum, cerebrospinal fluid, urine samples or feces	Serology generally requires serum, but plasma is often satisfactory. For serum samples, the blood should be drawn into a plain tube or a separator tube. The sample should be held at room temperature for 20–30 min to allow complete clot formation and retraction. The sample should then be centrifuged at high speed (~1000 g) for 10 min. In some instances, paired samples may be required for an adequate diagnosis	Specimens can be refrigerated for up to a week prior to shipment to the laboratory. Specimens should be frozen at −20 °C or −80 °C if stored for a longer period. Specimens can be stored frozen for years without loss of antibody levels. For specimens collected for assays for antigen detection, results may be more susceptible to variation with long specimen storage. The laboratory should be contacted in order to determine specimen storage and handling requirements
Molecular testing	Any specimen	Collect aseptically to prevent contamination. For blood or bone marrow and DNA analysis, use preferably EDTA or acid citrate dextrose (ACD) anticoagulant	For DNA analysis: submit specimens held at room temperature within 24 h of collection. Specimens can be stored at 2–8 °C for 72 h, or at −20 °C or ≤−70 °C for prolonged storage. For RNA analysis: use stabilization solution or send immediately to the laboratory on wet ice. For storage, freeze specimens at or below −70 °C
Isolation-culture	Any specimen	Collect aseptically to prevent contamination. Some agents might have special requirements such as anaerobic culture or special media. Culture from blood should be collected in special media bottles designed to prevent coagulation and neutralize antibiotic residues if animal was treated	Normally, specimens should be refrigerated and not frozen and delivered directly to the laboratory within 24 h

on physical examination. Blood-borne organisms such as *Babesia* (Figure 79.2) can be found in blood smears, concentrated and stained buffy coat or splenic specimens. Other important tissue samples used for the detection of these pathogens are lymph node aspirates, skin touch impressions, bone marrow, joint fluid, cerebrospinal fluid (CSF) or other body fluids and tissues.

Serologic Testing (Antibody and Antigen Detection)

Antibody Detection

Several serologic methods can be used to detect specific serum antibodies directed against protozoal and arthropod-borne pathogens. Methods include the indirect fluorescent antibody (IFA) test, the enzyme-linked immunosorbent assay (ELISA), immunochromatographic rapid in-house devices, direct agglutination assays, and western blotting. The most common serologic tests employed in clinical practice are quantitative assays (IFA and ELISA) and qualitative tests (rapid in-house devices). In general, most of these methods have good sensitivities and specificities but sensitivity and specificity greatly depend on the antigens employed. Whole-parasite extracts are sensitive for the detection of subclinical or clinical canine and feline infections but provide lower specificity. On the other hand, assays that employ recombinant protein antigens are very specific but may lack

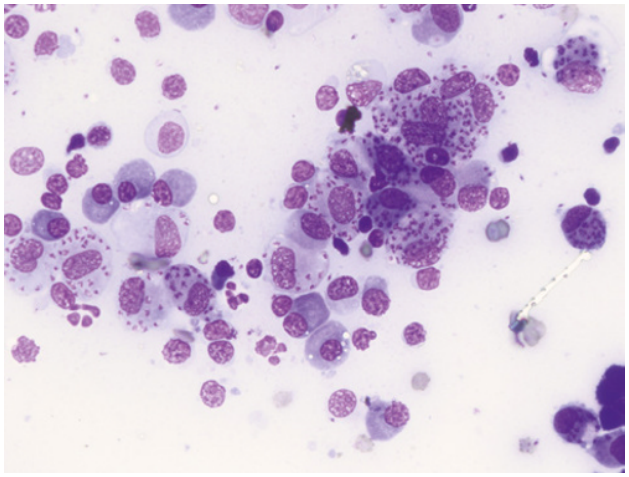


Figure 79.1 Lymph node aspirate from a dog. Note the increased numbers of plasma cells and macrophages with abundant intracellular *Leishmania* amastigotes (modified Wright stain, original magnification ×400).

sensitivity for the detection of infection, depending on the antigen employed and the level of serum antibodies.

Serologic cross-reactivity is common between pathogens of the same genus or otherwise closely related organisms. Therefore, cross-reactivity between antibodies directed at different pathogens is possible with some serologic tests, especially those based on whole-parasite antigen, and is less likely to occur when using recombinant protein antigens. It is important to note that the use of antigens of similar species will frequently result in cross-reaction at a high level. For example, antibodies against *Babesia canis* will cross-react with *Babesia vogeli* antigen. Pathogens of closely related different genera are more likely to cross-react at low levels, such as the cross-reactivity between antibodies to *Trypanosoma cruzi* and *Leishmania infantum*.

Antibody detection can indicate past exposure or present acute or persistent infection. Acute diseases may be difficult to diagnose due to the lack of detectable antibody production and low pathogen load in blood or other tissues. Therefore, false-negative results are possible in peracute or acute diseases. Evidence of seroconversion is fundamental in the diagnosis of some acute diseases. In these cases, the measurement of acute and convalescent antibody levels (paired samples) is confirmatory for acute infection. Antibody level determination may vary between different laboratories, and therefore, it is recommended to use the same laboratory and assay for comparison of antibody levels. Furthermore, variations are also likely between assays carried out on different days. Therefore, ideally, paired samples should be tested at the same time.

Seroconversion is considered when a fourfold or greater increase in antibody level is demonstrated in paired samples over a 2–4-week period, and in some particular infections longer than that, for instance in *L. infantum* infection where a serologic response develops months after initial infection. In addition, antibodies induced by vaccination may be detected by serologic assays, making it impossible to discriminate between vaccinated and naturally infected animals. Examples of this include vaccination against *B. canis* and *L. infantum*.

High antibody levels are associated with high tissue parasite loads and disease in some protozoal and arthropod-borne chronic diseases. In contrast, cases of animals with suspected clinical signs and compatible clinicopathologic abnormalities and low antibody levels require the use of additional detection methods to exclude or confirm the disease, because low antibody levels may also be detected in subclinical carriers suffering from a different clinical disease. Canine leishmaniasis is a good example of a disease in which moderate to severe clinical disease is usually manifested by medium to high antibody levels, whereas subclinical infection is more often associated with lower antibody levels or seronegativity.

Antigen Detection

The detection of circulating plasma or blood antigen specific for a pathogen is an additional and usually very specific serologic technique. This type of assay detects the presence of a circulating plasma or blood antigen. For example, the most common detection technique of canine heartworm infection caused by *Dirofilaria*

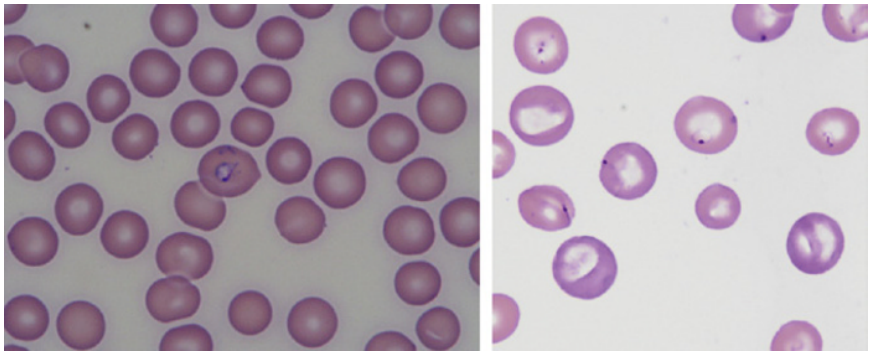


Figure 79.2 Blood smears from two different dogs. (*Right*) A large form of *Babesia*. (*Left*) Small forms of *Babesia* (modified Wright stain, original magnification ×1000).

immitis is based on detection of a circulating secretory antigen of the adult female worm.

Molecular Diagnostics

Polymerase chain reaction is a sensitive and specific diagnostic technique frequently employed for the diagnosis of protozoal and arthropod-borne diseases. It is used for diagnostic purposes, monitoring during and after treatment, research studies, and for screening of blood donors. Moreover, it is particularly useful for detection of infection in animals with low parasitemia levels and for speciation of pathogens. PCR can be carried out on DNA extracted from tissues, blood, body fluids, conjunctival and oral swabs, or even cytologic preparations or histopathologic specimens.

A large number of PCR assays and protocols using a variety of gene targets have been described for the detection of protozoal and arthropod-borne infections of dogs and cats. It is important to highlight that for diagnostic purposes, the best DNA target will often be the locus or gene with the largest number of copies per organism. For instance, the kinetoplast DNA (kDNA) of *L. infantum* is an excellent target as it has about 10 000 copies in each *Leishmania* amastigote. Other targets are more useful for distinguishing between species such as the leishmanial ribosomal internal transcribed spacer 1 (ITS1). Due to the fact that in some endemic areas, more than one species co-exist and infect animals, molecular techniques have been developed to discriminate DNA from different species of the same genus or related genera. These techniques include semi-nested PCR, reverse line blotting, PCR restriction fragment length polymorphism (RFLP), and high-resolution melting curve quantitative fluorescence resonance energy transfer PCR. Sequencing may also reveal infections with novel organisms that have not been described before.

It is important to highlight that negative results by molecular techniques only indicate that specific DNA was not detected under the assay conditions and should not be interpreted as absolute evidence for the absence of infection. In addition, false-positive results are possible due to DNA contamination or the amplification of DNA from other sources which may not be noticed if sequencing is not performed. Controls should be included in each step of the assay to ensure that DNA contamination has not occurred.

Isolation

Diagnosis may also be established by culture of the infectious agent. However, this technique is usually tedious and time-consuming. It sometimes requires special conditions and a long duration for obtaining results and therefore is less commonly used in clinical practice for parasites and arthropod-borne pathogens. This technique is employed in research studies because it permits the identification and maintenance of pathogens. It is important to highlight that some organisms, such as *Babesia* species, are difficult to culture. The culture method is pathogen specific and usually requires special media and temperature conditions. Special culture medium is used for the isolation of some protozoal pathogens, such as *L. infantum*.

Viral Infections

Microscopic Examination

Most viral infections are not diagnosed by microscopy. Viruses are too small to be detectable by light microscopy, but typical cytoplasmatic or intranuclear inclusion bodies caused by viruses may be detected in blood or tissue cells. Electron microscopy may be used for the detection of certain viruses such as canine parvovirus in feces of dogs shedding the virus, although this is a cumbersome, time-consuming technique which is often unable to specify the exact species involved in infection, as it relies on morphology.

Serologic Testing (Antibody and Antigen Detection)

Serologic tests are frequently used for the detection of viral infections in cats and dogs. There are a number of basic serologic techniques such as ELISA, IFAT, virus neutralization, complement fixation, agglutination, agar gel immunodiffusion, and western blotting. Serology can be aimed at detecting specific antibodies produced against a certain virus in the infected animal, as in the most common tests for feline immunodeficiency virus (FIV) which detect antibodies to the p24 core protein. It can also be aimed at the actual detection of a certain viral antigen in a body fluid such as the blood, as in the common feline leukemia virus (FeLV) antigen test based on the detection of the viral p27 capsid protein.

Rapid commercial tests are available for many of the common viral infections, and they are also frequently based on the detection of either antibodies against the virus or virus antigen. Rapid commercial tests are often based on immunochromatographic devices which produce a color response when antibodies against a virus are detected, or when the actual viral antigens are detected, if the assay is geared to the detection of antigen. These types of assays are often used for in-house rapid diagnosis in veterinary clinics and hospitals. Several manufacturers have produced such rapid assays for the detection of antibodies against FIV, antigenemia with FeLV, or the

presence of parvoviral antigen in the feces of dogs shedding this virus. The rapid assays that detect antibodies against a virus are often not quantitative and only produce a positive or negative result, in contrast to tests done in a specialized laboratory which frequently provide an antibody titer or quantitative measure related to the level of antibodies, such as the optical density in the ELISA.

Molecular Diagnostics

Molecular diagnosis of viruses includes the detection of specific nucleic acid sequences present in the targeted virus. Viruses may contain DNA or RNA, depending on the viral family to which they belong. PCR assays are commonly associated with the amplification of the nucleic acid sequence selected as the target for the assay and visualization of the product on a gel in conventional PCR, or its amplification and release of measurable fluorescence by real-time PCR which can also be quantitative. Amplification of nucleic acids from RNA viruses may require an additional reverse transcription step in which RNA is translated into cDNA and then amplified. RNA is less stable than DNA and is susceptible to rapid degradation unless stored in an RNA stabilization solution and frozen at –70 °C or below. A multiplex reverse transcription-nested PCR assay has been developed to differentiate between wild-type and vaccine strains of canine distemper virus.

An additional molecular diagnostic technique is the use of nucleic acid probes which attach specially to nucleic acid sequences in viruses and do not involve amplification of the virus's DNA or RNA.

Isolation

Isolation of virus from blood, secretions, or organ tissues is a common method of diagnosis for viral infections of dogs and cats. Isolation requires the use of appropriate media to transport the tested sample, a specialized laboratory, and rapid transportation to the laboratory in refrigeration. Viruses are usually taken from the transport media or the original fluid in which they were submitted (e.g., blood or CSF) and grown in various cell culture lines. Often virus isolation is attempted in multiple cell lines simultaneously as the host cell preference of the particular virus strain is unknown. Virus isolation from animals is usually performed with the addition of antibiotics and antifungal drugs to cell lines to prevent contamination with bacteria and fungi. While feline retroviruses such as FIV and FeLV are usually isolated from blood, isolation of canine distemper virus is usually attempted from the CSF, bronchoalvelor lavage, and transtracheal lavage specimens.

Bacterial Infections

Microscopic Examination

Most bacteria are detectable by high-power light microscopy of cytology specimens (Figure 79.3) but this is usually not sufficient for species identification and may serve as a relatively insensitive measure for the presence of bacteria in the sample. Furthermore, some anatomic sites such as the skin, oral cavity, gastrointestinal tract, and upper airway normally contain bacteria and it is usually difficult to distinguish between the normal flora and infection with pathogenic bacteria just by microscopic examination of the organisms. Gram stain, acid-fast staining, and other staining methods are ancillary techniques that can assist in the initial assessment of bacterial infection. Dark-field microscopy is helpful in the detection of spirochetes such as leptospires in urine samples.

Serologic Testing

Serology can be useful in the detection of some bacterial infections of dogs and cats. Detection of specific antibodies is helpful in the diagnosis of leptospirosis and a battery of serogroup antigens is used to find which serovar demonstrates the highest antibody titer and is either responsible for infection or closest to the *Leptospira* serovar present in the animal. Serology is also useful for the detection of exposure to intracellular bacteria such as *Ehrlichia canis* or *Anaplasma phagocytophilum*.

Isolation and Identification (Including Molecular Testing)

Culture has been the major technique for detection and characterization of bacterial pathogens for the past century. There are a number of different media for growth of bacteria from various groups with specific metabolic requirements. Often, one type of medium is used for the transport or initial growth of bacteria and other media are subsequently used for subculture with enrichment and selection of the bacteria suspected as cause of infection. The MacConkey agar medium selects for gram-negative bacteria. Cultures from an infection site are often placed initially into more than one medium when a broad spectrum of infective agents is suspected, for instance in aerobic and anaerobic specific media which also require specific growth conditions such as an anaerobic environment enriched with carbon dioxide for anaerobes.

Identification and characterization of isolated bacteria are usually done based on biochemical qualities and tests such as the catalase test and coagulase production.

Commercial biochemistry test strips enable the identification of cultured bacteria and automated commercial identification systems are often used in large bacteriology laboratories for rapid bacteria identification.

Some bacteria such as *Anaplasma platys* and hemotrophic mycoplasms (e.g., *Mycoplasma hemofelis*, *Candidatus Mycoplasma hemominutum*) are unculturable. The detection of these bacteria relies mainly on molecular biology techniques such as PCR amplifying DNA sequences which are specific for the suspected bacteria. Other bacteria such as *Rickettsia* spp., *E. canis*, and *A. phagocytophilum* are strictly intracellular and can only be grown in appropriate cell culture lines, restricting their isolation to research laboratories with expertise. Molecular techniques can also be useful for the identification of bacteria that have been propagated in culture and require classification to the species and strain levels. These can be sometimes be achieved by multigenic sequencing and characterization, with phylogenetic analysis.

Providing the bacteriology laboratory with a good clinical history, physical examination and initial blood test work-up and cytology findings can be very helpful in the selection of different isolation techniques. Sampling the correct organ sites is imperative and should be based on clinical judgment. Common body fluids and anatomic sites sampled for bacteriology from dogs and cats include urine, blood, feces, bronchoalveolar lavage, skin and ear, abdominal and pleural fluids, CSF, and cornea.

Interpretation of Culture Results

The results of culture should be interpreted cautiously, considering that the bacterium isolated, when culture is successful, may not actually be the cause of infection, or that in some other cases, culture is negative despite bacterial infection. This can be due to several reasons including technical difficulties in transporting the culture with infectious agent, use of incorrect isolation technique or culture site, intermittent shedding of bacteria to the blood or other body fluid, and previous antibiotic treatments.

Antimicrobial Susceptibility Tests

Determination of minimum inhibitory concentrations (MIC) for isolated bacteria can be helpful in deciding which antibiotic should be used for treatment of susceptible infections. This is also important in the detection of antimicrobial resistance, if present. The standard techniques for antibiotic susceptibility testing involve either gel diffusion or dilution methods. Although they can provide an idea of the antibiotics to which the isolated bacteria is susceptible *in vitro*, this does not always conform with the actual susceptibility due to *in vivo* factors such as accessibility to the infected tissue (e.g., decreased accessibility to abscesses), concentration of antibiotic in the affected tissue, and inhibition of antibiotics by body proteins.

Fungal Infections

Fungal agents have a remarkably varied spectrum of clinical picture: primary skin disease, single to multiple subcutaneous masses, mass lesions within body cavities, disseminated disease with multiple organ dysfunction, and disseminated disease that presents as single-organ dysfunction or as a cause of sudden death. Clinicopathologic findings are not specific but mild anemia of chronic disease, leukocytosis, hypergammaglobulinemia, hypoalbuminemia, and hypercalcemia can be present in some of these diseases. Primary (i.e., *Blastomyces*, *Coccidioides*, *Cryptococcus*, *Histoplasma*) and opportunistic pathogens, mainly saprophytic soil fungi (i.e., *Aspergillus*, *Basidiobolus*, *Cladosporium*, *Conidiobolus*), can be responsible for these diseases. Opportunistic fungi can cause disease by trauma and often present as a single subcutaneous mass. When dissemination occurs, it is often associated with decreased immunocompetence.

Microscopic Examination

Suspicion of fungal diseases should be made when macrophagic or macrophagic-neutrophilic inflammation is noted in any tissue by cytologic or histopathologic specimens. Bacterial inflammatory lesions (Figure 79.3) that are unresponsive to appropriate medical therapy should be investigated further to rule out underlying mycotic disease due to the fact that bacterial and fungal co-infections do occur.

Cytological evaluation of any tissue or body cavity fluid specimen is very useful for identification of fungal disease in dogs and cats. Cytology is a more rapid and simple technique for the detection of some fungal microorganisms than histopathology. Histopathology commonly requires special staining such as periodic acid–Shiff (PAS) or Gomori methenamine silver (GMS) to detect fungal infections. In addition, some laboratories offer immunohistochemistry for fungal organisms within tissues submitted for routine histopathology. Yeasts, different types of spores, and hyphae can be observed in cytologic specimens (Figure 79.4).

Cytologic features of most fungal pathogens are described elsewhere. Routine Romanowsky staining adequately stains most fungal organisms within cytologic preparations. Organisms that do not stain well appear as negatively stained elements (Figure 79.5).

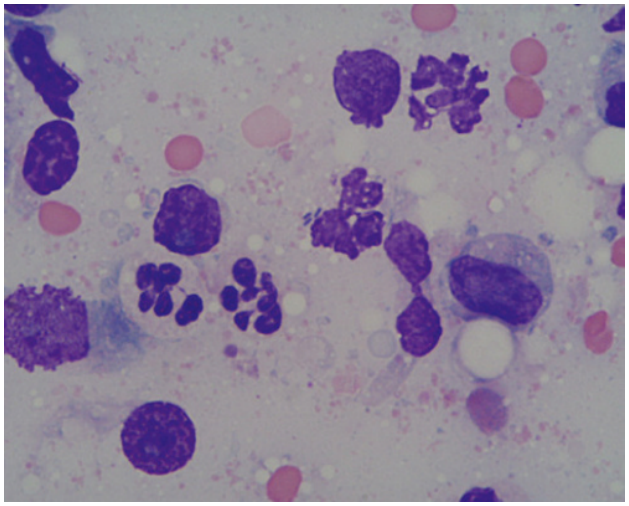


Figure 79.3 Kidney aspirate from a cat. Note neutrophilic-macrophagic inflammation with infection of rod-shaped bacteria (modified Wright stain, original magnification ×1000).

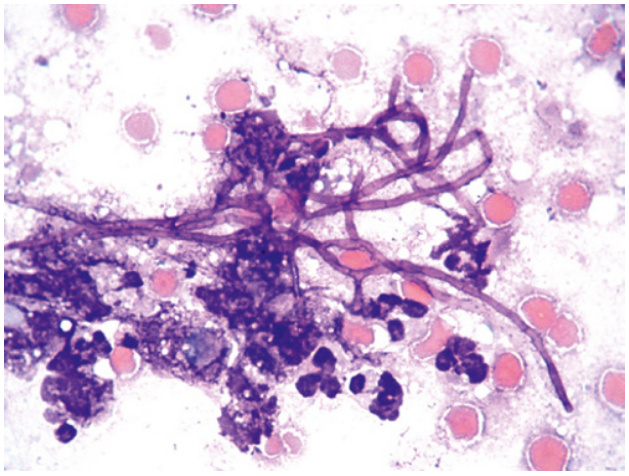


Figure 79.4 Thoracic mass from a German Shepherd dog. Note the necrotic background, increased numbers of neutrophils and *Aspergillus terreus* hyphae (modified Wright stain, original magnification ×1000).

India ink staining is commonly used for the identification of *Cryptococcus* species. The expertise of the individual evaluating the slide is the main variable in using cytology in the clinical setting. The sensitivity of cytologic and histologic evaluation varies considerably although specificity is high. Cytologic and histopathologic features cannot definitively identify the species and therefore culture and biochemical characterization or molecular analysis are mandatory for identification. It is important to highlight that morphologic features of fungi in tissue differ when grown on fungal media.

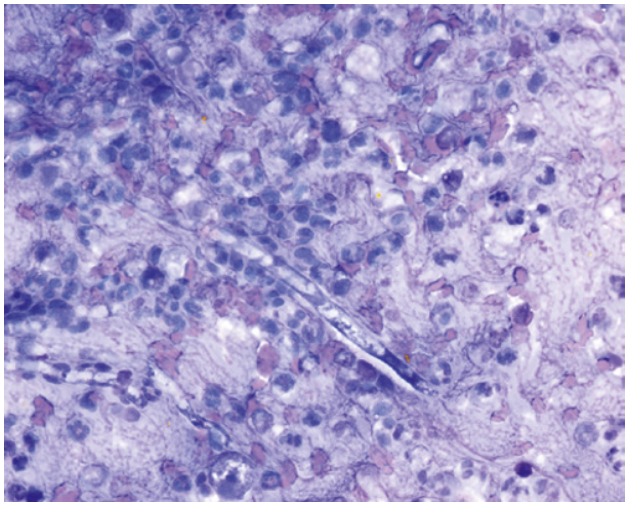


Figure 79.5 Inguinal subcutaneous mass in a dog. Note the marked neutrophilic inflammation and the evidence of unstained and partially pale basophilic hyphae (modified Wright stain, original magnification ×400).

Serologic Testing (Antibody and Antigen Detection)

Serology is used in the clinical setting to diagnose fungal disease in dogs and cats. However, interpretation of serologic results in some fungal diseases might be difficult and will benefit from additional cytologic or molecular evidence or culture. Limited studies are available regarding sensitivity and specificity of serologic testing of some fungal diseases. The majority of fungal serologic tests currently in use in veterinary medicine detect the antibody response to infection. A few tests detect fungal antigens, providing a definitive diagnosis if the antigen is sufficiently specific (such as the antigen-based latex agglutination test available for *Cryptococcus neoformans*). As with any serological test, cross-reactivity can exist between fungal agents. Positive serology provides evidence of exposure and supports the clinical findings. Paired serum samples (2–4 weeks apart) should be run at the same time. A fourfold increase or decrease in the antibody level is strong evidence of active disease. More details on current serologic tests available for fungal disease are described elsewhere in this section and in the literature.

Isolation and Identification (Including Molecular Testing)

Culture

The specific identification of fungal organism is based on culture of fluids or tissue. However, successful culture of fungal agents depends on several variables, including the

fungal organism itself, concentration of fungal elements in the sample, sample integrity, culture requirements of the fungal agent, and expertise of the laboratory performing the culture.

Obtaining and submitting the appropriate sample for culture and providing the laboratory with detailed history and clinical diagnosis are essential for a successful culture. Samples of urine, exudates, and body cavity fluids can be submitted in sterile serum collection tubes. Up to 10 mL of fluid is recommended. Samples of fresh tissue from a lesion can be submitted in a sterile container for culture.

Identification of fungal agents in cultures is time-consuming. The culture has to grow and form characteristic fruiting bodies, conidia, or arthrospores to allow morphologic identification of the fungus. Microscopic morphology of fungal reproductive structures is the most useful criterion for identification. It is strongly advised that fungal culture (other than for dermatophytosis) is performed in a reference diagnostic laboratory.

Molecular Testing

Molecular testing is less commonly employed for the diagnosis of fungal diseases in tissues or body fluids in veterinary medicine as it is for bacterial, viral, and protozoal diseases. Molecular techniques are the same as reported for other infectious diseases and include conventional, nested, and real-time PCR and sequencing. Common target genes are the 18S or 5.8S ribosomal gene or internal transcribed spacer (ITS) regions of ribosomal DNA. Fungal identification based on DNA sequencing is not always definitive because results depend on whether or not the DNA of the fungus in question has been previously sequenced and submitted to the genomic databases. Therefore, fungal identification based on DNA sequencing should include at least two DNA regions for comparison.

In contrast, PCR-based methods are commonly used to confirm identification of fungi culture in diagnostic laboratories. Commercial chemiluminescent-labeled DNA probes are available for some fungal agents such as *Blastomyces*, *Coccidioides*, and *Histoplasma*.

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Part 2

Select Infectious Diseases and Disease Agents

80

Canine Distemper

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Etiology/Pathophysiology

Canine distemper virus (CDV) is a large (100–250 nm) ssRNA virus belonging to the genus *Morbillivirus* of the family Paramyxoviridae. Mutations affecting the CDV H protein required for virus attachment to host cell receptors are associated with virulence and disease emergence in novel host species. CDV has a lipoprotein envelope and a nonsegmented negative-stranded RNA genome consisting of six genes that code for a single envelope-associated protein (matrix [M]), two glycoproteins (hemagglutinin [H] and fusion [F] proteins), two transcriptase-associated proteins (phosphoprotein [P] and large protein [L]) and the nucleocapsid (N) protein, which encapsulates the viral RNA. Only one serotype of CDV is recognized with several co-circulating genotypes based on variation in the H protein.

Canine distemper has affected dogs worldwide for centuries, with descriptions of disease outbreaks in the European literature dating back to the 17th century. It was first formally described in dogs in 1905. Despite the introduction of modified live vaccines in the 1950s and their extensive uptake, the disease remains prevalent.

Systemic CDV infection, resembling distemper in domestic dogs, can also be found in wild canids (e.g., wolves, foxes), procyonids (e.g., raccoons, kinkajous), ailurids (e.g., red pandas), ursids (e.g., black bears, giant pandas), mustelids (e.g., ferrets, minks), viverrids (e.g., civets, genets), hyaenids (e.g., spotted hyenas), and large felids (e.g., lions, tigers). In addition, besides infection with the closely related phocine distemper virus, seals can become infected by CDV. In some CDV outbreaks, including the mass mortalities among Baikal and Caspian seals and large felids in the Serengeti Park, terrestrial carnivores including dogs and wolves have been suspected as vectors for the infectious agent. Lethal infections have been described in noncarnivore species such as peccaries and nonhuman primates demonstrating the remarkable ability of the pathogen to cross species barriers.

Canine distemper virus infection of dogs is characterized by a systemic and/or nervous clinical course and viral persistence in selected organs, including the central nervous system and lymphoid tissue. Main manifestations include respiratory and gastrointestinal signs, immunosuppression and demyelinating leukoencephalomyelitis (DL). The primary mode of infection is via inhalation. After initial exposure, dogs may mount a robust immune response and recover. It is estimated that as many as 75% of infections may actually be subclinical. Initially, CDV replicates in lymphoid tissue of the upper respiratory tract. Monocytes and macrophages are the first target cells which propagate the virus. Impaired immune function, associated with depletion of lymphoid organs, consists of a viremia-associated loss of lymphocytes, especially of CD4+ T cells, due to lymphoid cell apoptosis in the early phase. After clearance of the virus from the peripheral blood, an assumed diminished antigen presentation and altered lymphocyte maturation cause an ongoing immunosuppression despite repopulation of lymphoid organs.

Following a variable incubation period (1–4 weeks), animals develop a characteristic biphasic fever. During the first viremic phase, generalized infection of lymphoid tissues with lymphoid depletion, lymphopenia, and transient fever are observed. Profound immunosuppression is a consequence of leukocyte necrosis, apoptosis, and dysfunction.

The second viremia is associated with high fever and infection of parenchymal tissues such as the respiratory tract, digestive tract, skin, and CNS. The early phase of DL is the result of direct virus-mediated damage and infiltrating CD8+ cytotoxic T cells associated with an upregulation of proinflammatory cytokines such as interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-alpha, and IL-12 and a lack of response of immunomodulatory cytokines such as IL-10 and transforming growth

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factor (TGF)-beta. A CD4+-mediated delayed-type hypersensitivity and cytotoxic CD8+ T cells contribute to myelin loss in the chronic phase. Additionally, upregulation of interferon-gamma and IL-1 may occur in advanced lesions. Moreover, an altered balance between matrix metalloproteinases and their inhibitors seems to play a pivotal role for the pathogenesis of DL.

Histologic manifestations include polioencephalitis and DL. The observations of $p75^{NTR}$-expressing bipolar Schwann cell-like glia in CDV-DL highlight the potential of Schwann cell-mediated remyelination and raise the hope for a beneficial regenerative process in CDV-DL. Though the central role of axonal damage as a triggering event is established in CDV-DL, the role of macrophage polarization in CDV-DL is currently unknown. In light of the fact that distinct macrophage responses have been linked to axonal regeneration, degeneration, demyelination, and remyelination, the elucidation of a potential macrophage polarization during CDV-DL appears to represent a promising field for future investigations and the development of new treatment strategies.

Recovery from CDV depends on the host immune response. A strong and effective cellular immune response can eliminate the virus prior to infection of parenchymal tissues, while weak and delayed cellular and humoral immune responses lead to virus spread and persistence, respectively.

Epidemiology

Canine distemper is a fatal disease of dogs with a worldwide distribution. With a mortality rate of around 50%, it is second only to rabies when it comes to virus-induced fatality in dogs.

Signalment

There is no breed or sex predilection. Animals <6 months are particularly vulnerable.

Clinical Signs

Signs most often involve the respiratory tract. Gastrointestinal (GI) signs may also occur. Affected dogs are listless and have a decreased appetite. In milder cases, signs may be similar to other agents of canine infectious respiratory disease complex. Subclinical infection with shedding may also occur, depending on the level of host immunity. Systemic signs are most common in unvaccinated dogs (e.g., puppies) as maternal immunity wanes. Conjunctivitis, nasal discharge, cough, and fever are classic signs. Respiratory infection may involve the lower respiratory tract with possible primary viral pneumonia. Secondary bacterial infection may occur. Vomiting and diarrhea may be present. Neurologic signs may be concurrent with epithelial signs (i.e., respiratory disease, conjunctivitis, vomiting, diarrhea) with encephalitis caused by direct viral replication. Alternately, neurologic disease may occur several weeks after resolution of epithelial invasion.

A significant amount of pathology results from the host's immune response to the virus, as well as the virus itself. Seizures and myoclonus are two of the more common signs. The latter may affect limbs or manifest as chewing motion of the jaw. Ocular disease may also occur. Lesions include anterior uveitis, optic neuritis, and retinal detachment. Infection during pregnancy may lead to abortion or stillbirth. Puppies infected before permanent dentition may have enamel hypoplasia. Digital hyperkeratosis ("hard pad disease") may be noted.

Diagnosis

Diagnosis is established via virus identification in a clinical sample through use of reverse-transcriptase polymerase chain reaction (PCR) of whole blood, a swab of conjunctiva or tissue, cerebrospinal fluid (CSF), or urine. When obtaining conjunctival scrapings, remove mucus and tears and using a sterilized, blunt metal spatula or dulled scalpel blade, repeatedly scrape the conjunctiva until a small amount of tissue can be lifted. Apply the tissue to a slide and submit the slide to an outside lab for immunofluorescence assay (IFA) testing. Urine is a good source for PCR testing in patients with CDV encephalitis after resolution of epithelial signs. CDV may be detected in urine for a longer period than other sample types. CDV detection in urine and CSF was equivalent in one study of neurologic cases. Postmortem evaluation and microscopic findings confirm infection. The specific lesion of CDV is eosinophilic intranuclear/intracytoplasmic inclusion bodies in glial cells, neurons, epithelial respiratory cells, and cells of the GI and urogenital tracts.

Virus isolation is the gold standard for diagnosis and is useful in low levels of viral infection through observation of typical syncytial cell formation. Immunocytology can be used to enhance the visibility of inclusion bodies by fluorescein-conjugated CDV antibodies.

Treatment

Treatment is supportive only (see Chapter 82). Antiviral medications are not routinely used or recommended. No single treatment is specific or uniformly successful.

Secondary bacterial infection frequently results in bronchopneumonia, which requires broad-spectrum antibiotic therapy +/− expectorants or nebulization. Parenteral therapy is required when GI signs or dehydration are present. Water, food, and oral drugs should be discontinued if vomiting and diarrhea are present, Parenteral antiemetics may be required. In dogs with status epilepticus, diazepam should be administered intravenously or per rectum, followed by phenobarbital for maintenance prevention.

Prevention

Control is accomplished through vaccination. Current vaccines include strains of the American lineage (Onderstepoort or Lederle strains). After recovery from natural infection or following booster vaccination, immunity can persist for years. Vaccination for CDV can begin as early as 6–8 weeks of age, with boosters every 2–4 weeks until at least 16 weeks of age. For naive puppies or adults vaccinated after maternal immunity has waned (approximately 16 weeks of age), a single attenuated live or recombinant vaccine may be sufficient to induce protection. In older vaccinated dogs, an annual or triennial distemper booster is recommended, depending on the risk for infection. Current AAHA guidelines should be consulted for specific vaccination recommendations in standard and high-risk situations. The AAHA 2017 canine vaccination guidelines state that measuring antibody levels provides a reasonable assessment of protective immunity. Information on antibody testing can be found at www.aaha.org/CanineVaccineTiters. No vaccine is 100% effective, but regular vaccination can help protect animals. CDV is susceptible to ultraviolet light, heat, drying, and all routinely used disinfectants.

Client education about purchasing puppies from crowded pet markets is important.

Prognosis

Prognosis is guarded, especially with CNS involvement.

Public Health Implications

Currently, CDV is not considered to be a public health concern. However, following the outbreaks of CDV infections in animal facilities in China, a CDV outbreak occurred in cynomolgus monkeys (*Macaca fascicularis*) in Japan in 2008. A corresponding CDV strain was isolated (CYN07-dV) and characterized, which efficiently utilized macaca CD150 as an entry receptor. Despite the similarity of the amino acid sequence of *Macaca mulatta* CD150 to the human sequence, the isolated virus did not efficiently infect human Vero-hSLAM cells. As long as a high percentage of the human population is immune to measles via vaccination, there is likely little concern for CDV making the transition to humans. However, that may change if measles should happen to be eradicated.

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81

Canine Herpesvirus

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Etiology/Pathophysiology

Canine herpesvirus (CHV), a member of the Herpesviridae family, is a DNA virus that infects and replicates in mucosal epithelial cells and lymphoid tissue. Clinical signs vary depending on the age and immune status at time of infection. The virus replicates most efficiently at temperatures lower than 98.6 °F. Therefore, the ability to mount a febrile response aids in fighting infection. In addition, replication is favored in cooler body locations such as mucous membranes. As is common for herpesviruses, CHV will exist as a latent form in ganglia or lymphoid tissue after initial infection. The virus can be reactivated by stressors at any time, leading to shedding and transmission.

In naive pregnant females, infection will lead to systemic viremia, resulting in fetal death, abortion, and mummification. Puppies typically acquire the infection *in utero*, during passage through the birth canal, via contact with oronasal secretions of the dam, or from contact with other infected dogs shedding the virus. Acute neonatal viremia is associated with very high mortality in puppies younger than 3 weeks. Pregnant females, previously exposed to the virus, will confer passive immunity through nursing, while remaining asymptomatic. Older, naive puppies and adult dogs will usually show disease of the genitals, respiratory tract or eyes.

Epidemiology

Canine herpesvirus is common in several canine species, including dogs, coyotes, and wolves, and has a worldwide distribution. Studies in Europe have shown a seroprevalence of 39–88% in dogs. Infection is more common in multidog environments, such as shelters and kennels. Studies in shelter dogs have also shown that CHV may be implicated as an etiologic agent in canine infectious respiratory disease complex.

Signalment

Neonatal puppies up to 3 weeks are at greatest risk for severe disease and death. Male and female dogs older than 3 weeks generally develop mild clinical signs and recurring infections.

History and Clinical Signs

Infection and associated clinical signs occur by exposure to other dogs, and may be particularly common in kennels and other multidog environments. Clinical signs may also occur due to reactivation of previous infection provoked by various stressors. Immunocompromised animals are at higher risk of reoccurring infections, particularly dogs with diabetes mellitus, immune-mediated diseases, and lymphoma.

In young puppies 1–3 weeks of age, signs include depression, respiratory signs, anorexia, soft yellow or green stools and diarrhea, persistent crying, abdominal pain, petechial hemorrhages on mucous membranes and occasional presence of vesicles on genitals. Death usually occurs within 24–48 hours of showing clinical signs. Surviving puppies will most likely develop neurologic signs.

Older puppies and adults may present with upper respiratory signs, but in rare cases, more severe lower respiratory disease can occur. Signs of primary genital infection are characterized by vesicular lesions on the genital mucosa. Ocular signs may include conjunctivitis, corneal ulceration or keratitis, blepharospasm, photophobia, and ocular discharge.

Diagnosis

History, clinical signs, physical examination, a history of stress or evidence of immunosuppression should

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increase the index of suspicion for infection. Sepsis is the primary differential for neonates. CHV can be isolated and grown from various tissues including liver, spleen, kidneys, and lymph nodes taken from puppies that died of systemic infection. Older animals showing signs of reproductive, respiratory or ocular disease will typically shed the virus in oral or genital mucosa, which can be sampled. In cases of active viremia, whole blood in EDTA can be used for virus isolation. Virus can also be detected using polymerase chain reaction (PCR), immunofluorescence assays, or electron microscopy. Serology will confirm presence of CHV antibodies, which indicates exposure but not necessarily active infection.

Therapy

Treatment options for young puppies with signs of systemic infection are limited. The progression of the disease is rapid and usually fatal. Supportive care is important. Intraperitoneal injection of 1–2 mL of pooled immune sera from female dogs that have given birth to CHV-infected litters has been suggested as a treatment for neonatal puppies. External warming may restrict viral growth, and it has been suggested that it may help prevent clinical signs in unaffected puppies. However, it is not effective in puppies that already show signs of infection. The efficacy and safety of antiviral drugs requires further research. Currently, there are no licensed medications for treatment of CHV in dogs. The antiviral drugs vidarabine and acyclovir have been described for treatment of neonatal puppies with CHV infection, but whether they are safe or effective has not been well studied, toxicity is a significant concern. There is no vaccination for CHV in the United States, but a vaccine is available in Europe.

Prognosis

The disease is usually fatal in neonates whereas milder or subclinical disease occurs in older animals with a competent immune system and the ability to thermoregulate. Immunosuppression may cause recrudescence of latent infection.

Public Health Implications

Like other herpesviruses, CHV is highly species specific and does not infect humans.

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82

Canine Viral Enteritis

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Dogs are susceptible to several viral diseases that present with gastrointestinal signs either as the primary complaint or as a component of multisystemic disease. Canine parvovirus type 2 (CPV-2) is the most common cause of viral enteritis in dogs, but enteric canine coronavirus (CCoV) and canine distemper virus must also be considered as possible viral etiologies. Canine rotavirus causes diarrhea in neonatal puppies, similar to type A rotaviruses in other animal species. A multitude of other viruses, including two newly discovered viruses of dogs, canine kobuvirus and dog circovirus, have been identified in some cases of canine enteritis.

Because CPV-2 is the most clinically relevant of the canine enteric viruses, this section will focus on its characteristics, pathogenesis, and management. Table 82.1 provides a comparison of CPV-2 with some of the other canine enteric viruses.

Etiology/Pathophysiology

Canine parvovirus is a small single-stranded, nonenveloped DNA virus that infects and replicates in a variety of rapidly dividing cells. Entry into the host cells depends on interaction between the major capsid protein of the virus, VP2, and the transferrin receptor on the cell surface. Initial replication usually occurs in the oropharyngeal lymphoid tissues, followed by viremia and systemic replication in other lymphoid tissues, leukocyte precursors in the bone marrow, and intestinal crypt epithelial cells. Clinical signs may appear as early as four days after exposure but more typically occur about a week after infection.

Pathologic findings include gastrointestinal inflammation and hemorrhage predominantly in the small intestine, with characteristic crypt cell destruction and severe villous atrophy. The virus also causes lymphoid depletion, thymic lymphocytolysis, and mitotic arrest of bone marrow hematopoietic cells. Perinatal infection with CPV-2 can result in cardiac myofiber lysis and multifocal necrosis.

Epidemiology

Canine parvovirus is closely related to feline parvovirus and similar viruses of wild carnivores, such as mink enteritis virus and raccoon parvovirus. Since its emergence and worldwide spread in domestic and wild canids in the mid-late 1970s, CPV-2 has mutated to form antigenic variants CPV-2a, CPV-2b, and CPV-2c, which are all defined by amino acid changes in the major capsid protein, VP2. Although CPV-2 is unable to infect cats, subsequent variants have expanded host ranges and can replicate in feline cells.

The main route of infection for CPV-2 (as with most other enteric viruses) is through oral or nasal contact with feces or feces-contaminated material. *In utero* transmission of CPV-2 can also occur. The small compact size and nonenveloped structure of the virus make it highly resistant to inactivation by environmental conditions and easily transmitted on fomites. Infected animals shed the virus in high concentrations beginning around day 4 of infection and can continue to shed for several days after the resolution of clinical signs. Parvovirus is rarely detected in the feces of healthy dogs with no history of enteritis.

At least in some regions, there is a distinct seasonality to the occurrence of parvovirus enteritis, usually peaking in late summer to early fall.

Signalment

While male and female dogs of all ages are susceptible to infection, CPV-2 is most significant as a cause of gastroenteritis in puppies 6 weeks to 6 months of age. Puppies become susceptible to infection as maternally

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Table 82.1 Comparison of CPV-2 and other canine enteric viruses

Virus	Molecular characteristics	Host specificity	Age most affected	Primary target cells and typical pathobiology	Clinical presentation	Additional information
Canine parvovirus 2 (*Parvovirus*, Parvoviridae)	ssDNA, nonenveloped, icosohedral capsid; variants CPV-2, 2a, 2b, 2c	Domestic and wild canids; CPV-2a, 2b, 2c – can also infect cats	6 weeks–6 months	Lymphoid cells, intestinal crypt epithelial cells, hematopoietic cells Intestinal crypt destruction/ severe villous atrophy; lymphoid, bone marrow and thymic depletion	Fever, depression, inappetence, vomiting, diarrhea (scant mucoid to profuse hemorrhagic); dehydration, electrolyte disturbances; endotoxemia	High level of genetic variation can lead to emergence of new antigenic variants
Canine enteric coronavirus (*Alpha- coronavirus*, Coronaviridae)	ssRNA, enveloped with large spike proteins, helical nucleocapsid; genotypes CCoV-I, CCoV-II (a & b)	Domestic and wild canids	>4 months Healthy dogs often shed CCoV	Enterocytes Moderate villous atrophy, deepening of crypts Pantropic variant has increased virulence and causes systemic disease	Usually mild, self-limiting diarrhea and vomiting Pantropic variant – fever, lethargy, hemorrhagic diarrhea, lymphopenia, neurologic signs	A distantly related *Beta-coronavirus* causes respiratory disease in dogs similar to SARS-CoV in humans
Canine distemper virus (CDV) (*Morbillivirus*, Paramyxoviridae)	ssRNA, enveloped; intracytoplasmic & intranuclear inclusions Closely related to human measles & rinderpest viruses	Domestic and wild canids; wild felids; variants infect raccoons, skunks, ferrets, marine mammals	3–6 months	Macrophages, lymphocytes, epithelial cells, neurons, glial cells (pancytotropic) Mild-moderate villous atrophy, hyperkeratosis, lymphoid and thymic depletion, encephalomyelitis	Multisystemic disease: lethargy, fever, vomiting, diarrhea, coughing, dyspnea, nasal and ocular discharge, conjunctivitis, keratitis, photophobia, seizures, dementia, ataxia, hyperesthesia, hyperkeratosis	"Old dog" encephalitis – rare form of CDV disease in older dogs years after primary infection
Canine rotavirus (*Rotavirus*, Reoviridae)	Segmented (11) dsRNA, non-enveloped; reassortment with A rotaviruses	Domestic and wild canids See Additional information column	Neonates	Mature enterocytes Mild villous atrophy	Usually mild, self-limiting diarrhea	Interspecies transmission and zoonotic potential with reassorted viruses
Canine kobuvirus (*Kobuvirus*, Picornaviridae)	ssRNA non-enveloped, icosohedral capsid	Domestic dogs and foxes, likely other canids – very few epidemiologic studies reported	Unknown	Not yet characterized	Has been isolated from stool samples of diarrheic dogs, but pathogenicity is currently unknown	Genetically similar to human Aichi virus A, a gastroenteritis transmitted through consumption of oysters
Dog circovirus (*Circovirus*, Circoviridae)	ssDNA, non-enveloped, icosohedral capsid Closely related to porcine circovirus	Domestic dogs; wild canids unknown	6 weeks–6 months	Not yet characterized	Unclear – has been associated with hemorrhagic gastroenteritis, vasculitis and vascular necrosis Granulomatous lymphadenitis, thrombocytopenia	Similar prevalence in healthy and sick dogs; probably most important as a co-pathogen with CPV-2 – increased mortality

derived immunity wanes and remain susceptible until they acquire active immunity, either through natural infection or through vaccination. The outcome of infection, ranging from subclinical infection to severe disease, seems to depend on individual host factors, with some breeds (notably American pit bull terriers, Rottweilers, Doberman pinschers, and German shepherds) having increased risk for severe enteritis.

History and Clinical Signs

Most puppies infected with CPV-2 present with a history of lethargy and inappetence. These signs are often accompanied by fever, abdominal pain, vomiting and diarrhea, which may lead to substantial dehydration. Although profuse, hemorrhagic diarrhea is a typical finding, many dogs with CPV enteritis will produce scant mucoid feces instead. Extensive damage to the small intestinal mucosa may result in coliform bacterial septicemia and endotoxic shock.

Lymphopenia is a consistent clinicopathologic finding; other changes may include neutropenia, anemia, thrombocytopenia, electrolyte imbalances (especially hypokalemia), hypoglycemia, and hypoalbuminemia. Serum C-reactive protein levels are often elevated in critically ill dogs and correlate loosely with increased risk of mortality.

Myocarditis occurs with perinatal infection of puppies born to naive bitches; puppies may present with dyspnea, weakness, and crying or experience sudden death. This syndrome is not commonly seen in vaccinated and/or CPV-endemic populations.

Diagnosis

Although parvovirus infection is the likely diagnosis in an unvaccinated puppy presenting with enteritis, fever, and lymphopenia, other enteric viruses may have a similar presentation. Diagnosis of parvoviral enteritis is best accomplished by observation of clinical signs along with detection of CPV-2 antigen (point-of-care enzyme-linked immunosorbent assay [ELISA] or hemagglutination) or DNA (polymerase chain reaction [PCR]) in feces or rectal swab specimens. PCR-based tests are more sensitive than antigen tests and can be used to identify the variant of the infecting CPV.

Therapy

Ideally, puppies infected with CPV-2 should be hospitalized and kept in isolation. Therapy for CPV-2 enteritis consists of aggressive supportive care to correct hydration, hypoglycemia, and electrolyte abnormalities such as hypokalemia, control pain and maintain nutrition. Antimicrobials should be administered to prevent and treat secondary bacterial infections (gram-negative and anaerobic) that arise from bacterial translocation across the compromised gastrointestinal tract or from neutropenia. Frequent (q8h) monitoring of blood glucose is necessary and supplementation of intravenous (IV) fluids with dextrose is often needed. Colloid therapy with hetastarch or plasma may be necessary in some patients, particularly those with severe hypoalbuminemia (Figure 82.1).

Red cell transfusion may be necessary in patients with significant blood loss. While treatment with recombinant human granulocyte stimulating factor and hyperimmune serum has not been shown to be of benefit, feline interferon-omega has shown promising results.

Prognosis

Puppies with severe enteritis have a very poor survival rate without treatment due to hypovolemic and septic shock and electrolyte/acid–base disturbances, while hospitalization with fluid therapy greatly improves their prognosis for recovery. A protocol for outpatient treatment of puppies whose owners cannot afford hospital care has been developed and is showing promise for improving the prognosis in these patients.

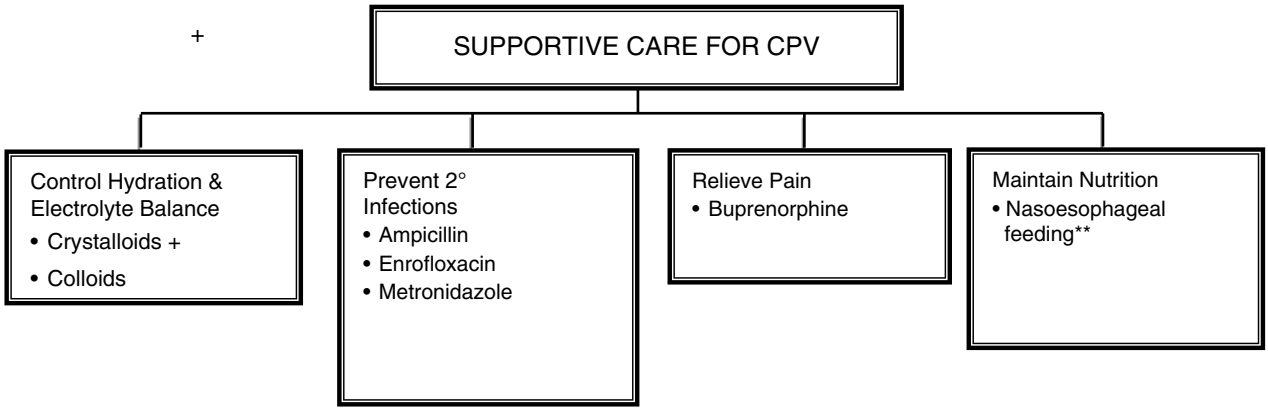
Prevention

Prevention of CPV-2 infection is accomplished by limiting contact of susceptible animals with potentially infected animals and premises while stimulating immunity with vaccination. Shelters, kennels, clinics, and other high-density units need to practice good sanitation, disinfection, and appropriate use of quarantine protocols and isolation facilities.

Because maternally derived antibody can interfere with immunization, vaccination with modified live virus vaccine is recommended every 3–4 weeks beginning at 6 weeks of age until the puppy is 16 weeks old (or 20 weeks old for high-risk breeds). Although current vaccines, which are composed of CPV-2 or CPV-2b, have been effective in protecting dogs against CPV-2c infection under experimental conditions, it is still unclear how protective these vaccines are under some field conditions.

Public Health Implications

Canine parvovirus-2 variants do not infect people, but feces should be treated as if other infectious agents that cause intestinal disease in people are present.



+ Potassium supplementation is important and should be adjusted based on frequent measurement of serum potassium.
# Ampicillin or cefazolin may be sufficient however improved gram-negative coverage may be needed. There is a risk of cartilage deformity in puppies treated with fluoroquinolones, however short-term(<7 d)therapy at 5 mg/kg q 24 hours may be warranted Once the patient is hydrated, aminoglycosides may also be considered for improved gram-negative coverage.
Metronidazole may be used to improve anaerobic coverage if needed.
** Use of the GI tract and trickle feeding is associated with improved survival compared to fasting, and is preferred over intravenous feeding due to the ability to provide nutrition to enterocytes and due to the risk of sepsis associated with parenteral nutrition.

Figure 82.1 Supportive care for CPV.

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83

Viral Papillomatosis

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Dogs and cats, like many other species, are susceptible to development of papillomatous growths (warts) on the skin and mucous membranes. Most of the time, viral papillomas are benign and transient lesions but they can significantly affect the health of an animal if they progress to premalignant or malignant neoplastic lesions. Canine and feline papillomas and the viruses that cause them share many features and will be discussed together in this chapter.

Etiology/Pathophysiology

Papillomaviruses (PV) are small nonenveloped viruses with a circular double-stranded DNA genome enclosed in an icosohedral capsid. They belong to the large and diverse viral family Papillomaviridae, which currently includes over 280 types of papillomaviruses infecting most (if not all) mammalian species and many nonmammalian species. Each PV type demonstrates a strong host and tissue/site preference, with only a few examples of interspecies transmission.

Papillomaviruses replicate in epithelial cells of skin and mucous membranes, beginning their life cycle in the basal layer and progressing as the cells mature. Viral assembly and particle release are restricted to the stratum granulosum and stratum corneum. This pattern of replication is orchestrated by the complex expression of a series of early and late genes.

Infections are often subclinical, with frequent detection of papillomavirus DNA in normal skin of healthy dogs and cats. The typical presentation of papillomatosis (cutaneous or oral warts) occurs when high levels of PV early gene expression induce rapid expansion of the basal epithelial cell population followed by cell differentiation, epithelial thickening, hyperkeratosis, and exophytosis. Progression to malignant lesions occurs rarely in both dogs and cats, with some species differences in histologic features and clinical presentation. Disregulation and overexpression of two early genes, E6 and E7, have been linked to the development of PV-associated squamous cell carcinomas (SCCs).

In most animals, mild inflammation and a cell-mediated immune response lead to spontaneous regression of papillomas within 6–8 weeks. A humoral immune response produces antibodies that protect against reinfection with closely related types of PV. Immunocompromised animals may develop persistent and generalized papillomatosis with an increased risk of progression to malignant neoplastic transformation.

Epidemiology

Papillomaviruses infect domestic and wild canids and felids throughout the world. Although only a few canine and feline PV have been sequenced to date, almost 150 human PV types have been reported. In general, PVs are highly host specific; however, bovine papillomavirus type 1 infection causes equine sarcoid tumors in horses, and ruminant-like PVs have been linked to the development of feline sarcoids.

Papillomaviruses are transmitted through epidermal microabrasions or transepidermal inoculation of virus with contaminated fomites. Because the virus lacks an envelope, it is relatively resistant to adverse environmental conditions and difficult to kill with disinfectants. These facts, along with the ubiquity and diversity of PVs, make it likely that most animals will be infected at some point in their lives, but there is little information on the prevalence of PV infection in canine and feline populations.

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Signalment

Dogs and cats of all ages and breeds can be infected with PVs. Young dogs are most likely to be affected by canine oral papillomatosis, while older animals with chronic persistent infections are more likely to develop bowenoid *in situ* carcinoma (BISC) and invasive SCC. Young pugs and miniature schnauzers seem to be disproportionately affected by canine pigmented plaques, suggesting that host genetic factors play a role in the development of this disease. Oral papillomas in dogs rarely progress to SCC but there is some indication that malignant transformation of canine oral papillomas may be increasing.

Oral and cutaneous papillomatoses are not observed as often in cats as in dogs; viral plaques are also uncommon but have been more clearly associated with PV infections in cats. Feline BISCs develop in middle-aged to older cats, occur disproportionately in cats with feline retrovirus infections, and are most severe in hairless breeds. Cutaneous and oral SCCs are common malignancies of older cats, with ultraviolet (UV) exposure being an important risk factor for some of these lesions. While feline PV DNA has been identified frequently in cutaneous SCCs found in UV-protected areas of the body, a strong association of oral SCC with PV infection in domestic cats has not been established.

Clinical Signs

Papillomatosis and viral plaque lesions are typically limited to the cutaneous or mucosal epidermis, sometimes occurring singly but more often in multiples. Lesions can range from papular or nodular lesions to pedunculated or cauliflower-like, hyperkeratotic masses. Infection rarely generates more than a mild inflammatory response, so systemic signs are not seen. Bowenoid *in situ* carcinomas develop as multicentric irregular regions of epidermal and follicular hyperplasia primarily on the face, shoulders, and limbs. These premalignant lesions are hyperkeratotic, pigmented plaques that may ulcerate. If progression to SCC occurs, it is usually as a single nonmetastatic but potentially highly invasive tumor. A summary of diseases associated with canine and feline PV infections is provided in Table 83.1.

Diagnosis

Diagnosis of oral papillomatosis is based on clinical presentation for most typical cases in young dogs. Other types of lesions require full-thickness excisional biopsy with histologic examination for a morphologic diagnosis. The etiologic diagnosis of papillomatosis can be

Table 83.1 Papillomavirus-associated disease in domestic dogs and cats

Disease	Species affected	Clinical presentation
Oral papillomatosis	Canine Feline – rare	Multiple, raised, smooth nodular to pedunculated, hyperkeratotic masses on oral mucosa and lips (dogs), or ventral tongue (cats); spontaneous regression is common
Exophytic cutaneous papillomatosis	Canine Feline – rare	Single to multiple pedunculated, hyperkeratotic masses often on head or feet; spontaneous regression is common
Endophytic cutaneous papillomatosis	Canine	Unpigmented, raised firm masses with central pores found on ventral abdomen or feet; do not usually regress
Pigmented plaques	Canine	Small to medium-sized flat to slightly raised, darkly pigmented, hyperkeratotic masses found in clusters on the limbs, axilla, ventral trunk or abdomen; do not usually regress; may progress to *in situ* carcinoma
Viral plaques	Feline	Multiple variably sized, slightly raised, hyperkeratotic masses that may or may not be pigmented; some may spontaneously regress while others progress to *in situ* carcinoma
Bowenoid *in situ* carcinoma (BISC)	Feline Canine – rare	Multiple scaly, crusting to ulcerating plaques frequently on face, neck and limbs; some may be slowly progressive and others become highly invasive or progress to squamous cell carcinoma
Squamous cell carcinoma (SCC)	Feline Canine – rare	Usually a solitary flattened ulcerated mass found in UV-protected areas of the body (as opposed to SCCs caused by UV exposure); rarely metastasize but can be highly invasive and damaging to surrounding tissue
Feline sarcoid	Feline	Slow-growing, solitary to multiple, smooth dense fibroblastic nodules that may ulcerate, located on head, neck and extremities; do not metastasize and are not highly invasive

UV, ultraviolet.

confirmed by immunohistochemical staining for PV group-specific antigens, *in situ* hybridization for PV nucleic acid detection, or electron microscopy to visualize viral particles. Polymerase chain reaction is a highly sensitive and rapid method for detection of PV DNA in biopsy specimens, but interpretation is difficult because PV DNA is frequently amplified out of normal canine and feline skin.

Therapy and Prognosis

Spontaneous regression of many nonmalignant PV-associated lesions makes treatment unnecessary in most cases. Immunosuppressive drugs like glucocorticoids and ciclosporin should be avoided, if possible, in infected animals. Provision of a high-quality diet and management of stress may help support an animal's immune response to the virus. Interferons and other immunomodulators have been tried in severe cases of papillomatosis, but solid evidence of their efficacy is not yet available. Azithromycin (10 mg/kg once daily for 10 days) was used in one small trial to treat canine oral and cutaneous warts with some apparent efficacy. The mechanism of action is unclear but it may be associated with immunomodulatory properties of the drug.

Surgical removal or cryotherapy may be effective if few lesions are present although new lesions may develop. Removal of premalignant and malignant lesions like BISCs and SCCs should include histologically confirmed normal tissue margins on all borders.

Prevention

Currently, there are no commercial vaccines available for canine and feline papillomatosis. Because most PV infections are subclinical or produce benign self-limiting lesions, immunization has not been a priority. The diversity of PVs makes it difficult to stimulate protective immunity against this family of viruses. If specific types of canine and feline PVs are demonstrated to be associated with the development of SCC, then targeting those viruses with vaccines would make sense. The use of vaccines against some types of human PVs associated with genital cancer suggests that vaccination could be effective against PVs in other species also.

Public Health Implications

Canine and feline papillomaviruses have not been demonstrated to be infectious to humans. However, human PV-9 was amplified from a cutaneous papilloma in a cat, and bovine PV causes equine (and possibly feline) sarcoids, proving that cross-species infection can occur under some circumstances.

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84

Canine Influenza Virus

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Etiology/Pathophysiology

While influenza A viruses had for many years not been considered pathogens of concern in dogs, they are today a serious differential for canine respiratory problems. In 2004, a previously known equine strain of H3N8 influenza A virus emerged as a canine respiratory concern during an outbreak in greyhound racing dogs in Florida. Twenty-two dogs suffered from fever, followed by coughing and either recovery or, in the case of eight dogs, peracute death occurred associated with extensive hemorrhaging of the lungs, mediastinum, and pleural cavity.

Severe respiratory illness with mortality was reported in dogs in 2008 in Korea and later in China and Thailand due to an H3N2 strain of influenza that has been shown to originate from the avian virus and to also transmit from dog to dog. In March 2015, canine influenza virus (CIV) H3N2 was identified in the United States in the Chicago area and during the same year identified in dogs in at least 30 states throughout southern, eastern and midwestern United States. In 2015, shelter cats in Indiana were also diagnosed with an H3N2 strain.

Typical of other influenza A viruses, CIV viral particles capable of cell-to-cell or host-to-host transmission carry H (hemagglutinin) and N (neuraminidase) proteins that are anchored in the bilipid envelope coating the viral particle. These glycosylated proteins, used to define subtypes, are prone to mutations that result in the evolution of new influenza strains. A hallmark of influenza viruses is the eight-segmented RNA genome which provides a mechanism of rapid genetic change through segment reassortment. Thus, infection with more than one type of influenza virus can result in progeny that are a combination of RNA segments from more than one parent strain. In addition, the RNA polymerase which generates the viral RNA segments for progeny virus is error prone, creating mutations that may contribute to altered viral tropism, pathogenesis, and antigenicity.

Epidemiology

Influenza viruses are highly contagious and easily transmitted from dog to dog by aerosol or contact exposure, but the H3N2 also was found to infect cats, resulting in respiratory illness. The H3N8 virus has been shown experimentally to also infect cats. Animals in high-density environments, such as shelters, competition events, and breeding facilities, are at greatest risk of infection.

The original canine H3N8 outbreak in greyhounds, first recognized in January of 2004, had spread in a few months to tracks in six states, and as of April 2013 had been reported in 40 states (dogflu.com). Similar to influenza in other animals, a dog may be infected and shed contagious CIV for up to four days before clinical signs occur. Currently, infection of dogs is estimated to result in 80% morbidity and 1–5% mortality although higher rates of mortality have been reported. Humans have been reported to also carry the virus from an infected animal to a naive animal although the Centers for Disease Control (CDC) states that human infections with the CIV strains are not a health concern. This may be a matter of adaptation and infection with or without clinical illness.

The virus isolated from the lungs of dogs in Florida during the first cases of CIV was found to be a canine-adapted H3N8 virus originating from an equine H3N8 subtype, recognized as respiratory pathogens of horses since 1963. Unlike previous reports of influenza infections in dogs, which were self-limiting and not transmitted from dog to dog, the greyhound H3N8 virus of 2004 originating from an equine H3N8 virus and the H3N2 originating from an avian influenza virus were easily transmitted from dog to dog and, at least the latter, also from cat to cat. The sequencing of genomes of CIV isolates identified signature mutations that indicate stable changes in the canine-adapted viruses.

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Cross-species infections frequently occur with influenza A viruses but adaptation to a new species is not common. Dogs are susceptible to infection with human strains, normally without clinical illness or transmission to other dogs. It is not known why the H3 strains seem to have adapted to the dog as a stable host, but it is possible that other strains could, with the appropriate mutations, evolve into true canine pathogens. In 2012, a novel H3N1 human H1N1 and H3N2 reassortant virus was reported to infect dogs subclinically in Korea but was not reported to transmit from dog to dog.

Signalment

Any dog that has not developed immunity specific for the H3N8 virus can be infected regardless of age, sex or breed. Being a highly contagious respiratory virus, the length of time that a dog may remain in a shelter has been associated with increased risk of infection with CIV. With available vaccines and greater likelihood of natural exposure, more animals will develop immunity and morbidity will likely decrease in all ages and breeds, and both sexes.

History and Clinical Signs

Clinical history is indistinguishable from other respiratory diseases of dogs and resembles influenza infections in other animals. Morbidity may be expected to be at least 60%, but it has been reported that as many as 80% of infected animals may develop clinical signs of infection. Between two and four days following infection, dogs may present with clinical illness, such as fever, sneezing, dyspnea, anorexia, depression and coughing, and ocular and nasal discharge that can become mucopurulent. Illness, especially coughing, may continue for 10–30 days post infection. The mortality is generally low. A minority of infected dogs will develop pneumonia with tracheitis and bronchitis. Complications of secondary infections from bacteria or mycoplasma may exacerbate lung involvement, such as hemorrhage in the lungs, mediastinum and pleural cavity, and greater mortality.

Diagnosis

Because clinical illness is similar to that of other respiratory illnesses in dogs, CIV involvement must be diagnosed by detection of viral antigen, viral RNA or the presence of specific antibody. Because of the short duration of virus infection, serology may be a more reliable means of diagnosing infection. Serologic evaluations usually require comparisons of paired sera to document seroconversion to confirm infection. CIV-specific antibodies can be detected as early as seven days after infection. Hemagglutination inhibition assays are used to determine antibodies specific for the H serotypes. However, convalescent sera, in the absence of widespread exposure, can often be used to identify specific infection. Enzyme-linked immunosorbent assay (ELISA) can be used to detect group-specific antibodies for influenza A viruses. The group-specific (not type-specific) ELISA is based on detecting specific antibody that binds to the nucleocapsid protein, which coats the viral genome segments and is highly conserved among all influenza A viruses.

Virus may be detected in samples collected with cotton or Dacron nasal swabs within four days after clinical signs are observed; that is, within seven days after infection. Necropsy-collected tissue from lungs or associated lymph nodes may be used to detect virus. Diagnosis of viral infection is often first determined using real-time reverse transcriptase polymerase chain reaction (PCR) of the gene that encodes the highly conserved matrix protein in influenza virion. A positive PCR result may be followed by viral isolation (after up to three passages) using Madin–Darby canine kidney cells or embryonated chicken eggs in order to determine the H and N subtypes of the isolated virus.

Subtyping the H and N of the viral isolates can also be determined by laboratories that have the tools for sequencing the viral genome. The hemagglutination inhibition assay is often used to determine the serotype of CIV strains in the US. Antibodies that react with virus inhibiting red blood cell agglutination of CIV serotype standards can be used to inhibit agglutination and thus identify the H subtype of the CIV isolate.

Therapy

Supportive therapy may be necessary to provide optimum conditions for the immune system to respond, eliminating infection and reducing the severity of clinical signs. Oxygen, intravenous fluids, and nebulization with coupage may be needed for dogs with pneumonia. Good nutrition and basic biosecurity measures that include disposable or dedicated protective clothing and the use of kennel-approved disinfectants can help to prevent viral spread. Soap and water hand washing which destroys the bilipid envelope membrane of influenza viruses is highly effective in inactivating the virus. Isolation of infected or suspected infected animals may protect dogs not exposed to the virus or vaccine although exposure is difficult to assess since infection occurs prior to the appearance of clinical illness.

Canine influenza virus survives in the environment for more than 24 hours. Because secondary bacterial and mycoplasma infections can cause complications, antimicrobials may be considered if clinical signs are severe or suggest co-infection. Antiviral drugs exist for influenza, but such treatments have not been approved for use in dogs. Information is lacking regarding their efficacy, doses or negative side-effects in dogs.

The Nobivac® Canine Influenza H3N8 and H3N2 inactivated bivalent vaccine from Intervet/Merck is labelled as effective at reducing disease severity. However, the capacity for influenza A viruses to mutate provides the risk of eventual adaptation and evasion of immunity from administered vaccines.

Prognosis

From 60% to 80% of CIV-infected dogs will present with clinical illness, but subclinically infected dogs will also shed contagious virus. Dogs will completely recover clinically within 2–3 weeks, sometimes, however, with a lingering cough. Animals that are generally in good health and well nourished are expected to recover without complications. While most infections will be self-limiting, mortality is considered to be between 1% and 5%.

Public Health Implications

With the reported transmissions of influenza from birds and other mammals to humans, we should consider CIV strains a potential public health concern. Influenza viruses are commonly transmitted across species although usually with subclinical infection and without further transmission within the second species. However, the CIV strains have not been reported to infect humans, even owners with known infected dogs, and the Centers for Disease Control does not consider the canine influenza viruses to be a human threat.

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85

Feline Parvovirus

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Feline parvovirus (FPV) is the causative agent of feline panleukopenia, a disease that has also been called feline infectious enteritis, feline plague or feline distemper.

Etiology/Pathophysiology

Feline parvovirus is so closely related to canine parvovirus type 2 (CPV-2), mink enteritis virus, and raccoon parvovirus that all these viruses are now classified as a single species, *feline panleukopenia virus*. The genome of this small single-stranded DNA virus is packaged tightly in an icosohedral, nonenveloped capsid that is very resistant to environmental conditions. The feline transferrin receptor allows FPV access to a broad range of host cells, where it replicates in actively dividing cells including lymphocytes, enteric crypt epithelial cells, and bone marrow myeloid progenitor cells. Similar to the pathology seen with CPV-2 infection in dogs, intestinal villi are severely blunted, absorptive capacity is impaired, and gastrointestinal integrity is compromised in FPV-infected cats. The interruption of myeloid cell proliferation along with lymphocytolysis and redistribution of circulating white blood cells to inflamed tissues results in the characteristic and severe panleukopenia seen with this disease.

Perinatal infection (approximately three weeks before birth to three weeks after birth) of kittens results in infection of the central nervous system and impacts development of the cerebellum. The virus replicates in the dividing neuroblasts of the external granule cell layer, causing cerebellar hypoplasia in kittens that survive the infection. There is also evidence of FPV replication in Purkinje cells of the cerebellum but it is unclear how the virus replicates in these presumably postmitotic cells.

Epidemiology

Domestic and wild felids are susceptible to FPV infection, along with some nonfelid species like mink, raccoons, and foxes. Although canids are resistant to FPV infection, only a few mutations in the VP2 capsid protein gene led to the emergence of CPV-2. Feline parvovirus-associated disease is most often seen in multicat housing situations like animal shelters and breeding catteries, especially if rigorous sanitation, isolation, and vaccination protocols are not followed. Parvoviruses are shed at high titer in the feces of infected animals for several days after infection. Transmission is through the fecal–oral route, either directly or indirectly on fomites such as shoes, clothing, or feeding dishes.

Extensive prevalence data are lacking. The prevalence of anti-FPV antibodies in cats entering a Florida animal shelter, indicating either past exposure or vaccination, was just under 40%. If other cat populations in the US are similar, about 60% of cats are at risk for FPV infection. Anecdotal reports also suggest a recent resurgence of feline panleukopenia outbreaks, possibly associated with antigenic variation in FPV variants and the associated decreased efficacy of commercial vaccines.

Signalment

Susceptible cats of all ages can be infected, but young kittens experience a higher mortality rate (up to 90%) than older animals if not treated. There are no breed or sex predispositions reported for FPV.

History and Clinical Signs

The typical FPV patient will have a history of exposure to other cats in a high-density multicat environment and

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little or no evidence of vaccination for FPV after 12 weeks of age. About two-thirds of FPV-infected cats will present with vomiting or diarrhea (occasionally bloody), but these signs may be absent or only transiently observed and reported as part of the animal's history. Anorexia, lethargy, and dehydration are also common clinical signs; fever is a less consistent finding. Sudden death with no apparent clinical signs may result from peracute FPV infection, especially in young kittens.

Leukopenia, due to neutropenia and/or lymphopenia, is present in most affected cats, but some cats are able to maintain normal leukocyte counts or may even have leukocytosis in response to secondary bacterial infections. Anemia, hypoalbuminemia, and electrolyte imbalances often occur in these cats. Sepsis can lead to the development of disseminated intravascular coagulation.

Diagnosis

Diagnosis of FPV infection is based on history (potential exposure, poor vaccination history) and clinical signs, including characteristic hematology changes. Confirmation of the diagnosis can be made through detection of fecal parvovirus antigens using point-of-care assays that are marketed for detection of CPV-2. Fecal samples or rectal swab specimens may also be submitted for PCR analysis of viral DNA.

Treatment

The same general principles of supportive care used for managing CPV-2-infected dogs can be applied to FPV patients (see Chapter 82). Rehydration and maintenance of electrolyte and acid–base balances, and blood glucose are of primary importance. Parenteral administration of broad-spectrum antimicrobial agents is also indicated to combat sepsis due to loss of integrity of the gastrointestinal tract lining and neutropenia. Extrapolation from canine research suggests that early reintroduction of enteral nutrition as soon as vomiting is controlled may be beneficial. Cats with severe anemia or hypoproteinemia may require blood or plasma transfusions, and intravenous nutrition should be considered for these cats if enteral feeding is not possible. Ancillary treatments may include immunomodulatory therapies such as passive immunoglobulin transfer using feline serum containing anti-FPV antibodies and active immune stimulation with feline recombinant interferon-omega, although one study showed no difference in survival for cats treated with the latter agent compared to controls.

Prognosis

Without treatment, a cat with severe enteric disease and leukopenia due to FPV infection has a poor prognosis. It is not clear just how effective good nursing care is at improving the prognosis for recovery. One study noted a 51% recovery rate of ill cats with a median hospitalization time of seven days, with a poor prognosis associated with leukopenia (specifically due to neutropenia), thrombocytopenia, hypoalbuminemia, and hypokalemia. Age was not associated with outcome in this group of treated cats. However, a recent retrospective evaluation of outcome predictors and survival time for FPV-infected shelter cats determined that only about 20% of hospitalized cats survived to discharge, with a median survival time of three days. In this population of cats, animals with signs of lethargy, low body weight, rectal temperature lower than 100.2 °F, and leukopenia during hospitalization had the poorest prognosis. Predictors of survival included history of antiparasitic therapy, and treatment with amoxicillin-clavulanic acid and maropitant.

Prevention

As with any virus infection, prevention of exposure to FPV would be the ideal method for preventing infection; however, the sturdy nature of the viral particles and high potential for environmental contamination decrease the feasibility of this approach. Good sanitation practices, strict isolation procedures, and prevention of overcrowding are all important methods for preventing outbreaks of FPV in multicat situations.

Vaccination of cats with commercial modified-live or inactivated FPV vaccines is considered to be a safe and effective method of FPV prevention, but recent studies showing a high degree of interference with vaccination by maternally derived antibodies have led to a change in vaccination protocols. Kittens should be vaccinated beginning at 6–8 weeks of age, continuing every 3–4 weeks until 16–20 weeks of age. Cats older than 16 weeks should be vaccinated twice, four weeks apart. Revaccination is at one year after the primary series and then every three years. If preexisting FPV antibody titers are relatively high, revaccination may have little or no benefit.

Public Health Implications

Feline parvovirus is not infectious to humans and does not pose a public health risk.

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86

Feline Coronavirus

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Etiology/Pathophysiology

Feline coronavirus (FCoV) is a highly contagious virus that exists as two bioforms. Feline enteric coronavirus (FECV) is ubiquitous in multicat environments. This virus commonly causes an asymptomatic infection, which can persist in certain individuals. Sporadically and unpredictably, the infection turns pathogenic, in which case the virus is referred to as feline infectious peritonitis virus (FIPV), causing the highly fatal, systemic immune-mediated disease feline infectious peritonitis (FIP). The current hypothesis is that FIPV arises from the FECV by mutation, replicates in monocytes and disseminates, resulting in vasculitis and pyogranulomatous inflammation. However, our understanding of the pathophysiology of FIPV is very limited due to difficulties in replicating the virus in laboratory settings.

Epidemiology

Feline coronavirus is distributed worldwide and is ubiquitous in virtually all cat populations. There is great variability in prevalence among different cat populations. Two serotypes exist, I and II, with most epidemiologic studies indicating that serotype I is more common. However, most studies have been conducted in countries outside the United States so further study on serotype prevalence in the United States is needed.

The enteric virus, FECV, is readily transmitted via the fecal–oral route herefore, the prevalence of FCoV infection is generally associated with the number and density of cats housed together. The length of time spent in multicat environments also increases the risk of exposure. For example, the risk of exposure was estimated to be five times higher for cats living in shelters for longer than 60 days than for cats staying for shorter periods of time. Housing and husbandry practices that reduce exposure to feces and contaminated environments have a tremendous influence on the number of cats exposed to the virus. Although transmission of the pathogenic FIP virus occurs is controversial outbreaks in shelters have been reported. Therefore, quarantine of suspected FIP-infected cats is advisable.

Signalment

Although typically a disease of young cats and kittens, the age distribution of affected cats appears to be bimodal. Cats younger than 2 years of age or geriatric cats are most commonly diagnosed with FIP. In addition, certain pure breeds, most notably Persians and Burmese, appear to be more susceptible. Male and female cats are affected equally in some studies while others show a male predisposition. Immune-compromised animals, such as cats infected with feline leukemia virus (FeLV) or feline immunodeficiency virus (FIV), are also at increased risk.

History and Clinical Signs

Typically, cats from shelters, catteries, and multicat households are at higher risk of exposure and development of FIP due to the ubiquitous nature of the enteric virus in these settings. Stress due to overcrowding may also contribute to immune compromise and increased susceptibility to infection. Genetic predisposition has also been hypothesized to play a role in increased susceptibility in certain breeds.

Clinical signs associated with the benign enteric virus are typically gastrointestinal, manifesting as mild vomiting and/or persistent or intermittent diarrhea. In cases of FIP, cats may be asymptomatic or present with different levels of lethargy and anorexia. Other common findings include

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weight loss, pale mucous membranes, fever of unknown origin, and uveitis. Commonly, a distinction is made between the wet (effusive) and dry (noneffusive) forms of FIP, but they are not mutually exclusive. In the wet form, abdominal distension due to the accumulation of exudative fluid is the most common presentation. A fluid wave on physical examination may be evident, but some cases will have less fluid accumulation, only detectable by abdominal ultrasound. Pleural effusion with secondary dyspnea, tachypnea, and muffled heart sounds may be present, whereas pericardial effusion is uncommon.

Common signs of the dry form are mild and intermittent fever, decreased appetite, weight loss, stunted growth, depression, pale or yellow mucous membranes, and palpable abdominal organ enlargement. Clinical signs may also reflect dysfunction of affected organs. Pyogranulomatous lesions may develop in one or more abdominal organs. If granuloma formation involves the intestine, constipation, diarrhea, or vomiting may be the major clinical signs observed. Enlarged mesenteric lymph nodes and palpable nodular irregularities on the surface of kidneys and liver may also be present on physical examination. Uveitis is the most common ocular abnormality documented in FIP cases, but other ocular lesions such as conjunctivitis, corneal precipitates, iritis, cuffing of the retinal vasculature and retinal detachment may be present. Neurologic signs can also be seen with FIP, the most common being behavioral changes, ataxia, central vestibular signs, hyperesthesia, nystagmus, and seizures. Any part of the CNS can become affected in this disease.

Diagnosis

With the exception of histopathology and immunostaining, no single laboratory test can definitely diagnose FIP. Therefore, the diagnosis of FIP continues to be based primarily on the combination of history of risk factors, signalment, clinical abnormalities, and laboratory findings. The diagnostic process starts with a good history and comprehensive physical examination.

Complete Blood Test and Biochemical Profile

Abnormalities may include anemia, which is usually nonregenerative. Evidence of hemolysis, with or without evidence of immune-mediated destruction, may be present. Lymphopenia, neutrophilia, sometimes with a left shift and toxic change, and thrombocytopenia also occur. Hyperbilirubinemia and elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) may also occur. Hyperproteinemia (>8.0 mg/dL) due to hyperglobulinemia is a consistent finding, present in approximately 60% of cats with FIP. The hyperglobulinemia is usually polyclonal, although monoclonal gammopathy may occur. Hypoalbuminemia can be present, possibly due to hepatic insufficiency, vasculitis, protein-losing nephropathy or enteropathy, or due to decreased production associated with the acute phase reaction. A normal or elevated serum albumin:globulin ratio can help rule out FIP as it is often decreased in affected cats.

Acute Phase Proteins

Acute phase proteins are a class of proteins whose plasma concentrations increase or decrease in response to inflammatory disorders. Levels of alpha-1-acid glycoprotein, an acute phase protein, of >1.5 g/L in plasma or effusions are suggestive of FIP in cats with compatible clinical signs.

Effusion Fluid

Effusions from the abdomen or pleural space are typically clear, straw-colored, or viscous due to the high protein content. Rivalta's test can differentiate transudate from exudate (www.abcdcatsvets.org/). A test tube is filled with 7–8 mL of distilled water and one drop of acetic acid (98%) and mixed thoroughly. One drop of the effusion fluid is layered onto the surface of this solution. Diffusion of the drop indicates a negative result, and therefore most likely indicates a FIP-negative animal. If the drop floats slowly down in a drop or jellyfish-like shape or stays at the surface, the Rivalta's test is positive and the fluid may be considered an exudate. Fluid analysis is usually high protein (>3.5 g/dL) with a low nucleated cell count consisting primarily of neutrophils and macrophages, although findings may be variable. An effusion albumin:globulin ratio below 0.4 is suggestive of FIP.

Serology

Although different assays that detect antibodies directed against FCoV are commercially available, it is not possible to distinguish between exposure to FECV and FIPV infection. High antibody titer in serum does not always correlate with occurrence of FIP, and titers may be negative in cats with FIP. It has been suggested that many cats without FIP and who would never develop FIP have been needlessly euthanized due to a positive FCoV titer.

Reverse Transcriptase Polymerase Chain Reaction

Reverse transcriptase polymerase chain reaction (RT-PCR) assays can detect FCoV in a variety of samples

(feces, blood, effusion, cerebrospinal fluid [CSF], tissue, and saliva) with high sensitivity. However, as with antibody tests, distinction of FECV from FIPV is not possible at this time. The finding of virus in blood or tissue also does not confirm FIP because FECV may be amplified from these tissues in cats without FIP. A quantitative PCR test for blood, effusion, and tissue is available. The test is based on the hypothesis that replicating virus in peripheral blood and tissues suggests FIPV rather than FECV. However, because viremia also occurs with FECV infection, healthy cats may also test positive using this assay.

Histopathology and Immunostaining

Relatively distinctive inflammatory infiltrates associated with FIP are characterized by variable degrees of severity and contain a combination of macrophages, lymphocytes, and plasma cells, mixed with lesser numbers of neutrophils. The hallmark of the histopathologic lesions is a granulomatous to pyogranulomatous reaction with vascular orientation and vasculitis. Detection of intracellular FCoV antigen in macrophages in effusions by immunofluorescence, or in tissue by immunohistochemistry, can confirm the diagnosis, and is considered the gold standard if properly performed. Immunostaining may be falsely negative if virus is not present in a given sample or if antibodies do not cross-react with a particular strain.

Therapy

Supportive care and reducing stress are important. Specific treatment has been primarily focused on reducing the inflammatory and hyperimmune response to the virus. Unfortunately, increased survival has not been proven with any of these interventions. Of the immunosuppressants, prednisolone at immunosuppressive doses is currently the most consistently recommended. Although prednisolone may induce remission in some cats, treatment is not curative and may only slow the progression of the disease. Other immunosuppressive drugs such as chlorambucil have been used in combination with prednisolone but the risk:benefit ratio and efficacy are unknown. Feline interferon-omega treatment is an immunomodulatory therapy that may be considered to treat FIPV-infected cats, though studies show differences in efficacy. Similarly, a recent study showed that the immunostimulant polyprenyl extended the life of three cats with mild dry FIP, with two cats still alive after two years of the diagnosis. However, follow-up studies suggested no benefit in cats with more severe forms of the disease and its use is not recommended by some authors.

Recent studies by Pedersen *et al*. have focused on antiviral therapy. Initially, the investigators performed a study using a 3C protease inhibitor (GC376) which showed some success in treating cats with FIP. Although 19 of 20 cats recovered, disease relapse occurred and 18 months after infection only six cats remained disease free. In another study, a small molecule nucleoside analog, GS441524, was used in 10 infected cats who were successfully treated and healthy eight months after treatment, with two cats requiring a second treatment after initial relapse. This nucleoside analog works by acting as an alternative substrate for the viral RNA polymerase terminating replication. These studies are promising developments for future clinical trials and treatments.

Prognosis

With the development of FIP, prognosis is poor to grave, with a reported median survival time of 49 days. Euthanasia should be considered especially when quality of life is poor and there is no response to therapy within a short period of time. However, newer research indicates that antiviral therapy might be successful in cats with complete reversal of clinical signs (see earlier).

Prevention

The formation of antibody enhances disease, so development of an effective vaccine is difficult. At the time of writing, the available vaccine is not recommended by the American Association of Feline Practitioners. Reducing stress and overcrowding, cleaning litterboxes daily, avoiding fecal–oral contact by keeping litterboxes away from food and water dishes, and separating newly acquired cats and cats suspected of being infected are recommended husbandry practices.

Public Health Implications

Feline coronaviruses are not thought to infect humans.

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87

Feline Leukemia Virus

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Etiology/Pathophysiology

Like all retroviruses, feline leukemia virus (FeLV) is an enveloped RNA virus. It carries an enzyme (reverse transcriptase) that transcribes the viral RNA genome into DNA (the FeLV provirus), which is then integrated into the host's cell genome. Exogenous FeLV isolates are grouped into four major subcategories: FeLV-A, -B, -C, and -T. The dominant FeLV-A subgroup is horizontally transmitted and is found in all FeLV-infected cats; it is the most infectious but low in pathogenicity. FeLV-B and particularly FeLV-C are less prevalent. They arise within the individual cat after FeLV-A infection: FeLV-B develops via recombination of FeLV-A with endogenous FeLV-related sequences and FeLV-C and FeLV-T evolve from FeLV-A via mutations or insertions in the surface glycoprotein gene.

Feline leukemia virus is shed in large quantities via saliva, but it can also be found in feces, urine, and milk. FeLV is unstable in the environment and transmission is thought to require intimate friendly (or aggressive) contact between infected and uninfected cats. Contact with infectious saliva or, less probable, infectious feces may also be sufficient to transmit the infection (sharing of food bowls or litterboxes). In addition, FeLV can be transmitted vertically from the queen to her kittens.

Feline leukemia virus infection usually starts at the mucosa of the oropharynx. Subsequently, viral replication takes place in the adjacent tonsils and local lymph nodes. The virus is spread in the lymphoid tissues throughout the body via lymphocytes and monocytes. Replication in the bone marrow and infection of neutrophil and platelet precursors favor the initiation of secondary viremia and systemic infection. Cats that undergo bone marrow infection usually develop progressive infection. In cats that do not undergo bone marrow infection, only lymphocytes are provirus positive and usually no viral RNA is detectable in peripheral blood cells. In addition, some cats seem to abort infection prior to provirus integration and an antibody response may be the only sign of previous FeLV exposure.

After FeLV exposure, some, mostly young, cats develop progressive FeLV infection, characterized by persistent antigenemia/viremia. Cats with progressive infection shed high copy numbers of FeLV and pose an infection risk to other cats. Progressive infection is usually confirmed by repeated testing for antigenemia of the cat several weeks or a few months apart; only repeated positive antigen testing verifies the presence of a progressive infection, which is linked to a poorer prognosis than regressive FeLV infection. Cats with progressive FeLV infection are at high risk to die within a few months to years with FeLV-associated diseases (see Prognosis).

If a cat tests positive for FeLV p27 antigen, but upon later retesting becomes FeLV antigen negative, it has developed a regressive FeLV infection. Cats with regressive infection have mounted an effective immune response and recovered from FeLV viremia. Fortunately, most adult cats are found to develop regressive infections. Cats with regressive infection usually do not develop FeLV-associated disease. Clearance of antigenemia is observed mostly within a few (2–8) weeks, but in rare cases it can also occur after many months although the chance for recovery decreases with increasing time. Following recovery from antigenemia (regressive infection), latent infection can be identified for a few months to years by culturing bone marrow cells in the presence of corticosteroids. Provirus polymerase chain reaction (PCR) from peripheral blood or bone marrow is positive in these cats and viral plasma RNA detected by reverse transcriptase (RT)-PCR may be positive. Infection may be reactivated in latently FeLV-infected cats. The potential for reactivation seems to be associated with the FeLV isolate and generally decreases with increasing timespan.

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Epidemiology

The prevalence of FeLV infection documented in cross-sectional surveys in North America has been declining throughout the past three decades and is attributed to testing and vaccination efforts. In the United States, 3.1% of cats in a large, nationwide dataset tested positive for FeLV in 2010, with increased risk among outdoor cats, unneutered males, and cats with other disease conditions (particularly respiratory disease, oral disease, and abscessation). Prevalence was highest in the midwestern and western regions of the United States and lowest in the northeast. Seroprevalence surveys of varying statistical power have found rates of positive test results to range from 3.6% in Germany and Canada to 4.6% in Egypt and 24.5% in Thailand.

In a national (United States) study, FeLV infection was diagnosed in 9% of cats undergoing treatment for bite wounds, approximately three times the rate for cats in general. FeLV is considered to be an age-dependent disease; young kittens are at higher risk of progressive infection and more rapid disease progression, whereas adults display some degree of age resistance. However, transmission can occur at any age, and factors affecting clinical course of disease are complex and incompletely understood.

Signalment

The susceptibility of domestic cats for FeLV infection varies and is mainly age dependent. Kittens are more prone to develop progressive FeLV infection than adult cats.

History and Clinical Signs

Feline leukemia virus-related disorders are numerous and include anemia, neoplasia, immunosuppression, immune-mediated diseases, reproductive problems, enteritis, neurologic dysfunction, and stomatitis. Some FeLV-B-infected cats develop lymphoid malignancies, while FeLV-C infection is associated with the development of aplastic anemia. FeLV-T is a T cell tropic cytopathic virus that causes lymphoid depletion and immunodeficiency in infected cats.

The anemia caused by FeLV is typically nonregenerative and normochromic. Less commonly, macrocytosis or regenerative hemolytic anemia is seen in 10% of FeLV-induced anemia cases. The cause of nonregenerative anemia is usually bone marrow suppression due to viral infection of the hematopoietic stem cells and the supporting stromal cells. Platelet dysfunction, thrombocytopenia, and neutropenia are all possible sequelae.

Lymphoma is the most frequently diagnosed malignancy of cats. Tumors such as lymphoma and lymphoid leukemia develop in as many as 30% of cats with progressive FeLV infections. Regressive infections are also implicated in the occurrence of these tumors in the absence of viremia, but cats with progressive infections may face an increased risk of lymphoma development as high as 60-fold. Most American cats with mediastinal, multicentric, or spinal forms of lymphoma are FeLV positive. However, these forms of lymphoma are becoming less common as the prevalence of FeLV decreases. Diffuse gastrointestinal (GI) lymphoma (small cell; T cell origin) is now more likely to be found in FeLV-negative cats of middle or older age and can be difficult to differentiate from inflammatory bowel disease. Fibrosarcomas and quasi-neoplastic disorders such as multiple cartilaginous exostoses (osteochondromatosis) can be associated with FeLV.

Leukemia is characterized by the neoplastic proliferation of hematopoietic cells originating in the bone marrow, including neutrophils, basophils, eosinophils, monocytes, lymphocytes, megakaryocytes, and erythrocytes. Feline leukemias are strongly associated with FeLV infection and typically involve neoplastic cells circulating in the blood. Lymphoid leukemias are further classified as acute and chronic. Acute lymphocytic leukemia is characterized by lymphoblasts circulating in the blood, whereas chronic lymphocytic leukemias have an increased number of circulating lymphocytes with mature morphology.

The immunosuppression caused by FeLV creates increased susceptibility to bacterial, fungal, protozoal, and viral infections. Numbers of neutrophils and lymphocytes in the peripheral blood of affected cats may be reduced, and those cells that are present may be dysfunctional. Many FeLV-positive cats have low concentrations of complement which may contribute to FeLV-associated immunodeficiency and oncogenicity, as complement is vital for antibody-mediated tumor cell lysis.

Immune complexes formed in the presence of moderate antigen excess can cause systemic vasculitis, glomerulonephritis, polyarthritis, and a variety of other immune disorders. In FeLV-infected cats, immune complexes form under conditions in which FeLV antigens are abundant and anti-FeLV IgG antibodies are sparse, a situation ideal for the development of immune-mediated disease.

Reproductive problems are commonly associated with FeLV infection. Fetal death, resorption, and placental involution may occur in the middle trimester of pregnancy, presumably as a result of *in utero* infection of fetuses by virus transported across the placenta in maternal leukocytes. Abortion typically occurs in late gestation.

Transmission during birth and nursing constitutes the greatest risk of producing live, viremic kittens. There is some evidence that regressively infected queens may pass virus on to their kittens either *in utero* or in milk. Neonatal kittens are at risk of rapidly progressive infection with clinical manifestations of hypothermia, dehydration, failure to nurse, and early mortality, collectively termed "fading kitten syndrome." It is likely that transmission from infected queens to their kittens is the single greatest source of FeLV infections.

Although neurologic disorders associated with FeLV are most often caused by compression of the brain and spinal cord by lymphoma tumor tissue, a mechanism for neuropathology is also suspected to result in peripheral neuropathies, urinary incontinence, and ocular pathology, including anisocoria, mydriasis, Horner syndrome, and central blindness even in the absence of visible compressive lesions on diagnostic imaging. If antineoplastic therapy is planned, it is important to distinguish neoplasia from neuropathy.

Stomatitis is more classically associated with feline immunodeficiency virus (FIV) infection, but FeLV infection can also predispose cats to chronic ulcerative proliferative gingivostomatitis. Clinical sequelae include pain, anorexia, and tooth loss. An immune-mediated mechanism is likely, particularly in combination with co-infections such as feline calicivirus.

Diagnosis

The outcome of a FeLV infection can be characterized using the results from virus isolation, immunofluorescence assays, detection of FeLV p27 capsid antigen in serum or plasma, and detection of FeLV provirus or viral RNA in the blood or some tissues by molecular assays. Serologic assays for the detection of FeLV-specific antibodies are currently not routinely used. Antigenemia (presence of p27 capsid antigen) is a marker of infection and in most, but not all cats, a parameter for viremia (presence of replication-competent virus). Detection of viremia by virus isolation is not widely available, laborious, and time consuming. In contrast, antigenemia can be easily detected using enzyme-linked immunosorbent assay (ELISA) in a specialized laboratory or by rapid point-of-care tests. Most cats will test antigen positive within 3–6 weeks after FeLV exposure. The detection of FeLV provirus in the peripheral blood or certain tissues like bone marrow using RT-PCR is more sensitive than the detection of antigenemia or viremia to demonstrate previous FeLV exposure. Thus, a certain proportion of pet cats can be found to be PCR positive but antigen negative. In an early study in Switzerland, 10% of pet cats were found to be FeLV provirus positive and FeLV antigen negative. Provirus PCR testing is positive sooner (1–2 weeks) after FeLV exposure than antigen detection in blood.

Some specialized laboratories offer RT-PCR for the detection of viral RNA. The detection of viral RNA in the saliva correlates well with the detection of antigen in the blood of infected cats. However, FeLV viral RNA in saliva and blood of experimentally infected cats was found as early as one week after FeLV exposure, at least two weeks before antigen detection in the blood.

Testing Cats for FeLV Infection

- Test sick cats for the presence of FeLV antigenemia/viremia (using antigen tests, virus isolation, RT-PCR from saliva).
  - Any cat that tests FeLV positive: retest the cat after 1–2 months to determine whether progressive or regressive infection prevails. Quarantine the cat during this period since the cat is a FeLV infection source for other cats. This procedure may be repeated if circumstances permit and/or the testing interval may be discussed with the cat owner.
- Test healthy cats for the presence of FeLV antigenemia/viremia (using antigen tests, virus isolation, RT-PCR from saliva).
  - Prior to the first FeLV vaccination, testing is recommended for every cat; prior to the second vaccination (booster of basic immunization), testing is recommended if the cat may have been exposed to FeLV in the last 4–8 weeks.
  - If the cat is at high risk for FeLV (outdoor access, multicat environment, any husbandry with changing cats, etc.).
  - If the cat has moved to a new environment (new home, shelter, cattery, etc.): if the cat tests negative, quarantine (keep from other cats and any potential FeLV exposure) and retest after 4–6 weeks for absence of FeLV antigen prior to introduction into the new environment.
  - Any cat that tests FeLV positive: retest the cat after 1–2 months to determine whether progressive or regressive infection prevails. Quarantine the cat during this period since the cat is a FeLV infection source for other cats. This procedure may be repeated if circumstances permit and/or the testing interval may be discussed with the cat owner.
- Test healthy cats for the presence of FeLV provirus in the blood (PCR). Confirmatory of positive or questionable antigen tests; true antigen-positive samples are highly provirus positive.
  - Early infection: provirus PCR from blood tests earlier positive than antigen tests.

  - If prior exposure to FeLV needs to be known: analysis of the FeLV situation in a cat colony with FeLV problems.
  - If the cat is used as blood or organ donor: FeLV can be transmitted by transfusion of FeLV provirus-positive blood. Antigen testing is not sufficient.
- Test sick cats for the presence of FeLV provirus in the blood (PCR). Confirmatory of positive or questionable antigen tests; true antigen-positive samples are highly provirus positive.
  - Early infection: provirus PCR from blood tests earlier positive than antigen tests.
  - If prior exposure to FeLV needs to be known: analysis of obscure clinical cases, analysis of the FeLV situation in a cat colony with FeLV problems, etc.
- Test any cat for the presence of FeLV viral RNA in the blood (RT-PCR). Early infection: RT-PCR tests earlier positive than provirus PCR and antigen tests. Not frequently used.

Kittens can be tested any time for antigenemia – maternal antibodies do not interfere with the p27 testing. A confirmed positive result is conclusive, while a negative result is not always; in some cases the kittens became positive only after weeks to months. Each kitten should be tested individually.

Treatment

Unfortunately, no curative treatment currently exists to cure retroviral infection. *In vitro* studies have yielded promising results suggesting virus-suppressing activity of human FDA-approved drugs used to treat HIV and other myelodysplastic syndromes against FeLV virus (e.g., raltegravir, tenofovir, gemcitabine, decitabine). Further research is needed to demonstrate efficacy and safety *in vivo* and in field trials, as well as to address affordability of these drugs for most cat owners. Feline interferon-omega and human interferon-alpha have been associated with improved survival, but concerns surrounding availability, cost, and absence of strong evidence in controlled field studies have limited their widespread integration into standard treatment protocols for FeLV.

Anecdotal reports of various antiviral and immunotherapeutic agents to reverse viremia, improve clinical signs, and prolong survival are abundant. Controlled studies using naturally infected cats have either not been performed or have not confirmed anecdotal observations. Treatment efficacy must be demonstrated in controlled clinical trials, because spontaneous reversion to seronegative status or prolonged survival is not uncommon, even in the absence of medical treatment. Some FeLV-positive cats can live without major disease complications for years with routine prophylactic care, good husbandry, minimal stress, and avoidance of secondary infections. Infected cats should be kept strictly indoors to reduce the risk of exposure to infectious agents and prevent transmission of the virus to other cats. Physical examinations focusing on external parasites, skin infections, dental disease, lymph node size, and body weight should be performed semiannually, along with a routine program for parasite control and annual fecal, complete blood count, chemistry panel, and urinalysis testing. All infected cats should be neutered. Owners should be advised to watch for signs of FeLV-related disease, particularly secondary infections.

Although FeLV-positive cats often respond well to treatment for secondary infections, therapy for such infections or other illnesses should be early and aggressive because of immunocompromise. Because FeLV is historically associated with rapid and grave disease, the modern prognosis varies considerably depending on husbandry, veterinary care, and individual immune system variation.

Prognosis

Large-scale studies have demonstrated an average survival of 2.4 years after diagnosis among positive cats (versus six years after testing for negative control cats), with 50% mortality in two years and 80% mortality by three years after diagnosis. Progression of disease is much more rapid in kittens, whereas some adult cats remain healthy for many years and may succumb to conditions unrelated to their retroviral status.

Prevention and Control

Feline leukemia virus is unstable in the environment and is susceptible to all common detergents and disinfectants. In a hospital or boarding setting, infected cats may be kept in the general population as long as they are housed in separate cages. Medical and surgical equipment contaminated with body fluids, even when dried, can be fomites for infection. Thorough cleaning and sterilization of equipment, strict attention to washing contaminated hands, and avoiding reuse and sharing of single-use and consumable supplies between patients are critical practices to prevent iatrogenic transmission.

Feline leukemia virus vaccines are noncore and are intended to protect cats against FeLV infection or reduce the likelihood of persistent viremia. Types of vaccines include killed whole virus, subunit, and genetically

engineered. Vaccines are indicated only for uninfected cats, because there is no benefit in vaccinating an FeLV-positive cat. Vaccination is the most effective way to prevent FeLV-associated disease. Currently, FeLV vaccines are very safe and have up to 98% efficacy. The American Association of Feline Practitioners (AAFP) Feline Retrovirus Management Guidelines include the recommendation that all kittens should receive the two-dose FeLV vaccination as a component of the routine initial vaccination series and should also receive a booster vaccination one year later. This is prudent, because rehoming and lifestyle changes such as outdoor access frequently occur as cats mature. Annual revaccination after maturity would depend on the cat's risk of FeLV exposure. The adult cat's risk of exposure to FeLV-positive cats should be assessed, and vaccines used only for those cats at risk. FeLV vaccines have been associated with development of sarcomas at the vaccination site, although the risk of tumor development is very low. Uninfected cats in a household with infected cats should be vaccinated; however, vaccination is not universally protective, and other means of reducing transmission to uninfected cats, such as physical separation, should also be used.

While testing of cats in an animal shelter environment is considered optional for individual housing, FeLV status should be determined before placement in group housing and is recommended at the time of adoption or foster home placement. Because tests are not 100% accurate, shelter cats placed in group housing should be vaccinated against FeLV, especially in long-term conditions such as sanctuaries. Because of the equivalent prevalence of FeLV among feral and free-roaming pet cats and the role of neutering in decreasing the spread of infection, expending resources on FeLV testing is not considered a mandatory component of community trap-neuter-return programs.

Public Health Implications

Some strains of FeLV can be experimentally grown in human tissue cultures, leading to concerns of potential for transmission to people. Studies addressing this concern have shown no evidence that any zoonotic risk exists, and there are no known cases of zoonotic transmission.

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88

Feline Immunodeficiency Virus

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Etiology/Pathophysiology

Feline immunodeficiency virus (FIV) is a member of the *Lentivirus* genus in the *Retroviridae* virus family. As such, it is an enveloped virus, has an icosahedral capsid, and a genome composed of two (nearly identical) linear, positive sense, single-stranded RNA molecules.

Much has been learned about FIV since it was first described in 1987, particularly in regard to its application as a model to study the closely related lentivirus human immunodeficiency virus (HIV). In particular, FIV and HIV share remarkable structure and sequence organization, utilize parallel modes of receptor-mediated entry, and result in a similar spectrum of immunodeficiency-related diseases due to analogous modes of immune dysfunction.

The disease course for FIV is variable, likely dependent upon the route of infection, strain of virus, age of the animal at time of infection, and the robustness of the immune response generated to the virus. Transmission is primarily through the bite of an infected cat, though sexual transmission has been shown to occur in experimentally infected cats. Infection by blood transfusion may also potentially occur. Initially, FIV is transported by tissue macrophages to lymphoid tissues, where it replicates in lymph nodes, thymus, spleen, bone marrow, brain, lung, gastrointestinal tract, and kidney. FIV gains entrance into the cell primarily through receptor mediation. The main cellular receptors for FIV are the chemokine receptor, CXCR4, and CD134, a receptor expressed by T lymphocytes and activated macrophages. Other mechanisms of virus entry may also be important, such as the use of other receptors and antibody-mediated entry through FC receptors.

Experimentally, virus is detected in the blood of animals usually by two weeks post infection, and remains easily detectable for up to six weeks post infection. Generally, FIV induces a strong but only partially effective immune response. However, there are reports of detectable levels of FIV DNA in cats without a detectable antibody response. Generally, antibodies to FIV are detected by two weeks post infection, and most cats develop antibody by 60 days post infection, although it may be delayed further in some cats. Over the next few weeks after antibody development, the virus levels in the blood are gradually reduced to undetectable quantities and become clinically latent. However, the virus is not truly latent, as it continues to replicate at low levels. During this clinical latent phase, the virus infection gradually is eroding normal immune function of the infected cat. FIV causes the T helper cell numbers to decrease with an inversion of the CD4:CD8 ratio. The effect of FIV on feline lymphocyte numbers is likely due to several mechanisms operating simultaneously: virus-induced lysis of infected cells, virus suppression of the ability of bone marrow and other lymphoid tissues to produce new lymphocytes, immune-mediated lysis of infected cells, and apoptosis. The ability of lymphocytes from FIV-infected cats to proliferate in response to both B and T cell mitogens is impaired, as is the expression of lymphocyte cell surface receptors that are important in control and proliferation of the immune response, such as cytokine receptors and MHC class II antigens.

The pathophysiology of FIV neurologic dysfunction is not completely understood as it occurs in the apparent absence of virus replication in neurons, with minimal inflammatory lesions in infected cat brains, and only low levels of replication in astrocyte and microglia cells. Infected astrocytes have impaired glutamate uptake function, which may lead to an increased susceptibility of glutamate toxicity, oxidative stress, and ultimately neuron loss. Additionally, FIV envelope protein is toxic

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to rat neurons in culture and may play a role in neurologic disease pathogenesis. The neurologic disease is more prevalent with certain isolates of the virus, which may point to certain envelope protein sequences being more toxic and/or relate to the ability of virus to replicate in the feline nervous system.

Epidemiology

Feline immunodeficiency virus infection is common around the world. The incidence of FIV varies (from 4% to 47%) geographically, correlating with the percentage of free-roaming and feral cats in the population.

Signalment

Although it is possible for any cat to be infected with FIV, free-roaming, nonpure-bred, sexually intact, mature, male cats are more likely to contract an FIV infection. This is largely due to cat bites being the primary mode of virus transmission.

History and Clinical Signs

Acute clinical signs of the infection are generally mild and often consist of the nonspecific signs of lethargy, anorexia, pyrexia, diarrhea, and lymphadenopathy. Generally, these clinical signs coincide with the viremia. Once the viremia subsides, the virus appears to go into a clinical latent phase, with virus not detected in the blood and the apparent absence of most clinical signs. This clinical latent phase is of variable length but often lasts for years, as the virus slowly suppresses the immune system. The last phase of the infection is feline acquired immune deficiency syndrome (FAIDS). Clinical signs of FAIDS are the result of opportunistic infections, various neoplasias, and/or neurologic disease. Thus, clinical signs are variable depending upon how the immune suppression is manifested. Stomatitis is very common and can occur during any phase of the infection. Persistent diarrhea is also fairly common, as is respiratory disease. Neoplasia is common in FAIDS, with B cell lymphoma being the most frequent. Neurologic signs such as behavioral changes, disrupted sleep, impaired learning, paresis, and seizures have been reported. A wasting condition has also been described late in the FAIDS phase of the disease. Increased circulating immune complexes can result in immune complex disease manifested as uveitis and glomerulonephritis.

Diagnosis

Complete blood count (CBC) abnormalities may include anemia, lymphopenia, and neutropenia. Thrombocytopenia may sometimes occur. Hyperglobulinemia is the most common biochemical abnormality. Proteinuria may be seen in cats with glomerulonephritis.

Antibodies to FIV infection persist for life and thus patient-side ELISA antibody testing is recommended as a screen for FIV infection. However, false-positive and -negative results may occur. If a kitten under 6 months of age is antibody positive, it should be retested after 60 days, as maternal antibody could be the cause of the positive assay. If an animal is negative after a recent possible exposure, it should be retested after 60 days, allowing sufficient time for an active immune response to develop. Tests used to detect antibody cannot distinguish between infection and vaccination. Positive tests in healthy cats should be confirmed using ELISA from another manufacturer, western blotting, or PCR. In cases where the vaccination history is not known, real-time quantitative PCR should be considered, as this assay can detect a low-grade viremia, indicative of an active infection. However, sensitivity and specificity of PCR are variable. PCR may be negative due to low levels of viremia or mutations, and false-positive results have been reported in vaccinated cats.

Management

The best therapy for FIV is prevention. Keeping cats indoors and only allowing exposure to known FIV-negative cats is the best way to prevent the infection. The vaccine for FIV is controversial, as efficacy is variable. Additionally, using standard FIV screening assays, a vaccinated cat currently cannot be distinguished from an infected cat. Since shelters may not perform a confirmatory assay on an animal that is found FIV positive by a screening assay, it is advised to microchip the cat at the time of vaccination with a chip whose data are linked to vaccination status to assist shelter personnel in the interpretation of a positive result.

The use of the routine feline vaccines in FIV-positive cats is controversial due to the suppressed immune system of the FIV-infected cat. Since it is best to keep infected cats indoors to reduce the risk of FIV exposure to other cats, the exposure of the infected cat to other common pathogens is also reduced, thereby decreasing the need for vaccination. Additionally, the duration of immunity to most of the vaccinatable feline pathogens likely lasts for years. If the cat has been vaccinated earlier in life, protective immunity likely still remains. If, however, vaccines are to be used,

killed vaccines are preferred. Even if they are kept indoors, housing cats in overcrowded conditions has been significantly associated with disease progression in FIV-positive cats. Therefore, reducing stress and limiting exposure to potential infectious agents are important husbandry practices that can decrease morbidity and mortality.

For cases of prolonged severe stomatitis, removal of all the teeth is the treatment of choice. Zidovudine (AZT) at a dose of 5–10 mg/kg PO or SC q12h has also been shown to be effective in some cases of stomatitis. AZT is also used, to some effect, in cases with neurologic signs of disease. AZT can cause bone marrow suppression. CBCs should be monitored closely. AZT should not be used in cats with myelosuppression. Alfaferone (natural human alpha-interferon) has been reported to increase the survival of FIV-infected cats. Recombinant feline IFN-omega may improve clinical signs and reduce inflammatory cytokine production but does not appear to affect viral load. A recent publication demonstrated that an analog of tenofovir, a widely prescribed anti-HIV drug in human medicine, may also be effective as a therapy for FIV, though further investigation is needed. Griseofulvin treatment of fungal disease should be avoided as bone marrow suppression has been reported in FIV-infected cats.

Prognosis

Though the virus can never be cleared from an infected cat, most infected cats have long life spans. While many die from conditions that are unrelated to the infection, many ultimately succumb to an FIV-related disease.

Public Health Implications

Feline immunodeficiency virus infection of humans has never been documented, even in veterinarians or individuals who have been bitten multiple times by FIV-infected cats. However, FIV has been shown to replicate in human cells *in vitro* and cause disease in monkeys experimentally infected with FIV-infected autologous cells. Thus, caution is still advised.

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89

Feline Viral Upper Respiratory Tract Disease

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Etiology/Pathophysiology

Feline viral infectious upper respiratory tract disease is primarily caused by two viruses: feline herpesvirus (FHV-1) and feline calicivirus (FCV). Infection is common in multicat environments, and most cats have been exposed. FHV-1 is an enveloped single-stranded DNA virus belonging to the alpha-herpesvirus family. As such, the virus exists in a latent form in the trigeminal ganglia after initial infection and can be reactivated by stressors. This leads to shedding via secretions from oral, nasal, and conjunctival membranes. Viral replication is usually restricted to the upper respiratory tract, due to viral preference for lower temperatures. However, in young kittens and possibly immunosuppressed cats, more severe systemic disease can occur.

Feline calicivirus belongs to the Caliciviridae family, and consists of a single-stranded positive RNA genome. This genome structure has a high mutation rate and therefore the isolates are highly variable. Strains can vary in their pathogenicity. Like FHV-1, transmission occurs via secretions from oral, nasal, and conjunctival membranes. FCV persists in tonsillar and other oropharyngeal tissues, leading to a carrier state, but the mechanism of persistence is not well understood. In addition to causing upper respiratory disease, FCV can be associated with lameness due to acute synovitis, possibly due to antigen-activated macrophages residing in the synovial membrane. Rarely, FCV can cause virulent systemic disease (VSD). Lesions associated with VSD are severe and include oral and dermal ulcerations, bronchointerstitial pneumonia, necrosis of the liver, spleen and pancreas, and death. The pathogenesis of VSD is not fully understood.

Epidemiology

Infection with both FHV-1 and FCV is widespread in the general cat population. The prevalence of infection and clinical disease is higher in multicat households, colonies, catteries or shelters. Viral reactivation may occur in latently infected cats when they are stressed or if their immune system is compromised. FHV-1 is short-lived in the environment, and transmission occurs mainly by direct contact with an infected cat. However, transmission through fomites in crowded environments is also important.

Cats infected with FCV may be carriers who shed virus while appearing clinically healthy. Virus may be shed in the urine and feces in addition to respiratory secretions. FCV survives in the environment much longer than FHV-1 and is resistant to quaternary ammonium compounds. Therefore, in addition to direct and aerosol contact with respiratory secretions, fomites are a very important means of transmission for FCV.

Signalment

Cats of any sex and age can develop respiratory disease caused by FHV-1 or FCV, with kittens being more susceptible.

History and Clinical Signs

Cats from multicat households, colonies, catteries or shelters are commonly infected. A history of stress or immune suppression may be noted. FHV-1 may cause severe respiratory disease, especially in

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immune-compromised animals. Nonspecific signs of FHV-1 infection may include depression, anorexia, and pyrexia. Respiratory signs include sneezing and conjunctivitis associated with serous ocular and nasal discharge. Nasal turbinate destruction can lead to recurrent rhinitis and sinusitis. Coughing and dyspnea can develop in more severe cases. Ocular and nasal discharge that becomes mucoid or purulent may signal secondary bacterial infection. In addition to conjunctivitis, keratitis and corneal ulcerations also occur with FHV-1 infection. Dendritic corneal ulcerations are considered pathognomonic for infection with FHV-1. FHV-1 might also play a role in other forms of ocular disease. Skin ulceration and herpetic dermatitis may also be caused by FHV-1.

Feline calicivirus causes a range of clinical signs due to strain variability. Similar to FHV-1, upper respiratory signs predominate. Sneezing and ocular discharge associated with conjunctivitis are common. In contrast to FHV-1 infection, corneal ulceration does not typically occur with FCV infection. However, oral ulceration is common, making FCV a top differential diagnosis for oral ulcerations in cats. Stomatitis may be severe, and lead to excessive ptyalism. Other signs of FCV infection include depression, pyrexia, anorexia, enlarged lymph nodes, and acute lameness. Infection with highly virulent strains of FCV causing VSD results in severe signs such as high fever, cutaneous edema, jaundice, other signs of multiorgan failure, and death.

Diagnosis

History, clinical signs, and evidence of possible immunosuppression (due to retroviral infection, stress or drug administration, for example) should increase the index of suspicion for infection with one or both viruses. For cats with signs of upper respiratory disease, diagnosis is usually made based on clinical signs alone. Specific laboratory tests documenting infection or exposure may be used to help confirm infection, particularly in patients with more severe or atypical clinical signs, although each has limitations. Complete blood count (CBC) and serum chemistry findings are not specific in cats with upper respiratory disease caused by FHV-1 or FCV, although cats with stomatitis caused by FCV may be hyperglobulinemic. Cats with VSD may have anemia, thrombocytopenia, neutrophilia, and lymphopenia. Hypoalbuminemia, elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST), elevated bilirubin, and increased creatine kinase (CK) also occur.

Direct testing for the presence of virus may include culture, polymerase chain reaction (PCR), histopathologic examination, and immunofluorescence staining. False-negative results may occur with any of these assays as virus may not be present in specimens. Laboratories should be contacted for appropriate sample acquisition and transport techniques for culture. The sensitivity and specificity of PCR may vary depending on the laboratory and design of the test. It should also be kept in mind that PCR may not detect all strains, particularly for calicivirus, due to variability in nucleic acid target sequences. Positive PCR results may occur in healthy cats, so a positive result does not necessarily mean that clinical signs may be attributed to infection. In addition, vaccination with attenuated virus may cause false-positive PCR results. Serologic testing is also available, but it is not easily interpreted as vaccination and previous exposure are common for both viruses and the presence of antibody may not indicate active infection.

Therapy

In cases of acute respiratory disease, supportive care including fluid therapy and/or nutritional support may be indicated. Clinical signs resolve within 2–3 weeks. Judicious administration of appropriate antibiotics is indicated if evidence of secondary bacterial infection or co-infection with *Chlamydia*, *Mycoplasma* or *Bordetella* is present. For more severe or recurrent disease, or if keratoconjunctivitis or stomatitis is present, more aggressive specific therapy may be indicated, including antiviral or immunomodulating agents, and for stomatitis, dental extractions, antimicrobial treatment, and antiseptic mouthwashes.

Most antiviral therapies developed for human herpesviruses are too toxic for oral administration in cats, although the use of famciclovir appears promising. Topical use of idoxuridine, vidarabine, and other select nucleoside analogs appears beneficial for treatment for ocular disease. The therapeutic potential of feline interferon-omega on FHV-1 replication is under investigation. The use of oral L-lysine to decrease clinical signs or infection with FHV-1 infection has shown conflicting results.

Prognosis

In general, cats will recover but both viruses persist, with reactivation of FHV-1 occurring due to stressors. FCV carriers can shed virus continuously, increasing the likelihood of infecting other cats. FCV infection with strains associated with VSD has been associated with greater than 50% mortality.

Prevention

Vaccination information and guidelines are available for free online from the American Association of Feline Practitioners (https://catvets.com/guidelines/practice-guidelines/feline-vaccination). Vaccination, stress reduction, avoiding overcrowding and implementing strict disease prevention techniques in shelters and kennels are important to prevent infection and associated clinical signs (see Chapter 117).

Public Health Significance

These viruses are not known to infect people.

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90

Rabies in Dogs and Cats

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Etiology and Pathophysiology

The rabies virus is an enveloped, single-stranded RNA virus in the family Rhabdoviridae and the genus *Lyssavirus*. There are 16 known lyssaviruses worldwide capable of causing rabies-like symptoms in mammals. Bats are the reservoir for most of them. Rabies virus itself is by far the most prevalent lyssavirus, and the only one known to exist in the Americas. Rabies has the highest mortality rate of all known infectious diseases.

Rabies is usually transmitted by the bite of a rabid animal. It may also be transmitted when virus-laden saliva is introduced into mucous membranes. Theoretically, scratches may transmit the virus, if the claws are contaminated with fresh infectious saliva, but this mode of spread is very rare in people. Because the virus may be present in tissues throughout a rabid animal, exposure may occur during necropsy. Rabies has occasionally been spread by corneal and internal organ transplantation, transplacentally, through aerosolization in closed spaces such as caves, and by ingestion of infected tissues. Because it is readily destroyed by UV light, desiccation, and most disinfectants, the rabies virus is not effectively transmitted by fomites.

When the rabies virus first enters the body, it multiplies at a very low rate in a small amount of muscle cells and fibrocytes, and curtails the local immune reaction by inhibiting type I interferons. The majority of the incubation period, which can last for 3–12 weeks or more in dogs and cats, likely passes with the virus localized at the site of entry. The virus then enters the nervous system through a peripheral motor nerve, and is drawn up the axon at a rate of about 100 mm per day. Once the virus reaches the neuronal cell body, it multiplies and disseminates rapidly, although unevenly, throughout the central nervous system (CNS). Histologic analysis of brains from rabies victims typically reveals little tissue damage. When increased inflammation and damage do occur in the CNS, they are usually found in patients in which paralytic clinical signs predominated. The total amount of virus in the brain tends to be significantly higher in cases of encephalitic, "furious" rabies than in cases of paralytic, "dumb" rabies.

Some details of what happens at the molecular level of rabies pathogenesis remain a mystery. The rabies virus has an uncanny ability to evade early recognition and clearance by the immune system, and to preserve the health of cells of the nervous system throughout most of the infection. In laboratory studies, rabies virus strains that stimulate a significant immune response are less pathogenic than those that suppress it.

Epidemiology

Over 60 000 people die worldwide from rabies each year. The vast majority of rabies victims are children who were infected by bites from rabid dogs. Most cases occur in countries where rabies vaccination rates for dogs are below 50%, primarily in Asia and Africa.

The human death toll from rabies is much lower in countries where animal control policies are well established and vaccination of pets is widespread. Over the past two decades in the United States, an average of three people per year died from rabies. Typically, the cases occurred after a person failed to obtain timely rabies postexposure prophylaxis, often due to lack of awareness about the risk of rabies. About 70% of the cases were caused by bat bites, and most others were caused by a dog bite inflicted while the person was visiting another country.

The primary reservoirs for rabies are bats, domestic dogs, raccoons, skunks, foxes, mongooses, and jackals. In the past decade, 6000–7000 rabid animals per year

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were detected in the US. Over 90% were wild animals, with raccoons, bats, and skunks constituting over 80% of the total. Rabid foxes add another 5%. The island of Puerto Rico has consistently reported about 30–40 rabid mongooses each year.

Rabid cats (4% of rabid animals) have outnumbered rabid dogs (1%) for many years, most likely because of better vaccination coverage in dogs. In North America, rabies cases are more frequent in spring and summer. The number of rabid animals reported typically reflects only those confirmed by laboratory testing; it is thought that the number of undiagnosed rabies cases in wild animals is far higher.

There are multiple rabies virus substrains (aka variants), that are uniquely adapted to their reservoir hosts. Rabies variants tend to be found in identifiable geographic locations. This phenomenon is very useful for investigating the source of individual rabies cases. As an example, if a stray dog in the US was found to be rabid, analysis of the variant could reveal the source of the infection. Finding a North American bat, skunk, or raccoon variant in the dog would reveal that it caught the virus from indigenous wildlife. Finding a Thai dog variant would suggest the dog had recently been imported from Thailand, or had been bitten by a rabid dog from Thailand.

In the Americas, insectivorous bat rabies variants are widely distributed. Vampire bat variants are found in certain areas in South America, Central America, and southern Mexico. The canine rabies virus variant has been eradicated from the US but is still present in parts of Central and South America. So far, no feline variant has been reported. The pathogenicity and virulence of the variant, the behavior of the reservoir species (natural behavior and behavior when rabid), and the degree of overlap in habitat between the reservoir species and other mammals all affect the risk of rabies transmission to pets and people.

The risk of rabies exposure for domestic animals is higher in areas where variants associated with terrestrial animals (i.e., not just insectivorous bat variants) are prevalent. The risk is highest where the canine variant is enzootic (example: India), and much lower in areas where only insectivorous bat rabies variants are found (example: southern California). Many islands in the world, such as Hawaii, are considered completely rabies free.

The raccoon variant is found throughout the eastern quarter of the US and in parts of eastern Canada. Multiple variants of skunk rabies are found in large areas in the center of North America, California, and parts of Mexico. Fox variants have been found in Alaska, Arizona, New Mexico, and Texas in the US, and in Ontario, Canada. One variant found periodically in southern Texas and northern Mexico appears to be adapted to both dogs and coyotes.

Humans have spread rabies variants in the US by moving infected animals. Before the late 1970s, the raccoon variant had been limited to the southeastern area of the US. It was translocated to the mid-Atlantic states by people shipping raccoons from south to north for hunting purposes. The canine variant of rabies, which was considered officially eliminated from the US in 2007, could be reimported at any time from countries where canine rabies is still enzootic. Rabid dogs have been imported into the US many times but fortunately were quickly detected, isolated, and euthanized. If imported rabid dogs were released into populations of unvaccinated dogs, such as into a city with a significant stray dog population, canine rabies could become reestablished in the US.

Mice, rats, and rabbits can be experimentally infected with rabies, but rabies is very rare in them in nature. Rabies has been detected in larger rodents in the US, such as woodchucks, groundhogs, and beavers, usually in areas where the raccoon variant is enzootic. It has also been rarely seen in rabbits attacked by raccoons.

Opossums are partially resistant to experimental rabies infection. So far, no marsupial has been found to be a rabies reservoir. Nonetheless, opossums can become infected. In California (where skunk and bat rabies variants are enzootic), 11 rabid opossums were detected between 1983 and 2012 (data from Dr Curtis Fritz, California Department of Public Health). The omnivorous nature of opossums would make it natural for them to investigate a dying, rabid animal, and to potentially be bitten.

Practitioners should have full understanding of the rabies variants that are common in their area. However, since rabies may be imported, a thorough travel history for all patients should also be taken, with special focus on the previous six months. The Centers for Disease Control and Prevention (CDC) maintains an online list of nations that present a higher risk for importation of rabies in animals.

Signalment

Any breed of dog or cat may present with rabies. Rabies is highly unlikely in animals less than 4 weeks of age.

History

Taking a thorough history is vital for clinical diagnosis. The risk of rabies depends on the geographic area where the pet lives or has spent time, especially in the previous six months. Knowledge of the clinical course of illness before presentation is also essential for diagnosis.

A history that *increases* the likelihood of rabies may include the following.

- *Travel*. Pet imported within the last six months from a country where canine rabies is enzootic (includes many countries in Africa, Asia, and Central and South America). Imported strays or street animals present especially high risk. See the Public Health Implications section below for more information.
- *Unvaccinated*. No rabies vaccination in pet's history. Dogs and cats that were vaccinated only once or twice against rabies may not be fully protected. Repeated vaccination (>2 times) significantly reduces the risk of rabies.
- *Exposure to wild animal or suspected rabid pet*. History of interaction with a wild animal (especially a known rabid animal or rabies reservoir species) 10 days to six months before presentation. Bite from the wild animal will likely be healed by the time rabies signs begin. Bites inflicted in thick fur or in the oral cavity, or bites from bats, may have gone unrecognized.
- *Onset of clinical signs is gradual and steady*. Once clinical signs begin, they worsen over days or hours. Animals are *unlikely* to be rabid if they have a peracute onset of neurologic signs, stabilization or improvement, or have survived through more than 10 days of overt illness.

Clinical Signs

Rabies is rarely recognized on physical exam alone. The initial clinical signs mimic other diseases and may not seem neurologic. The most consistent finding is a steadily worsening clinical course over hours or days, with an accumulation of signs that eventually reveal their neurologic origins. The pet will not respond to therapy, and will usually die within 10 days. Close monitoring, with the patient kept in isolation, is the most important premortem clinical tool.

The incubation length is highly variable. Most dogs and cats develop clinical signs within six months after exposure, but some may become ill in as few as 10 days. The most common incubation period is 3–12 weeks.

In general, the clinical signs of rabies may be divided into a prodromal phase, followed by a furious (excitatory or encephalitic) phase, then a dumb (paralytic) phase, then death. However, the clinical course can vary considerably. Phases may be absent or overlap. The majority of cases are associated with a prominent furious phase, followed by a short paralytic phase before respiratory arrest and death. Approximately 20% of cases lack a furious phase (i.e., dumb or paralytic rabies).

Clinical signs in the prodromal phase are nonspecific. Dogs and cats may have fever, lethargy, dehydration, anorexia, vomiting or diarrhea. The animal may withdraw and hide, or may appear to become more sociable than usual. They may lick or chew at the site of the original bite wound. Activation of the autonomic nervous system may lead to piloerection, drooling, and dilated pupils.

Furious (excitatory) phase clinical signs may include the following.

- *Restlessness*. When confined, animals may pace or constantly readjust their body posture. When crouching, they may continuously shift the front paws. Unconfined animals may walk or run for miles.
- *Hyperreactivity* to sounds, movements, and touch.
- *Bizarre behavior*. The animal may bite or strike at unseen things, or stare at things in an unsettling manner. Dogs may lick their own urine or eat unusual objects (pica), and may present with gastrointestinal foreign bodies.
- *Vocalization*. Dogs or cats may repeatedly howl, with a noticeable change in voice because of alterations in laryngeal function. Cats may make aggressive screeching sounds, especially in response to stimuli.
- *Aggression*. Bites from rabid dogs usually occur without warning or behavioral cues (i.e., without snarling, growling or posturing). Cats may combine striking and biting. Confined rabid animals may repeatedly bite and gnaw at cage doors and walls. Rabies has sometimes been associated with spectacular levels of aggression, with the rabid animal repeatedly attacking even while receiving grave injuries from the bite victim. Bites are often firmly inflicted, with the rabid animal latching onto the object or individual.
- *Grand mal seizures*.
- *Fine muscle tremors*, especially in cats.

Dumb (paralytic) phase clinical signs may include the following.

- *Persistent lethargy*.
- *Cranial nerve deficits*. Pharyngeal paresis may cause a change in voice and dysphagia, leading to accumulation of saliva in the mouth and drooling. The animal may repeatedly lap at water in unsuccessful attempts to drink. Dogs often develop a dropped jaw and hanging tongue, and may gag and cough, causing them to appear to be choking on an object.
- *Ataxia*.
- A *stiff or hunched gait*.
- *Paresis*, usually beginning in the body part where the original bite was inflicted. May be unilateral at first, and the animal may present with an apparent limp. Progresses as an ascending flaccid paralysis.

Rabid animals may exhibit a combination of excitatory and paralytic signs, in which disorientation and anxiety may be coupled with restlessness and weakness. Some animals die acutely. Most rabid animals eventually progress to generalized paralysis, respiratory arrest, and death.

Diagnosis

There is no validated test available for diagnosing rabies in a clinically ill, living animal. The direct fluorescent antibody (DFA) test is the gold standard for diagnosing rabies, and is performed on brain tissue. This test is almost always performed by a public health laboratory, and is the test that must be used when human rabies exposure is possible. For most species, the DFA test requires submission of the head or whole brain. When decapitation or debraining is required, only trained, rabies-vaccinated staff should perform the procedure. Keep the specimen fresh and refrigerated; *fixation with formalin renders it untestable by DFA*. Freezing the sample will delay testing and complicate performance of the test. For bats, the entire body may often be submitted. The laboratory should be contacted in advance for requirements on specimen preparation, shipping, and submission.

Serology is not useful in the diagnosis of clinical rabies in animals. Patients previously vaccinated against rabies before the illness may have positive titers. Young, unvaccinated animals may have measurable maternal antibodies against rabies, clouding interpretation.

Fixed brain tissue may be examined for rabies through immunohistochemistry (IHC) by certain laboratories. Histopathology may reveal Negri bodies in rabies-infected neurons, but they are not consistently present.

Polymerase chain reaction (PCR) testing is used as an antemortem test for rabies in people. The test is usually performed on saliva and on skin from the back of the neck of the human patient. The sensitivity of PCR testing on tissue outside the CNS is too low to be used to make decisions in managing a potential rabid animal, and is not routinely used in animals because of the risk to public safety. PCR testing may be used to supplement DFA testing on brain matter.

A direct, rapid immunohistochemical test (DRIT) is used during surveys of rabies in wildlife.

There is no test available for evaluating healthy animals for exposure to rabies, primarily because the virus usually remains localized and undetected by the immune system during much of the incubation period.

Therapy

If an animal is rabid, all clinical interventions will fail and the animal will die. No antivirals have been shown to be effective against rabies. Secure isolation and observation, or euthanasia, of the suspect rabid animal is the primary clinical intervention.

Prognosis

Grave – rabies is fatal.

Prevention

A robust immune response is the only effective defense against rabies. Standard rabies vaccination, when administered through proper protocols, affords protection against all variants. Vaccine failure does occur, but is very rare.

Numerous vaccines are licensed for use in the US. Vaccines are either inactivated (killed) or recombinant, in which a live canarypox virus expresses rabies proteins. Most rabies vaccines are first administered at age 3 months, boostered a year later, and then every one or three years thereafter. The vaccine label should be reviewed carefully for the exact protocol required. Adult dogs or cats being vaccinated for the first time should have a booster a year later. An animal is considered immunized about four weeks after its first rabies vaccination, or immediately after a booster.

Indoor-only cats should be vaccinated against rabies. Insectivorous bats, an important rabies reservoir in North America, are sometimes found inside buildings. In Los Angeles County (where the authors work), at least one rabid bat is identified indoors every year.

The risk of injection-site fibrosarcoma exists when vaccinating cats. Recombinant vaccinations appear to be associated with a lower risk than killed vaccines.

All states require rabies vaccination for dogs, and several require vaccination of cats. Individual cities or counties may require vaccination of cats even when their state does not require it. Some states allow exemption from rabies vaccination in cases where it may present a severe risk to the health of the animal. The criteria for granting exemption, and the protocol for obtaining one, vary by state and locality. Note that rabies serologic testing is *not* accepted in lieu of vaccination in most areas of the US.

Vaccination is not the only way to reduce the risk of rabies exposure. Encourage clients to keep dogs leashed when off property, and to keep cats indoors. Clients can reduce the attractions for wildlife on their property by keeping all pet food (and other consumables) and water indoors, by bat-proofing their home, and by keeping crawl spaces and the underside of decks sealed off.

Clients who rescue stray, feral or wild animals, and especially those who may participate in international rescue efforts, may face a higher risk of rabies exposure.

They should be given detailed information about rabies, and be encouraged to budget for thorough veterinary examination as part of the processing of each animal. Rescue groups that import animals should be educated about associated legal requirements (see later).

Public Health Implications

Veterinarians routinely face rabies-related circumstances in which they are called upon to protect not only their patient but also people and other animals. National guidelines on rabies control are routinely published by the National Association of State Public Health Veterinarians (http://nasphv.org/documentsCompendia.html). Local animal control and public health agencies usually play the most prominent role in rabies control. Contact your local agencies in advance for information on rabies-relating reporting, testing, and other protocols. Ask for the phone number to call in case of an emergency. Place the information in an easy-to-find location and review it with clinic staff.

Four rabies-related circumstances occur routinely in small animal practice.

- *Dog or cat bit a person*. Legally reportable. Rabid dogs and cats can potentially shed rabies virus in their saliva for a few days before clinical signs of rabies begin. Quarantine and/or testing are typically required regardless of the rabies vaccination status of the animal. The quarantine protocol may vary depending on the severity of the bite and the requirements of the jurisdiction. If the dog or cat remains healthy for 10 days or longer, the risk of rabies for the bite victim is negligible. If the animal dies or is euthanized during this 10-day period, it should be tested for rabies. The pet should not be vaccinated for rabies during this 10-day quarantine.
- *Dog or cat vs wild mammal*. Legally reportable in many areas. (Note that certain wild mammal species may be exempt – for example, in California, bites from wild rabbits and small rodents are not reportable.) Bite wounds from the wild animal exposure may or may not be obvious. Pets found unattended near a wild mammal may have wounds hidden in the fur or mouth. Bite wounds from bats are especially hard to see, even on human skin. Pets with unexplained bite wounds may also have been exposed to a rabid animal. Ask the pet owner about the location of the biting wild mammal. If it is deceased, its body should be retrieved for testing – *a negative rabies test on the wild mammal eliminates concerns about rabies*. If the wild mammal is not available for testing, or tests positive for the virus, the pet is considered exposed to rabies. Regardless, the bite wound should be thoroughly cleaned to remove virus particles. The next steps depend on the pet's rabies vaccination status.
  - **Pet's rabies vaccination was current before incident**. Revaccinate the pet immediately. The owner should be advised that there is a risk of the pet becoming rabid. The postexposure quarantine and observation period in this case is usually 30–45 days, depending on the jurisdiction. The quarantine may potentially be performed at the pet owner's home or may require a more secure setting, depending on the risk of rabies and local requirements.
  - **Pet was not vaccinated at all before incident**. Tell the owner that there is an elevated risk of the pet becoming rabid, presenting risk to them and their family members. National guidelines call for the pet to be euthanized to prevent it from becoming rabid. Alternatively, the pet may be immediately vaccinated and then quarantined. In most states the quarantine period is 4–6 months. Texas requires only 90 days of quarantine, but also requires unvaccinated pets to be vaccinated three times while in quarantine: the first week, then three and eight weeks afterward. This three-vaccine postexposure "Texas Protocol" may provide some protection against the development of rabies, and is sometimes recommended in other localities.
  - **Pet overdue for rabies vaccine at time of incident**. These cases are often managed similarly to unvaccinated pets with a rabies vaccination being given immediately followed by a 4–6-month quarantine period (see earlier). However, the risk of rabies transmission is lower, especially if the pet has a lifetime history of multiple rabies vaccinations, and some jurisdictions may allow for a shorter quarantine of 45 days if there is proof of the earlier vaccination. If there is no proof of earlier vaccination, national guidelines suggest a procedure called prospective serologic monitoring to determine if the animal was likely vaccinated in the past. It involves documenting a very rapid rise in rabies antibody titers following boostering, by measuring antibody levels in serum samples drawn just before the booster and again 5–7 days later. This procedure may or may not be accepted as proof of earlier vaccination, depending on the state and local law.
- *Dog or cat suspected of being rabid*. Legally reportable. Isolate the animal. Create a list of all people who may have been bitten or exposed to the saliva of the animal, and refer them to physicians for consultation. After the animal dies or is euthanized, submit the head or brain to your local rabies control agency following its protocols. Inform all the exposed individuals of the rabies test result once available.
- *Pet imported from another country*. Over the past decade, the globalization of the puppy trade and animal

rescue efforts has led to dramatic increases in animal translocation. Rabid dogs have been imported into the US several times. As a result of the increasing number of imported dogs and an increase in noncompliance with import regulations, dog import requirements in the US were modified in 2014 to reduce the risk of importing rabies.

CDC Requirements

As of 2019, a health certificate is not required to import a dog or cat, but the imported pet must appear healthy on arrival. Importers of dogs must provide proof of rabies vaccination when the dog is imported from countries designated as high-risk for rabies importation (see www.cdc.gov/importation/bringing-an-animal-into-the-united-states/rabies-vaccine.html). The vaccination must have been given 28 days or more before entry, when the dog was at least 3 months of age.

Unvaccinated dogs may only be imported if they have lived in a country with a very low risk for rabies exposure for the past six months or longer, are being imported for research purposes, or on a rare case-by-case basis. See www.cdc.gov/importation/bringing-an-animal-into-the-united-states/index.html.

USDA Requirements

The US Department of Agriculture (USDA) requires dogs and cats to be at least 8 weeks old when shipped without their mothers. Dogs imported specifically for resale or adoption (i.e., importation by international dog rescue groups) must be healthy, at least 6 months old and be accompanied by a health certificate, rabies certificate, and proof of vaccination against distemper, leptospirosis, parvovirus, and parainfluenza (DHLPP). See www.aphis.usda.gov/aphis/pet-travel/bring-pet-into-the-united-states.

Federal, state, and local regulations regarding pet importation may vary over time, and can include additional requirements depending on the animal's country of origin. Veterinarians are recommended to check the latest information on the websites for both CDC and USDA-APHIS as well as any additional requirements from US Customs and Border Protection (https://help.cbp.gov/app/answers/detail/a_id/3695/kw/3695) and from the state where the animal is arriving.

Unfortunately, many imported dogs and cats are not physically inspected on arrival, so it is still possible that sick animals, or those incubating rabies, will be imported. Private practice veterinarians play a crucial role in detecting imported cases of rabies, since they may the first person to examine the pet after arrival. If a clinician suspects an imported pet has rabies or any other unusual disease, they should immediately contact their local authorities.

Bats and Public Health

Bats represent a special case when it comes to rabies. Rabid insectivorous bats may transmit rabies via very shallow bites, even bites that do not bleed. In fact, two bat variants appear to have greater ability to infect through shallow bites than the canine variant. Clinic staff may hear about clients or staff who have handled bats. They should urge such people to seek public health or medical consultation. Bats found near pets, children or sleeping people, or people with lowered levels of consciousness, may have bitten a person or pet, and *rabies testing of the bat should be prioritized*. If the bat is not tested, it should be assumed to have been rabid for the sake of safety, and the exposed person needs to be referred for medical care.

Oral Rabies Vaccination and Public Health

Clients and their pets may encounter oral rabies vaccines (ORVs) that are intended for wildlife. ORVs distributed in wildlife habitats in North America and Europe have been very successful in controlling the spread of rabies in raccoons, coyotes, and foxes. Government agencies typically work to alert the local population as to when and where the baits are being distributed. These vaccines contain a live, attenuated *Vaccinia* virus-vectored rabies recombinant liquid vaccine in a packet surrounded by a flavored bait. There is no live rabies virus in the vaccine. The *Vaccinia* virus may cause illness in immunocompromised people if the liquid vaccine comes into contact with abraded skin or mucous membranes. Human exposure to ORVs is rare. During 10 years of distribution of over 86 million ORVs in 18 states, only 296 incidents of human exposure were reported, with six illnesses. Most people were exposed when trying to remove the bait from their dog's mouth. Clients should be advised to keep their dogs leashed when in areas that are part of an ORV baiting program. If a client may have had direct contact with the liquid vaccine inside the bait, they should wash their hands, and collect the vaccine without touching it directly, such as by wearing gloves or covering their hand with a bag. There is a toll-free phone number printed on the side of the ORV bait that the person should call to report the incident and seek medical consultation.

Rabies Preexposure Prophylaxis for Humans

The CDC recommends preexposure vaccination for all people who routinely handle animals. Clinical staff, such as veterinarians and veterinary technicians, should be prevaccinated against rabies. The preexposure vaccine series consists of three intramuscular human rabies vaccinations given on days 0, 7, and either 21 or 28. Antibody titer levels should be checked every two years to insure

that the body is still producing antibodies against the virus. Preexposure vaccination alone is not considered protective in the event of a rabies exposure.

Rabies Postexposure Prophylaxis

For people with a known, or suspected, exposure to rabies, postexposure treatment is recommended. In healthy, previously unvaccinated people, treatment includes a dose of human anti-rabies immune globulin (HRIG) injected into the bite wound (with the excess given intramuscularly) plus a series of four rabies vaccines over two weeks (on days 0, 3, 7, and 14). A fifth vaccine dose may be needed for immunosuppressed individuals on day 28. The HRIG should not be injected in the same muscle as the rabies vaccine. Previously vaccinated people only need a series of two vaccinations, on days 0 and 3, after an exposure.

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91

West Nile Virus

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Etiology/Pathophysiology

West Nile virus (WNV) is a mosquito-borne viral disease that causes disease primarily in birds, humans, and horses. Sporadic disease has also been reported in a number of other species including squirrels, chipmunks, bats, dogs, cats, white-tailed deer, reindeer, sheep, alpacas, alligators, and harbor seals during periods of intense local viral activity. WNV is a zoonotic mosquito-transmitted arbovirus belonging to the genus *Flavivirus* in the family Flaviviridae. The virus can cause inapparent infection, mild febrile illness, meningitis, encephalitis or death. Dogs and cats are susceptible to WNV infection and may become infected through the bite of a mosquito, but they are significantly more resistant to disease than horses, humans, and some species of birds. It is unlikely that healthy dogs or cats will become ill. Limited information is available on WNV infections in dogs and cats but experimental studies have shown that the virus targets the meninges, dorsal horn, brainstem, cerebellar Purkinje cells, and cerebral cortex. In two naturally occurring cases in a dog and a wolf cub, myocarditis was also a finding.

Epidemiology

Like other arboviruses, WNV is maintained in nature by cycling through birds and mosquitoes. Migratory birds are thought to be primarily responsible for virus dispersal. Serologic studies of dogs and cats have shown high seroprevalence but little evidence of disease, suggesting that dogs and cats suffer little to no ill effect. In a 2002 study in Louisiana, the incidence of seropositivity was 19 times higher in outdoor dogs than in indoor dogs. Another study suggested that stray dogs and cats may serve as better sentinels than chickens. There is a single report of WNV being isolated from a sick dog in Botswana in 1982 and in a 3-month-old wolf cub and older dog with immune-mediated disease. There are three reports of naturally occurring WNV illness in cats, including one cat in New Jersey in 1999 and two cats in New York City in 2000. Experimentally infected dogs did not develop clinical signs of illness or infectious levels of viremia. Experimentally infected cats did develop brief episodes of febrile illness, lethargy or decreased appetite of short duration. Cats develop slightly higher levels of virus in their bloodstream but it is unclear if it is sufficient to infect mosquitoes. Cats fed infected mice developed viremias similar to those caused by a mosquito bite, suggesting that prey animals may serve as an important source of infection for carnivores and that outdoor cats are at greater risk of WNV infection. All dogs and cats cleared WNV from the bloodstream within days and mounted an antibody response. No evidence of prolonged or persistent infection was found. Neither dogs or cats are likely to serve as an important amplifying host epidemiologically.

Signalment

Clinical signs of WNV infection are nonspecific and diagnosis cannot be made on clinical presentation alone. Based on a small number of naturally occurring cases, dogs may present with lethargy, depression, ataxia, difficulty rising, weakness or paresis, muscle tremors or twitching, abnormal head posture, fever, and nonlocalizable pain. Other differential diagnoses for these signs would include bacterial meningitis, distemper, rabies, fungal or rickettsial infections, and primary neurologic disease. Cats develop nonspecific mild febrile illness.

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Diagnosis

Diagnosis of WNV in the live patient requires paired acute and convalescent serum samples for neutralizing antibody. Due to the widespread seropositivity, single serum samples are nondiagnostic. If a necropsy is performed (with appropriate biocontainment gear or facilities), the following tissues should be collected and submitted chilled, not frozen, for WNV polymerase chain reaction (PCR), immunohistochemistry and/or virus isolation: heart, kidney, brain/brainstem, a section of spinal cord.

Therapy

There is no specific therapy for WNV infection. Supportive care should be provided. An experimental recombinant canarypox vectored WNV vaccine protected dogs and cats against mosquito challenge but is not commercially available.

Prognosis

Full recovery is likely.

Public Health Implications

As WNV is a biologic safety level (BSL) 3 pathogen, anyone performing a necropsy should wear protective apparel and, if possible, work in a laminar flow hood. In most cases, it would be preferable to send the body to a diagnostic laboratory with appropriate facilities for testing. There is no documented evidence of dog- or cat-to-person transmission of WNV. WNV has not been detected in the saliva of dogs so dog bites would not appear to be a risk factor for human infection. Neither dogs or cats are considered epidemiologically important amplifying hosts, although peak viremias in cats may be high enough to infect mosquitoes at low efficiency.

Suspect cases should be reported to your state veterinarian, state diagnostic laboratory or reference laboratory. Positive cases should be promptly reported to your local Department of Health. Clients may ask about methods of mosquito protection in dogs and cats. It is important to emphasize that DEET-containing products are not approved for use in pets and should not be used. The same holds for citrus-based oils that have been found to cause contact dermatitis. Owners should be advised to eliminate mosquito habitat and avoid outdoor exposure of pets during peak mosquito feeding activity (early morning and dusk).

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92

Ebola Virus

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Etiology/Pathophysiology

Ebola virus is an enveloped, negative-sense RNA virus belonging to the genus *Ebolavirus* in the family Filoviridae. Filoviruses cause severe lethal hemorrhagic disease in people. The Ebola viral genome encodes a nucleoprotein (NP), a glycoprotein (GP), an RNA polymerase (L), and four structural proteins (VP 24, VP30, VP 35, and VP 40). A soluble form of GP thought to be important in evading humoral immunity is produced through receptor editing.

The primary target cells of Ebola virus are dendritic cells (DC) and macrophages. Other cells, including hepatocytes, endothelial cells, fibroblasts, and cells of the adrenal gland, can be infected.

Ebola virus can both inhibit and evade innate and adaptive immunity. For example, the virus inhibits interferon (IFN)-alpha, IFN-beta, and IFN-gamma production. Infection also inhibits DC expression of CD 40, CD 80/86, and MHC II, co-stimulatory molecules that are important in the induction of adaptive immunity. Examples of evasion tactics include shielding of GP epitopes that may be recognized by the immune system, and releasing soluble GPs that act as "decoys" that bind protective antibodies.

Despite being able to avoid immune recognition, infection is associated with massive production of proinflammatory cytokines. Thus, additional cells are recruited and available for the virus to infect. The systemic effects of cytokines cause systemic inflammatory response syndrome (SIRS). Increased vascular permeability and endothelial cell activation associated with infection are in part mediated by GP. Disordered hemostasis may arise from endothelial cell dysfunction and damage. Tissue factor expression induced by virus or cytokines appears to play a major role in activation of coagulation and induction of disseminated intravascular coagulation (DIC).

Epidemiology

Ebola was first discovered in 1976 near the Ebola River in what is now the Democratic Republic of Congo. Several epidemics have occurred in Africa. The largest outbreak began in 2014 and involved several West African countries. It was considered ended in 2016. Infection has been reported in healthcare workers returning from Africa in a few countries, including the United States, Spain, and the United Kingdom. Further spread in these countries has not occurred.

Handling of dead infected animals or consumption of infected primates was thought to be the mechanism of entry into the human population. Human-to-human spread is the primary means of infection in people. Infection occurs by exposure to bodily fluids through mucous membranes or broken skin, or inoculation via needle sticks. Importantly, fomites may also play a role in transmission. The incubation period is thought to be 2–21 days.

Bats are believed to be the reservoir host in Africa but this has not been confirmed. A summary of surveillance studies of naturally infected species in outbreak areas detected virus in nonhuman primates and bats and an ungulate. Recovered human patients can still shed the virus in semen and virus has been amplified from bodily fluids in patients with uveitis and meningoencephalitis after recovery.

Antibodies have been detected in additional species, including dogs; 27.2% of dogs had formed antibodies to the virus in a survey of a 2001–2002 outbreak of Ebola in people in Gabon. Dogs in the study were not ill. The dogs were thought to be exposed to Ebola virus by eating carcases of dead infected wild animals (bush meat) and vomit of infected people. No virus was amplified from the blood samples. A recent *in vitro* study suggested that both canine and feline cells are less susceptible to infection than primate and human cells.

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At the time of this writing, whether Ebola can cause viremia and be shed by or cause clinical signs in dogs and cats is not known. As a precautionary measure, during the 2014 Ebola outbreak, a healthy dog owned by an infected Spanish nurse was euthanized by officials without testing. Global public outcry was significant given that it had not been shown that dogs can be infected with or shed the virus and that the risk was unknown. A call for testing and not automatic euthanasia was made by the World Small Animal Veterinary Association. Shortly thereafter, a dog owned by an infected nurse in Texas was quarantined and tested rather than euthanized. Reverse transcriptase polymerase chain reaction (RT PCR) testing of blood, urine, and feces was negative, and the dog showed no evidence of illness during the 21-day quarantine.

Clinical Signs

Ebola causes severe disease in humans and nonhuman primates. Whether the virus causes clinical signs in dogs and cats is not yet known. In people, flu-like symptoms occur, including fever, headache, and muscle pain. Gastrointestinal signs also occur. Dramatic signs of disordered hemostasis such as maculopapular rash, petechiae, conjunctival hemorrhage, epistaxis, and hematemesis are common. Encephalopathy also occurs.

Diagnosis

Diagnosis in people depends on the phase of infection. Direct detection of the virus is attempted if clinical signs have been present for a short period of time. Detection techniques include virus isolation, antigen-detecting ELISA, immunohistochemistry, and RT PCR. RT PCR is used in the emergent clinical setting. Detection of IgM antibody or demonstration of seroconversion can facilitate diagnosis of acute infection.

Therapy

Treatment of infection in people is primarily supportive. Experimental therapies that appear to hold promise were utilized in some cases in the 2014 outbreak. Vaccines are in development.

Prognosis

The mortality rate in people and nonhuman primates is high. Prompt and adequate supportive care appears to be important for survival.

Public Health Implications

In the fall of 2014, the AVMA Ebola Companion Animal Response Plan Working Group developed recommendations regarding dog and cat quarantine after exposure to a human with confirmed Ebola virus disease. These recommendations are available at www.cdc.gov/vhf/ebola/pdf/dog-cat-quarantine.pdf. Public health officials and state veterinarians should be contacted immediately on an emergency basis if a pet is exposed to a person with Ebola virus infection. Regardless of whether infection occurs in dogs and cats, recommendations for people with exposure to Ebola virus include avoiding contact with their pets due to the potential risk of fur acting as a fomite.

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93

Ehrlichiosis and Anaplasmosis

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Etiology/Pathophysiology

Ehrlichiosis and anaplasmosis are tick-borne diseases caused by a group of gram-negative intracellular bacteria belonging to the family Anaplasmataceae, order Rickettsiales (Figure 93.1). These organisms are capable of causing an array of clinical signs and even death in dogs. Some bacterial species from this family are capable of infecting cats, horses, other animals, and humans. Cats are generally subclinically infected so this chapter will focus on infection in dogs.

Ehrlichia and *Anaplasma* preferentially parasitize leukocytes or platelets and form intracytoplasmic clusters called morulae (Figure 93.2). Understanding the differences in the target cell type, clinical signs, primary vectors, and geographic distribution can help clinicians differentiate the likely infecting organism, which has therapeutic and other clinically relevant implications. For dogs, *Ehrlichia canis* is the most pathogenic organism (see Figure 93.2a,b), targeting monocytes and rarely lymphocytes. *Ehrlichia canis* is transmitted by the brown dog tick, *Rhipicephalus sanguineus*, which has a ubiquitous distribution (Figure 93.3).

Like *E. canis*, *E. chaffeensis* also targets monocytes but causes comparatively mild to moderate signs, and is transmitted in the United States by *Amblyomma americanum* (the Lone Star tick), which has a more limited geographic distribution (see Figure 93.3). *Ehrlichia ewingii* and *Anaplasma phagocytophilum* target granulocytes (see Figure 93.2c,e,f) and often cause acute lameness or polyarthritis in dogs. These organisms are transmitted by different ticks (*A. americanum* and *Ixodes* spp., respectively) with distinct but overlapping areas of distribution in the United States (see Figure 93.3). *Anaplasma platys* is the only organism from this family to target platelets (see Figure 93.2d), causing cyclic thrombocytopenia and bleeding tendencies. *A. platys* is probably transmitted by the brown dog tick so co-infections with *E. canis* are not uncommon and result in more severe clinical disease than either agent alone. A summary of the species of importance in dogs and cats, their associated vectors, target cell, and geographic distribution is given in Table 93.1.

With advances in molecular methods of diagnosis, a growing number of species of *Ehrlichia* that infect humans have been documented in dogs, including *E. muris* and Panola Mountain *Ehrlichia* sp.

After transmission via tick saliva, the incubation period for *E. canis* and *A. phagocytophilum* ranges from one to three weeks. The acute phase of the disease can last 1–4 weeks, when the organism rapidly multiplies within the targeted blood leukocytes and, in the case of *E. canis*, tissue macrophages (spleen, liver, lungs, and lymph nodes). Intracellular multiplication is achieved by impairing the antimicrobial activity of host monocytes or granulocytes by inhibiting lysosome fusion, decreasing the formation of reactive oxygen species, and inhibiting phagocytosis. The organisms also increase host cell survival by inhibiting apoptosis and leukocyte migration to tissues. In addition, *Ehrlichia* and *Anaplasma* spp. avoid the immune system by repressing the early innate immune response, and by antigenic variation of outer membrane proteins. Consequently, infected monocytes or granulocytes remain in circulation longer, facilitating subsequent transfer to ticks. Genetic analyses have demonstrated that multiple strains of *E. canis* and *A. phagocytophilum* exist, which may be associated with differences in pathogenicity. In addition, host susceptibility, size of the inoculum, and concurrent infection with other tick-borne diseases transmitted by the same tick affect the clinical presentation.

An exacerbated host immune response against the infection is likely an important mechanism of the disease. Dogs infected with *E. canis* may develop polyclonal

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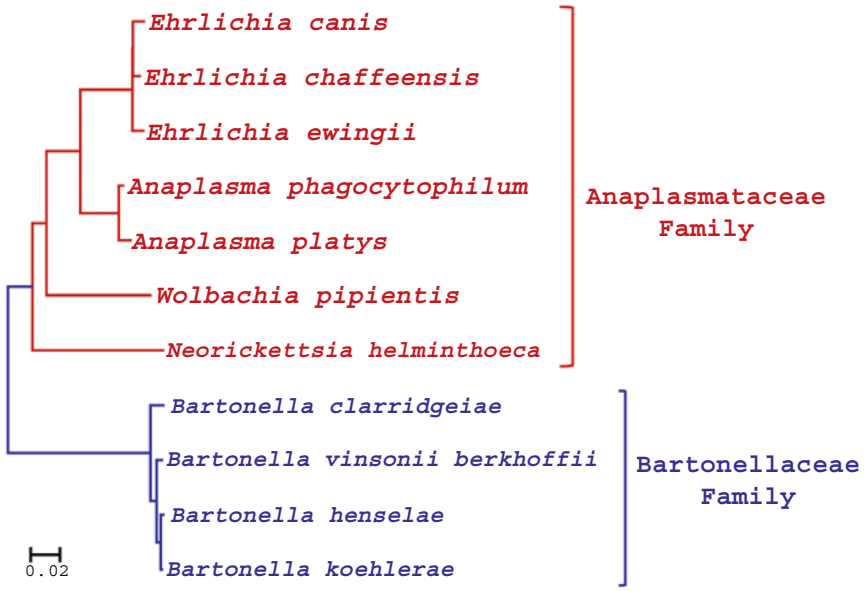


Figure 93.1 Phylogeny of selected organisms of veterinary importance from Anaplasmataceae and Bartonellaceae families. The scale bar indicates 0.02 substitutions per nucleotide position of the 16S rRNA gene.

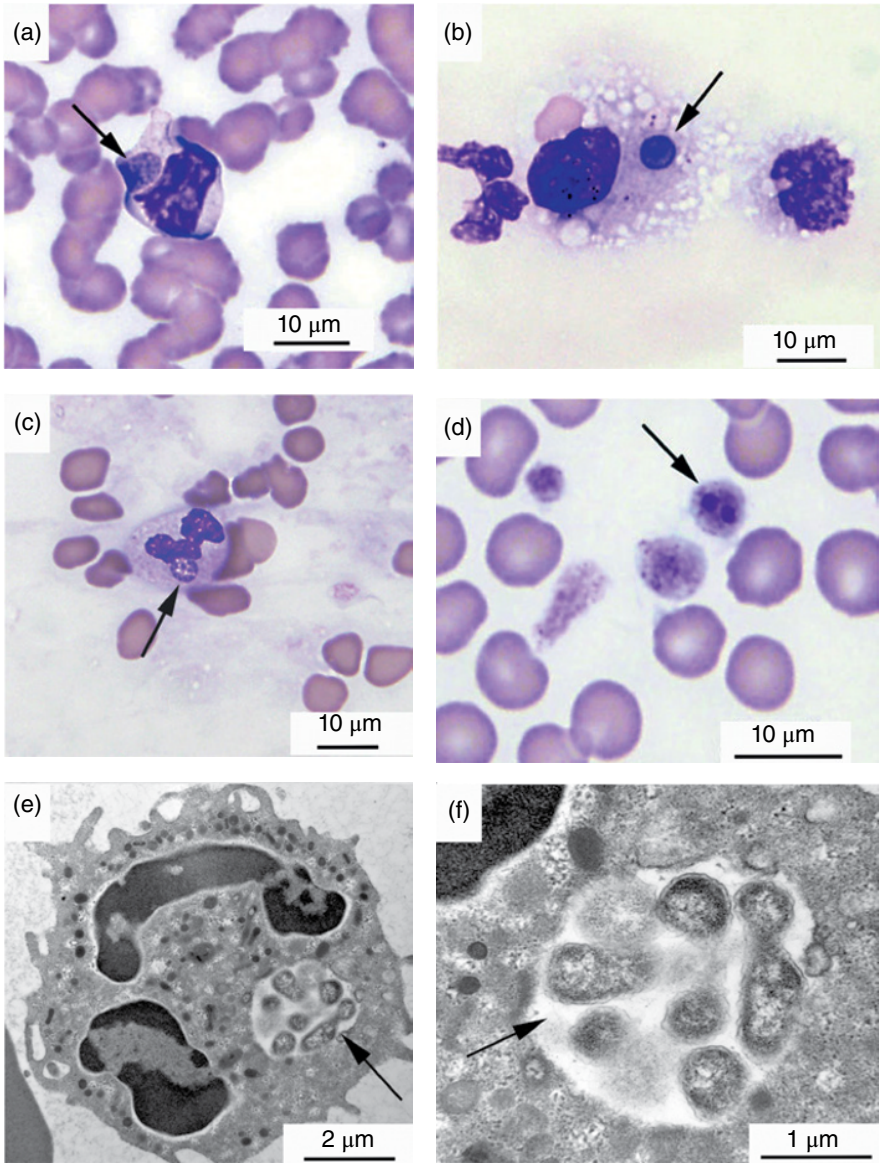


Figure 93.2 Ehrlichial morulae (*black arrows*) in canine leukocytes as seen in blood smears (a–d) and by electron microscopy (e,f). (a) *E. canis* morula in a monocyte. (b) *E. canis* morulae in a lymphocyte. (c) Morula in a neutrophil compatible with *A. phagocytophilum* or *E. ewingii*. (d) *A. platys* morula in a platelet. (e) Electron microscopy of a morula in a granulocyte. (f) Magnification of the morula seen in (e). *Source:* (a–d) from Allison and Little (2013). Reproduced with permission from John Wiley & Sons. (e,f) Courtesy of Kristin Nunez, Purdue University, USA.



Figure 93.3 Distribution of *Amblyomma americanum*, *Dermacentor variabilis*, *Ixodes pacificus*, *Ixodes scapularis*, and *Rhipicephalus sanguineus* ticks in the USA. *Source:* Centers for Disease Control and Prevention, www.cdc.gov/ticks/geographic_distribution.html.

or monoclonal hypergammaglobulinemia. Immune-mediated consumption of platelets is thought to contribute to thrombocytopenia in dogs infected with these organisms. Other mechanisms of thrombocytopenia such as splenic and vascular sequestration may also be involved. Thrombocytopathia may also occur due to antiplatelet antibodies. Deposition of immune complexes and infected cells in the vascular endothelium of kidneys, joints, and eyes may predispose to glomerulonephritis, polyarthritis, and uveitis. Systemic inflammation associated with *E. canis* infection may also contribute to myocarditis, meningitis, thrombosis, hyperviscosity, and vasculitis. The development of high circulating levels of antibodies against *Ehrlichia* or *Anaplasma* spp. does not promote protective immunity against reinfection.

The progression of the disease appears to vary according to the cell type targeted by the parasite. Granulocytic anaplasmosis caused by *A. phagocytophilum* appears to be an acute illness in naturally infected dogs that can be self-limiting. However, chronic persistent infection has been shown in experimentally infected dogs, and has been suspected in some naturally infected dogs. Similarly, granulocytic ehrlichiosis caused by *E. ewingii* appears to be self-limiting, but persistent infection was detected in experimentally infected dogs.

In contrast, monocytic ehrlichiosis associated with *E. canis* infection causes an acute illness, which may vary from mild to severe depending upon the pathogenicity of the parasite, followed by subclinical phase of months to years in duration. It is unclear if dogs are able to eliminate E. *canis* or if the organism remains sequestered in the spleen, bone marrow or other primary niche indefinitely. Some dogs develop a chronic phase characterized by hyperglobulinemia and bone marrow suppression, which is more difficult to treat. *E. chaffeensis* also appears to cause chronic infection in dogs, but dogs are generally asymptomatic.

Epidemiology

The presence of *Ehrlichia* and *Anaplasma* spp. primarily follows the geographic distribution of their vectors and mammalian reservoir hosts (see Figure 93.3). *E. canis* has worldwide distribution, being one of the most common tick-borne pathogens in dogs in tropical and subtropical regions. The ubiquitously distributed brown dog tick (*R. sanguineus*) is well adapted to urban environments. Consequently, dogs with no access to wooded areas are still at risk of *E. canis* infection. In contrast, the Lone Star tick (*A. americanum*), vector for *E. ewingii* and *E. chaffeensis*, is most frequently found in woodland habitats, especially where a high number of white-tailed deer are present. The geographically limited distribution of dogs

Table 93.1 Species of *Ehrlichia* and *Anaplasma* of importance to dogs and cats

Disease	Monocytic ehrlichiosis		Granulocytic ehrlichiosis	Granulocytic anaplasmosis	Cyclic thrombocytopenia
Organism	Ehrlichia canis	Ehrlichia chaffeensis	Ehrlichia ewingii	Anaplasma phagocytophilum	Anaplasma platys
Main targeted cell	Monocyte	Monocyte	Granulocyte	Granulocyte	Platelet
Main vector	*Rhipicephalus sanguineus*	*Amblyomma americanum*	*A. americanum*	*Ixodes scapularis*, *I. pacificus*, *I ricinus*, *I persulcatus*	*R. sanguineus*
Other potential vector(s)	*Dermacentor variabilis*	*Dermacentor variabilis*	*Otobius megnini*	*I. spinipalpis*, *I. trianguliceps*	
Main animal host	Dog	Dog	Dog	Dog, horse	Dog
Other animal hosts	Cat	Coyote, lemur, raccoon		Cat, cattle, goat, sheep	
Main reservoir	Dog	White-tailed deer	White-tailed deer	White-tailed deer, white-footed mouse, dusky-footed woodrat, wood mouse	Dog
Other potential reservoir(s)	Jackal, fox, coyote				
Zoonotic disease	Yes	Yes	Yes	Yes	No
Geographic distribution	Worldwide	USA (southeastern and south central US)	USA (southeastern and south central US)	Worldwide	Worldwide

exposed to *E. chaffeensis* and *E. ewingii* in the United States has recently been described (Figure 93.4).

A. phagocytophilum is transmitted by the blacklegged tick (*Ixodes scapularis* or *I. pacificus*) in the United States and by the castor bean tick (*I. ricinus*) and the taiga tick (*I. persulcatus*) in Europe and Asia. In the United States, *A. phagocytophilum* is more prevalent in the Northeast and upper Midwest regions, and in northern California. Updated prevalence maps of canine ehrlichiosis (*E. canis* and *E. chaffeensis* combined) and anaplasmosis (*A. phagocytophilum* and *A. platys* combined) in the United States are available at the Companion Animal Parasite Council website (https://capcvet.org/maps/#2019/all/anaplasmosis/dog/united-states/). A detailed world map of vector-borne diseases and vectors by country is available at the Canine Vector-Borne

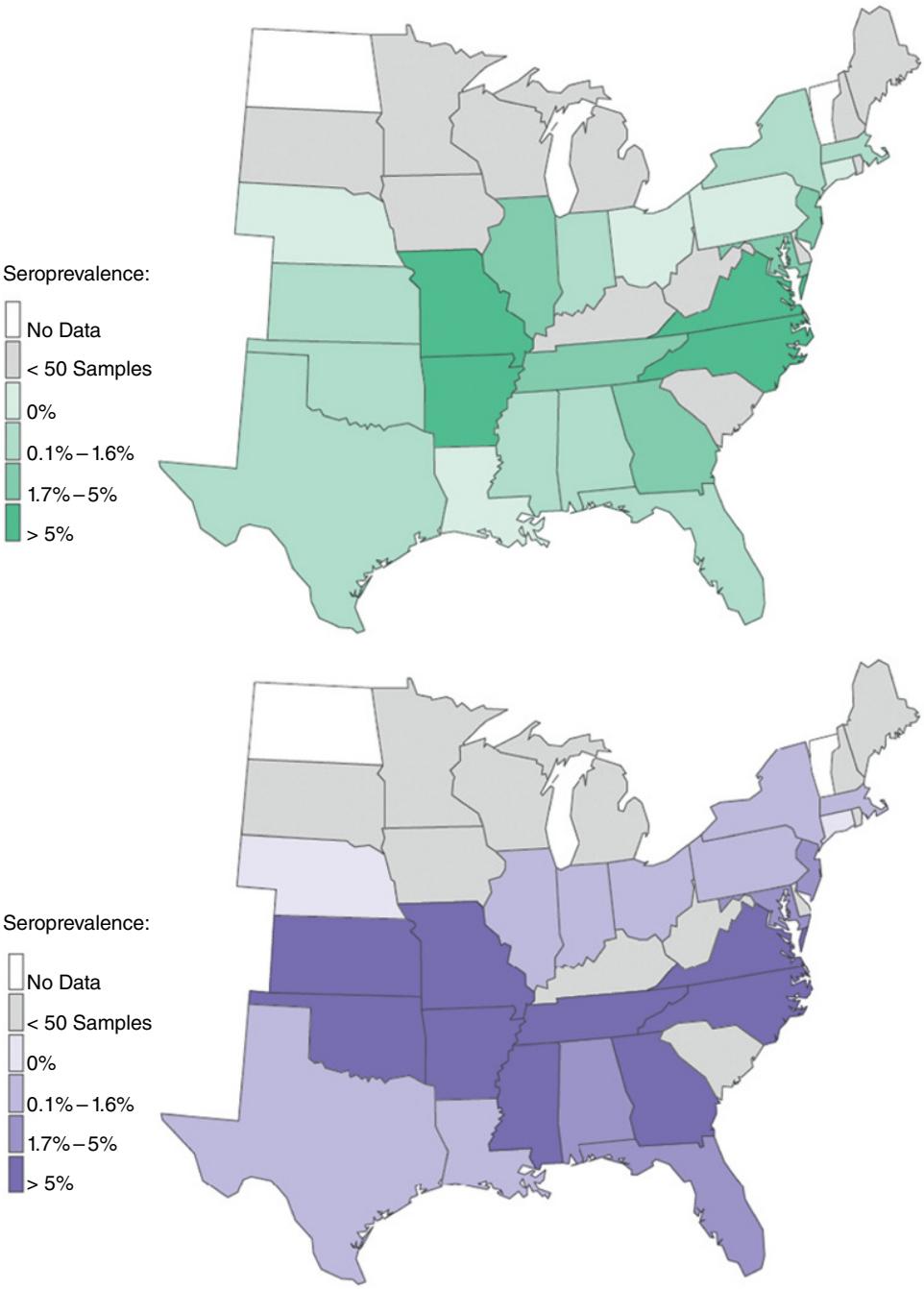


Figure 93.4 Seroprevalence by state of *E. chaffeensis* (*green*) and *E. ewingii* (*purple*) in dogs. *Source: Beall MJ, Alleman AR, Breitschwerdt EB, et al*. Seroprevalence of *Ehrlichia canis*, *Ehrlichia chaffeensis* and *Ehrlichia ewingii* in dogs in North America. *Parasites Vectors* 2012; **5**(29): 1–11. Reproduced under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0).

Disease World Forum website (www.cvbd.org/en/occurrence-maps/world-map/).

Recently, two new species of *Ehrlichia* have been described in dogs in the United States: *E. muris* from a sick dog in Minnesota, and Panola Mountain *Ehrlichia* (PME) from a sick dog in North Carolina. *E. muris* is believed to be transmitted by *I. scapularis* in the United States, with wild rodents as reservoir, whereas PME is transmitted by *A. americanum*, with white-tailed deer as the probable vertebrate reservoir in the United States.

Signalment

Male or female dogs at any age can develop the disease. German shepherd dogs are predisposed to a more severe illness during *E. canis* infection. Despite the fact that cats are naturally exposed to *Ehrlichia* and *Anaplasma* spp. infection, clinical manifestations are rarely reported.

History and Clinical Signs

The classic presentation in dogs is characterized by depression, lethargy, mild weight loss, and anorexia. Frequently, pet owners will not recall tick exposure, since infection may have occurred weeks to months prior to illness. Canine monocytic ehrlichiosis is more frequently associated with history of epistaxis and signs of pallor, petechiation, and uveitis (Table 93.2, Figure 93.5). Canine granulocytic ehrlichiosis and anaplasmosis are more frequently associated with history of reluctance to stand or walk and signs of joint effusion and lameness (see Table 93.2).

Anaplasma platys infection rarely causes clinical signs in the United States, but moderate to severe manifestation has been described in Europe, the Middle East, and South America. Fever, lymphadenopathy, and splenomegaly are common findings in monocytic or granulocytic ehrlichiosis. Severe cases of monocytic ehrlichiosis caused by *E. canis* may present with central nervous system (CNS) signs, retinal hemorrhage and detachment, and/or cardiac arrhythmias. The hallmark of the chronic phase of *E. canis* infection is pancytopenia from hypoplasia of all bone marrow cell lines, but protein-losing nephropathy, diffuse muscle wasting, and secondary infections, presumably due to immunosuppression, have been described. Chronic illness associated with granulocytic ehrlichiosis/anaplasmosis has not yet been well documented in naturally infected dogs.

Table 93.2 Main features of ehrlichiosis and anaplasmosis in dogs

Disease	Monocytic ehrlichiosis	Granulocytic ehrlichiosis/anaplasmosis	Thrombocytic anaplasmosis
Disease course	Acute, subclinical, chronic	Acute	Acute, subclinical
History	Lethargy, depression, inappetence, weight loss, epistaxis	Lethargy, depression, inappetence, weight loss, weakness, reluctance to stand or walk, lameness, stiff or stilted gait	Generally asymptomatic. Weight loss, epistaxis
Common signs	Fever, lymphadenopathy, splenomegaly, petechiae, pallor, uveitis	Fever, lymphadenopathy, splenomegaly, joint effusion	Fever, lymphadenopathy, petechiae
Less common signs	Ecchymosis, bleeding gums, melena, ocular and nasal discharge, scleral congestion, hyphema, retinal detachment, ataxia, seizures, vestibular signs, peripheral edema, muscle atrophy, cardiac arrhythmias, vomiting, diarrhea, erythema multiforme	Pallor, scleral congestion, uveitis, head tilt, tremors, anisocoria, vomiting, diarrhea	Pallor, uveitis
Common laboratory findings	Thrombocytopenia, neutropenia, nonregenerative anemia, lymphocytosis or lymphopenia, monocytosis, eosinophilia, hyperglobulinemia (polyclonal or monoclonal), increased ALT and ALP activities, proteinuria, pancytopenia	Thrombocytopenia, lymphopenia, eosinopenia, mild nonregenerative anemia,spherocytes, polyclonal hyperglobulinemia, increased ALT and ALP activities, proteinuria, neutrophilic polyarthritis	Thrombocytopenia, mild nonregenerative anemia, mild hypoalbuminemia
Main differential diagnoses	Rocky Mountain spotted fever, idiopathic immune-mediated hemolytic anemia, multiple myeloma, lymphocytic leukemia, systemic lupus erythematosus	Lyme disease, idiopathic immune-mediated polyarthritis, idiopathic immune-mediated hemolytic anemia, systemic lupus erythematosus	Idiopathic immune-mediated thrombocytopenia

ALP, alkaline phosphatase; ALT, alanine aminotransferase.

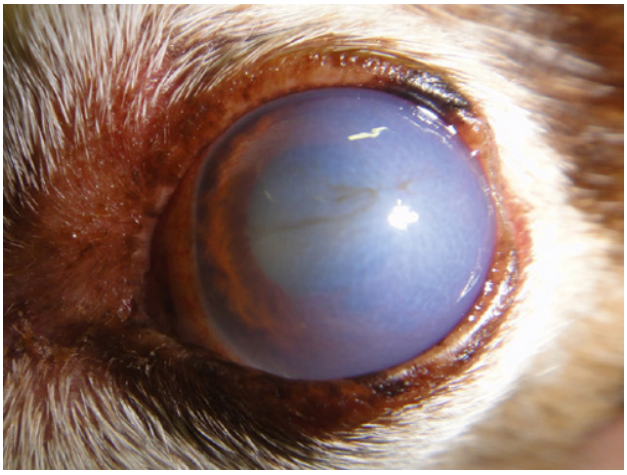


Figure 93.5 Corneal edema, opacity, and pigmentation in a dog with uveitis caused by ehrlichiosis. Source: Courtesy of José Luis Laus and Ivan Ricardo Martinez Padua, UNESP, Brazil.

Diagnosis

No single laboratory test is capable of detecting *Ehrlichia* or *Anaplasma* infection in all cases, so clinicians should be aware of the limitations of each diagnostic test (Table 93.3).

Diagnosis is generally based on clinical and hematologic abnormalities, response to therapy and presence of specific antibodies against *Ehrlichia* and *Anaplasma* spp. Common hematologic abnormalities are listed in Table 93.2. In addition, it is worth noting that *E. canis* is an important differential for lymphocytic leukemia or multiple myeloma, as infection has occasionally been associated with marked granular lymphocytosis and monoclonal, rather than polyclonal gammopathy. *E. canis* infection may also be associated with positive Antinuclear Antibody (ANA) tests, so it should be ruled out in suspected cases of systemic lupus erythematosus.

Table 93.3 Features of diagnostic assays available for ehrlichiosis and anaplasmosis in dogs

Assay	Advantages	Disadvantages	Recommended testing time
Morulae detection	• Fast and cost-effective • Can be performed in practice	• Sensitivity and specificity are low • Requires trained operator	Acute phase (first days of illness)
IFA serology	• Gold standard, widely used • Antibodies can be quantified (titer) • *E. canis* antigens cross-react with Panola Mountain *Ehrlichia* • Can be used to monitor therapy (decrease in titers generally associated with successful therapy)	• Cannot be performed in practice • Procedure not standardized among veterinary laboratories • Indicates exposure, not infection • Four-fold increase in titer is required for definitive diagnosis • Assay not available for *A. platys*, *E. ewingii* and *E. muris* as they cannot be cultured • Lack of antibody titer in the first weeks does not rule out exposure	After 2–3 weeks post infection. Low antibody titers may be detected as early as 7 days
ELISA serology: SNAP 4Dx Plus	• Fast and cost-effective • Can be performed in practice • Procedure is standardized • *E. canis* spot cross-react with *E. chaffeensis* • A. phagocytophilum spot cross-react with A. platys • Detects five *Ehrlichia* and *Anaplasma* spp., including *E. ewingii*	• Does not quantify antibody response • Intended to be a screening test, not a diagnostic test • Indicates exposure, not infection • Negative results in the first weeks do not rule out exposure • May not detect Panola Mountain *Ehrlichia* • Unknown sensitivity for *E. muris* • Limited use for monitoring therapy, as it remains positive for months after exposure	After 2–3 weeks post infection • *A. phagocytophilum* and *E. canis*: after 7–21 days post infection • *A. platys*: after 10–21 days post infection • *E. ewingii*: 3–4 weeks post infection

(*Continued*)

Table 93.3 (Continued)

Assay	Advantages	Disadvantages	Recommended testing time
Spinning-disc interferometry serology: Accuplex4 Bio-CD	• Detects antibodies against *E. canis* and *A. phagocytophilum* • May detect *E. canis* antibodies earlier than the ELISA	• Cannot be performed in practice • Indicates exposure, not infection • Does not quantify antibody response • May have less accuracy and reproducibility than the ELISA for *Anaplasma* spp. • Unclear if detects antibodies against *A. platys*, *E. chaffeensis*, *E. ewingii*, Panola Mountain *Ehrlichia*, and *E. muris*	Currently unknown. Recommended after 3–4 weeks post infection
Western immunoblotting	• Detects specific antibody response to ehrlichial species • Less cross-reactivity among species than other serology methods	• Cannot be performed in practice • Technically difficult • Not widely available • Primarily used on research	Subclinical or chronic phases
Polymerase chain reaction	• Early detection of active infection • Highly sensitive for acute phase • Identifies pathogens at the species level, and even new species or strains • Can test a wide variety of samples (whole blood, buffy coat, cavitary effusions, synovial liquid, tissue aspirates or fragments, and ectoparasites) • Can test frozen historical samples • Widely available	• Cannot be performed in practice • Procedure not standardized among veterinary laboratories • Sensitivity and specificity depend on assay design • Risk of false-positive results if laboratory quality control is not implemented • Limited sensitivity for chronic infection • Negative results do not rule out infection, even after therapy, as bacteria levels may be lower than limit of detection of assay • Not recommended as a single screening test for blood donors	Acute phase. May detect carrier state and chronically infected, but sensitivity ranges from 25% to 68%

ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescent antibody.

Visualization of morulae in blood smears using light microscopy can facilitate diagnosis, but it is insensitive. In addition, stain artifacts or basophilic precipitates can be confused with inclusions so other diagnostic techniques are recommended. Serology based on assays such as immunofluorescent antibody (IFA), enzyme-linked immunosorbent assay (ELISA), spinning-disc interferometry or western blotting is the most common method used for diagnosis. Most of the serology methods cannot precisely identify the species of *Ehrlichia* or *Anaplasma* involved due to serologic cross-reactivity. Serology only documents exposure to, not infection with, one or more organisms, so previous exposure or self-limiting infection should be considered in a patient with a positive result. Results of serology should be interpreted in light of clinical signs, laboratory abnormalities, and other potential differential diagnosis. A single positive serology result in a healthy dog with no clinical, hematologic or biochemical abnormalities or proteinuria may not require therapy. Because serology depends upon production of specific antibodies, false-negative results may occur in the first 1–2 weeks post infection. Seronegative dogs with compatible clinical signs should be retested 2–3 weeks later to demonstrate seroconversion, and alternative methodologies, including polymerase chain reaction (PCR), should be utilized. Continuous decrease in antibody titers after antibiotic therapy may suggest clearance of infection; however, it may take several months to years for titers to decrease. In addition, dogs with chronic infection may be seronegative due to the ability of the pathogen to evade the immune system.

Generally speaking, in contrast to serologic assays, PCR assays are very sensitive during the acute phase of infection when organisms are circulating in high numbers. PCR panels are widely available, and many can identify the species of the pathogen(s) involved. Some PCR panels can also detect and differentiate new species or strains. Bodily fluids, effusions, cytology aspirates, tissues, and ectoparasites may all be tested using PCR. However, a negative PCR result never rules out infection. PCR assays have low to moderate sensitivity for subclinical or chronic infections because the pathogen may be sequestered in the spleen or bone marrow, or be circulating in the bloodstream at very low levels, below the limit of assay detection. Since the length of time since infection is generally unknown for a given patient, it is recommended that serology and PCR assays are used in combination (see Table 93.3).

Therapy

Doxycycline remains the treatment of choice for ehrlichiosis and anaplasmosis. In this author's experience, a dose of 5 mg/kg PO q12h is associated with fewer gastrointestinal (GI) adverse effects (vomiting, anorexia) but has the same clinical efficacy as 10 mg/kg PO q24h. For cats and small dogs, liquid formulations are preferred, because tablets may become stuck in the esophagus and cause esophageal damage and stricture. Alternatively, at least 6 mL of liquid should be given PO following each tablet.

The optimum duration of therapy is unknown. Since tetracyclines are bacteriostatic, it may require several weeks of therapy. A *minimum of 28 days* is recommended for acute and subclinical monocytic ehrlichiosis, and a *minimum of 14 days* for granulocytic ehrlichiosis and anaplasmosis for dogs and cats. Chronic cases may require much longer treatments, and consequences of long-term infection such as bone marrow suppression may not resolve despite appropriate antibiotic therapy. Because clinical improvement generally occurs as early as 24–48 hours after the beginning of therapy, clients should be reminded not to interrupt or terminate the therapy early. Aggressive tick control should be implemented. After appropriate treatment of a dog with acute or subclinical infections, the pathogen should no longer be detected in the bloodstream by PCR or culture, but dogs with chronic infections may remain intermittently positive. Decrease of antibody titers within 6–9 months post infection may indicate clearance of the pathogen, but titers can remain elevated for more than 30 months after infection.

If the patient does not tolerate oral antibiotics, IV doxycycline, oxytetracycline (7.5–10 mg/kg IV q12h) or chloramphenicol (25–50 mg/kg IV or SC q8h) can be used until GI signs subside. Of note, chloramphenicol should be avoided in dogs with severe anemia and pancytopenia. The use of enrofloxacin is associated with initial clinical improvement, but it is not recommended as single therapy due to antibiotic resistance by *E. canis*. Imidocarb dipropionate should be avoided due to limited efficacy.

Supportive therapy may be crucial for survival in advanced cases. IV fluids and blood transfusions are frequently used in severe anemic and thrombocytopenic cases. Granulocyte colony-stimulating factor and recombinant human erythropoietin were used with success in one case of bone marrow suppression. Desmopressin acetate (DDAVP), a synthetic vasopressin analog, has been successfully used to treat bleeding associated with ehrlichiosis when used at 1 µg/kg SC q24h for three days. In addition, low immunosuppressive doses of prednisone (1–2 mg/kg PO q24h for 2–7 days) are recommended when thrombocytopenia fails to resolve with antibiotic therapy, or when severe or life-threatening thrombocytopenia is present. Treatment of seropositive dogs without clinical or laboratory abnormalities is currently not recommended.

Prognosis

Acute ehrlichiosis and anaplasmosis have very good prognosis if antibiotic therapy is initiated immediately. Dogs with severe anemia, severe leukopenia, hypokalemia, prolonged activated partial thrombin time (APTT) and protein-losing nephropathy have a higher risk of mortality. Prognosis is guarded in cases of bone marrow hypoplasia or aplasia.

Public Health Implications

Several ehrlichial species have been detected in humans worldwide. Most human cases are presented with acute evolution of fever, malaise/fatigue, myalgia and arthralgia, and fully respond to doxycycline therapy. No direct transmission from dogs to humans has ever been documented, but dogs can serve as environmental sentinels, as well as natural reservoirs of some species. Blood from infected dogs should be handled with caution and needle sticks should be avoided.

Humans get infected by the bite of an infected tick so measures to prevent exposure to ectoparasites are fundamental to avoid disease in humans. *E. chaffeensis* is the etiologic agent of human monocytic ehrlichiosis, while *A. phagocytophilum* is the etiologic agent of human granulocytic ehrlichiosis, and *E. ewingii* causes human

monocytic ehrlichiosis. They are considered emerging diseases in the United States, with over 7400 human cases reported in the United States in 2017. Human ehrlichiosis is most frequently reported in the southeastern and south-central regions of the United States. Three states (Oklahoma, Missouri, and Arkansas) account for 30% of all reported cases. Conversely, human anaplasmosis is most frequently reported in the upper midwestern and northeastern US, with six states (New York, Connecticut, New Jersey, Rhode Island, Minnesota, and Wisconsin) accounting for 90% of all reported cases. Additionally, *E. chaffeensis* has been documented in Africa, Asia, the Middle East, Central and South America, while *A. phagocytophilum* has been documented in Europe, Asia, and South America. The fatality rate of human ehrlichiosis and anaplasmosis ranges from 0.2% to 3.7%. *Ehrlichia canis* infection in humans has been documented by molecular methods, but only in Venezuela (named Venezuelan human ehrlichiosis). In 2008, Panola Mountain Ehrlichia was first detected from a sick human in Georgia. In addition, infection with E. muris eauclairensis, formerly E. muris-like agent (EMLA), has been reported in 115 human cases in the upper Midwest. No deaths have been described.

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94

Salmon Poisoning Disease

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Etiology/Pathophysiology

Neorickettsia helminthoeca, also known as salmon poisoning disease (SPD), belongs to the family *Anaplasmataceae* (Figure 94.1). The organism causes an acute febrile and often fatal disease in dogs. In contrast to other pathogens of this family, *N. helminthoeca* does not depend on blood-sucking ectoparasites for transmission. Dogs acquire the infection by ingesting fish infected with the SPD vector, the trematode *Nanophyetus salmincola*. In order to complete its life cycle, this trematode requires a snail (*Oxytrema silicula*), a fish (salmon, trout, lamprey, goldfish, stickback, among others), and a mammal or a bird (human, dog, coyote, raccoon, fox, river otter, bobcat, rat, heron, merganser, among others). Once the trematode matures and attaches to the gastrointestinal (GI) tract of the dog, *N. helminthoeca* is transmitted, initially multiplying in the epithelial cells and intestinal lymphoid tissue and then spreading systemically to visceral and somatic lymph nodes, where proliferation within macrophages occurs. After 8–12 days post infection, the organisms circulate in high numbers in the bloodstream, spreading to brain, liver, lungs, and spleen, causing systemic signs. Death of the dog occurs around 18 days post infection. The disease also occurs in other canids (foxes, coyotes) and bears, but it has not been described in domestic cats.

Epidemiology

Salmon poisoning disease is endemic in the Northwest Pacific of the United States (coastal regions of northern California, Oregon, and Washington) and southern British Columbia in Canada. A similar syndrome has been described in dogs from south Brazil.

Signalment

Dogs from any breed, age, and sex can be infected with *N. helminthoeca* and develop SPD. In one study, intact male dogs and Labrador retrievers were overrepresented, probably associated with the popularity of this breed.

History and Clinical Signs

History of consumption of raw or improperly cooked fish, obtained by fishing or purchased at the supermarket, is very common among sick dogs. However, dogs can also be infected by swimming in rivers and lakes where contaminated cercaria are present.

Inappetence and depression are usually the first findings, followed by progressive weight loss. Fever and peripheral lymphadenopathy are frequently seen during initial physical exams. Because of the multiplication of the pathogen in mesenteric and ileocecal lymph nodes, with consequent inflammation and tissue edema, vomiting, diarrhea, and dehydration are present in over 70% of the cases. Melena, hematemesis, and abdominal pain may occur in one-third of cases. The hemorrhagic gastroenteritis may be indistinguishable from canine parvoviral enteritis in some dogs. Less frequently, polyuria, polydipsia, serous to purulent ocular discharge, neurologic signs, tachypnea, peripheral edema, hyphema, splenomegaly, scleral injection, and epistaxis may be seen. If left untreated, the illness progresses quickly,

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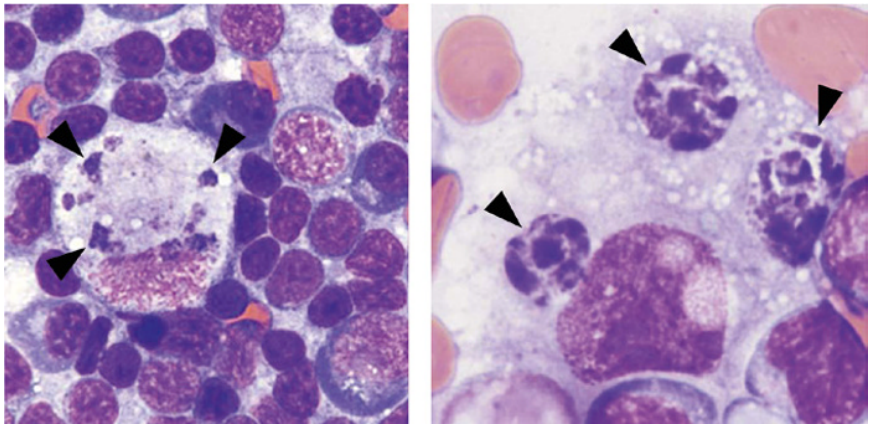


Figure 94.1 Fine-needle aspirate of mesenteric lymph node of a dog with salmon poisoning. Black arrowheads indicate the presence of intracytoplasmic inclusions (morulae) within macrophages. Left figure: close-up of a macrophage with three morulae. Wright's-Giemsa stain, x100 objective. *Source:* Johns et al. (2006). Reproduced with permission of John Wiley & Sons.

which can cause severe hypotension, mucosal pallor, cardiac arrhythmias, and death.

Diagnosis

Thrombocytopenia, anemia, lymphopenia, and neutrophilia with a left shift are the most consistent hematologic abnormalities. Hypocalcemia, hypoalbuminemia, hyponatremia, and hypokalemia are frequent abnormalities in the serum biochemistry. Urinalysis may reveal bilirubinuria and proteinuria. Coagulation testing may indicate evidence of disseminated intravascular coagulation.

Fecal microscopy for the detection of *N. salmincola* is a fast, cost-effective, and specific diagnostic procedure that can be performed in practice. Both the sedimentation and the zinc sulfate centrifugal flotation tests should be performed for better sensitivity. Light brown operculated eggs are present in fecal samples 5–8 days after ingestion of infected fish. However, eggs may not be detected in the feces of every infected dog. Fine needle aspirates from peripheral and mesenteric lymph nodes or spleen may reveal intracytoplasmic neorickettsial bodies within macrophages and histiocytic inflammation. However, the absence of morulae does not rule out the disease.

Currently, serologic assays for *N. helminthoeca* are not available from commercial diagnostic laboratories. However, due to acute presentation of the disease and the time needed for production of specific antibody, serology tests may not help the diagnosis. Polymerase chain reaction (PCR) assays are available for the specific detection of *N. helminthoeca* DNA from blood, aspirates of lymph nodes, spleen or liver, tissue samples, and feces. Because PCR assays can be specific and highly sensitive, they may aid the diagnosis of SPD if the laboratory has a short turnover time. Due to the high mortality of SPF, clinicians should not wait for laboratory confirmation before starting appropriate antibiotic therapy.

Therapy

Tetracyclines are the antibiotic class of choice, and clinical improvement is seen within 24–72 hours. If the patient can receive oral medication, doxycycline 5 mg/kg PO q12h for 1–2 weeks is recommended. Vomiting dogs should receive doxycycline (5 mg/kg IV q12h) or oxytetracycline (7–10 mg/kg IV q8h) until GI signs subside. Trematode infection should be treated with praziquantel (10–30 mg/kg PO q24h for 1–2 days). For complicated cases, hospitalization and intensive care may be required.

Prognosis

Survival is directly related to early diagnosis and introduction of appropriate antibiotic therapy and support care, achieving >85% success rate. Most untreated animals die within 6–10 days of the onset of clinical signs. In contrast to other pathogens in the family *Anaplasmataceae*, infection with *N. helminthoeca* generates protective immunity against the same strain; however, alternate strains can still cause illness.

Public Health Implications

No confirmed case of human infection has ever been reported, although humans can be naturally infected with the trematode *N. salmincola*, which may cause abdominal discomfort and GI signs.

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95

Wolbachia pipientis Infection

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Etiology/Pathophysiology

Wolbachia pipientis is a gram-negative bacteria belonging to the family *Anaplasmataceae*. The organism is found in all developmental stages of *Dirofilaria immitis*, the filarial helminth that causes heartworm disease in dogs and cats. *Wolbachia* is an endosymbiont of *D. immitis* (Figure 95.1) and supports the nematode's survival, maturation, and reproduction. It is transmitted by the mosquito vector along with the nematode, and is released into the bloodstream in large numbers during parasite molts, microfilaremia, and upon death of the parasite.

It was originally believed that *Wolbachia* was not pathogenic to mammals. However, in recent years, studies have shown that components of their surface membranes stimulate production of inflammatory and vasoactive cytokines from neutrophils and endothelial cells, resulting in inflammatory lesions and pulmonary artery vasoconstriction. Experimental infection with *D. immitis* free of *Wolbachia* results in a reduced inflammatory response after anthelminthic therapy. Furthermore, antibiotic therapy that targets *Wolbachia* results in a significant reduction in inflammatory reactions when anthelmintic drugs are used to kill *D. immitis* in infected dogs. It has been shown that cats naturally infected with *D. immitis* and seropositive for *Wolbachia* surface proteins (WSP) have a greater acute inflammatory response at bronchial, vascular, and parenchymal levels when compared to healthy cats. WSP have also been detected in glomerular capillaries and may contribute to the glomerulonephropathy seen in heartworm disease. It is currently unclear if *Wolbachia* can cause disease in animals without the presence of *D. immitis*, because the bacterium has never been cultured *in vitro*.

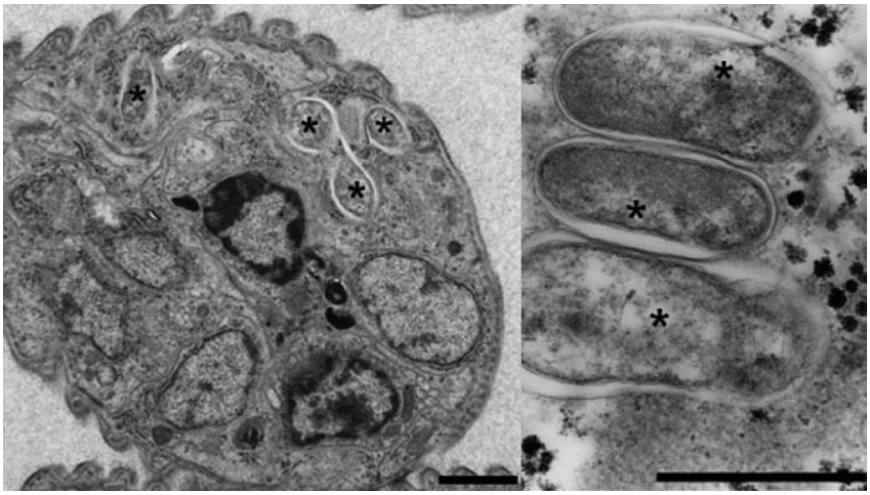


Figure 95.1 Ultrastructural location of Wolbachia within their filarial host (black asterisks), characterized by bacteria within host vacuoles. Scale bar = 5 µm (left) and 1 µm (right). *Source:* Taylor *et al*. (2013). Reproduced with permission of John Wiley & Sons.

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Epidemiology

Wolbachia is ubiquitous in *D. immitis*, being present in 100% of the helminths. Therefore, the distribution of *Wolbachia* follows the presence of *D. immitis*, which is endemic in North, Central, and South America, the coastal regions of Africa, southern Europe, India, north, central-east and south China, Southeast Asia, and Australia. Updated prevalence maps for heartworm are available at the Canine Vector-Borne Disease World Forum website (www.cvbd.org/en/occurrence-maps/world-map/).

Signalment

Because of the life cycle of *D.* immitis, clinical signs are generally detected in animals older than 1 year. Dogs are more frequently affected than cats.

History and Clinical Signs

While *Wolbachia* may collaborate in the pathogenesis of *D. immitis* infection, clinical signs are indistinguishable from heartworm disease.

Diagnosis

Wolbachia DNA can be detected using polymerase chain reaction (PCR) on EDTA–anticoagulated blood samples. Interestingly, using PCR to detect *Wolbachia* has been proposed as a tool to detect early *D. immitis* infection. WSP can also be detected using serology, but because all *D. immitis* stages are infected with *Wolbachia*, the presence of the organism is assumed in a dog with a positive test for occult heartworm antigen. Interestingly, one study suggested that dogs infected with *D. immitis* and seropositive for WSP were more likely to have proteinuria than WSP-seronegative dogs.

Therapy

Because of the symbiotic relationship between *Wolbachia* and *D. immitis*, decreased bacterial load affects embryogenesis, maturation, and survival of heartworm. Treating dogs infected with *D. immitis* with an antibiotic that targets *Wolbachia* results in a decrease in microfilaremia, and when combined with ivermectin, fewer pathologic pulmonary lesions are observed compared to adulticide therapy alone (melarsomine). Therefore, the current therapeutic recommendation from the American Heartworm Society is to administer doxycycline at 10 mg/kg PO BID for four weeks in combination with ivermectin prior to adulticide therapy. Doxycycline eliminates >90% of the *Wolbachia* organisms from the nematode for at least three months.

Prognosis

Because all *D. immitis* are infected with *Wolbachia*, the prognosis of *Wolbachia* infection follows the prognosis for treatment of heartworm infections. Patients with no abnormal physical examination findings or radiographic changes have an excellent prognosis. Those with mild clinical signs and mild thoracic radiograph abnormalities have a good prognosis if adequately treated. Patients with moderate to severe disease, including caval syndrome, have a poor prognosis.

Public Health Implications

Dirofilaria immitis is able to infect humans, where it generally causes granulomatous lesions in lungs and subcutaneous tissue. Similar to what has been documented in dogs and cats, inflammatory reactions to these parasites in humans may be associated with their co-infecting *Wolbachia*, but it is unclear if *Wolbachia* can cause disease without the presence of filarial nematodes.

Further Reading

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96

Bartonellosis

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Etiology/Pathophysiology

Bartonellosis is a complex syndrome caused by gram-negative bacteria of the genus *Bartonella*, which are transmitted by blood-sucking arthropods and have tropism for mammalian erythrocytes, endothelial cells, and bone marrow progenitor cells. There are at least 14 species, subspecies or species candidatus of *Bartonella* capable of infecting dogs, with at least six species capable of infecting cats (Table 96.1).

Most species of *Bartonella* reported from dogs and cats can also infect humans. Few *Bartonella* spp. are host specific, such as *B. bacilliformis* in people, with the vast majority of species having a preferred host but being capable of infecting other terrestrial mammals and even some marine animals. *Bartonella* spp. cause absent to minimal clinical manifestations in their preferred hosts. However, when a *Bartonella* sp. infects a nonadapted incidental host, clinical abnormalities are commonly seen. Severe illness is more frequently seen in immunosuppressed hosts or when co-infection with other vector-borne disease agents occurs. *Bartonella* causes chronic infections in dogs, cats, and humans, many of which are misdiagnosed and misreported.

Unlike some other vector-borne disease agents, species of *Bartonella* that infect dogs and cats do not form intracytoplasmic morulae. Therefore, they cannot be seen on blood smears or cytologic specimens without the use of special staining. Based on genetic analysis and presence of virulent factors, *Bartonella* spp. are divided into four lineages, with *B. bacilliformis* being the ancestor of all other species. The vast majority of *Bartonella* spp. capable of infecting dogs and cats (lineages 3 and 4) have virulence factors that mediate erythrocyte adhesion in a host-specific manner (Trw type IV secretion system [T4SS]) and transfer effector proteins into host cells (VirB T4SS) to promote chronic infection. Consequently, *Bartonella* can invade and multiply in erythrocytes and endothelial cells and evade the host's immune system. Other virulence factors also participate in the pathogenesis of the infection. These include adhesion molecules, regulatory systems and a factor capable of inhibiting proinflammatory responses mediated by Toll-like receptor IV. *Bartonella* spp. also infect dendritic cells, microglial cells, monocytes, macrophages, and CD34+ progenitor cells in the bone marrow. From these primary niches, *Bartonella* spp. are periodically shed into the bloodstream.

Like bacteria belonging to the family Anaplasmataceae, *Bartonella* spp. inhibit apoptosis of host cells. This allows infected cells to remain in circulation longer, and increases the likelihood of acquisition by a blood-sucking arthropod vector. The pathogen often establishes subclinical bacteremia that can last from weeks to several months. It is still unclear why some dogs or cats may develop clinical manifestations while other animals infected with the same *Bartonella* species are asymptomatic. Factors such as host immune response, species virulence, predisposing factors (congenital valvular disease), infection chronicity, and concomitant infections may play a role in disease manifestation.

Epidemiology

Bartonella spp. can be transmitted by an increasing number of arthropod vectors. In dogs and cats, cat fleas (*Ctenocephalides felis*) have been well defined as the major mode of transmission. However, epidemiologic evidence also supports the role of ticks in transmission to companion animals. Other suspected vectors include *Pulex* flea species, lice, and biting flies.

The prevalence of *Bartonella* infection differs significantly between dogs and cats, being generally low in dogs and high in cats. There are also differences in infecting species, with the most common species detected in dogs being *B. henselae* and *B. vinsonii* subsp. *berkhoffii*, and the most common species in cats being *B. henselae*,

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Table 96.1 Species of *Bartonella* detected in dogs, cats, and other hosts

Bartonella spp.	Preferred host	Other hosts	Vector
B. bovis	Cattle	Dog, cat, deer, elk	Biting flies?
B. clarridgeiae	Cat	Dog, human	Cat flea
B. elizabethae	Rat	Dog, human	Rodent fleas
B. grahamii	Wild mouse, vole	Dog, human	Rodent fleas
B. henselae	Cat, dog	Human, other terrestrial and marine mammals	Cat flea
B. koehlerae	Cat	Dog, human	Cat flea
B. quintana	Human	Dog, cat, monkey	Body louse
B. rochalimae	Dog and other canids, raccoon	Human	Fleas
B. taylorii	Wild mouse	Dog	Rodent fleas
B. vinsonii subsp. *arupensis*	Wild mouse	Dog, human	Ticks?
B. vinsonii subsp. *berkhoffii*	Dog and other canids	Cat, human, sea turtle	Fleas? Ticks?
B. volans-like	Squirrel	Dog, human	Unknown
B. washoensis	Squirrel	Dog, human, rat	Unknown
Candidatus *B. merieuxii*	Dogs and other canids	Unknown	Unknown

followed by *B. clarridgeiae* and *B. koehlerae*. It is believed that infection with these *Bartonella* species in dogs and cats has a worldwide distribution, but epidemiologic data are limited. *Bartonella* spp. are more frequently documented in temperate regions of the world, especially in warm and humid areas.

Bacteremia documented by polymerase chain reaction (PCR) ranges from 1% to 17% in sick or healthy dogs, depending upon the geographic location evaluated. In the United States, up to 10% of sick dogs with clinical manifestations compatible with tick-borne diseases are infected with *Bartonella* spp. Exposure to *Bartonella* spp. in dogs, documented by serology methods, is generally ≤10% of tested dogs, with higher prevalence detected in sick dogs and in some tropical countries. Conversely, bacteremia prevalence in cats ranges from 5% to 40%, with prevalence of ≥ 80% in some populations (feral cats, colonies with frequent flea infestation). Seroprevalence is also frequently high, with some colonies having over 90% of cats seroreactive to *Bartonella* species. Because of its ubiquitous presence in cats, establishing a causal relationship between *Bartonella* infection and illness is challenging in this species.

Signalment

Dogs from any breed, sex, and age can be infected but in one study, over 95% of dogs bacteremic for *Bartonella* spp. were older than 12 months. Outdoor access, residence in a rural environment, and tick exposure are considered risk factors for infection in dogs. Similarly, cats from any breed and sex can become infected with *Bartonella* spp. Young cats (≤1 year) are more likely to be bacteremic, while older cats are more likely to be seropositive. Stray or feral cats are more likely to be infected than pet cats.

History and Clinical Signs

Bartonella spp. have been associated with a wide range of diseases in dogs and cats (Box 96.1). Endocarditis is the most commonly reported manifestation in dogs (Figure 96.1).

In one study, *Bartonella* spp. infection was confirmed as the cause of culture-negative endocarditis in 20% of canine cases presented at a US tertiary hospital. Aortic valve involvement and congestive heart failure are more frequent in dogs with endocarditis from *Bartonella* spp. infection despite most of these patients having no fever.

Because of the cyclic shedding of the pathogen into the bloodstream, several other organs can be affected. Consequently, the most frequent signs in dogs are nonspecific, including fever (40% of cases), lethargy (40%), weight loss (34%), anorexia (32%), and lymphadenopathy (30%). In one study, weight loss was significantly associated with *Bartonella* when compared to other dogs suspected of vector-borne diseases. Although Bartonella spp. DNA has been detected in dogs and cats with diverse signs and syndromes (see Box 96.1), causal relationships have mainly been confirmed in dogs and cats with endocarditis, myocarditis, fever of unknown origin, and specifically in cats, fetal reabsorption and stillbirth. (see Box 96.1).

Box 96.1 Clinical signs and syndromes potentially associated with *Bartonella* infection in dogs and cats

Reported from dogs and cats
Endocarditis
Fever of unknown origin
Hepatitis
Lameness
Lymphadenopathy
Myocarditis
Skin lesions
Uveitis

Only reported from dogs
Bacillary angiomatosis
Cavitary effusion
Chronic erosive polyarthritis
Epistaxis
Granulomatous hepatitis
Hyperviscosity syndrome
Meningoradiculoneuritis
Peliosis hepatis
Polyarthritis
Systemic pyogranulomatous disease

Only reported from cats
Cholangitis
Diaphragmatic myositis
Gingivitis
Hepatitis
Interstitial nephritis
Lower urinary tract disease
Neurologic signs (nystagmus, focal motor seizures, behavior changes)
Osteomyelitis
Reproductive failure (fetal reabsorption, stillbirth)
Stomatitis

Chronic infection in dogs is associated with pyogranulomatous disease, which can be located in several sites, including lymph nodes, liver, and the central nervous system (Figure 96.2). Consequently, clinical signs vary depending upon the extent of damage caused in one or more organs. *Bartonella* infection in humans is associated with vasculoproliferative disease (bacillary angiomatosis and peliosis hepatis), which has been also described in dogs (Figure 96.3).

Despite the growing number of reports of sick dogs infected with *Bartonella* spp., two recent studies failed to reproduce clinical signs in dogs that were experimentally infected with *B. henselae*, *B. vinsonii* subsp. *berkhoffii*, and *B. rochalimae*. In addition, another study documented that 18% of asymptomatic dogs carry *Bartonella* DNA in the blood or lymph nodes. In one study, 8% of *Bartonella*-infected dogs were seropositive for at least one other vector-borne pathogen. Therefore, the pathogenesis of bartonellosis in dogs is still unclear, and clinicians should rule out other relevant differentials before considering this diagnosis.

In naturally infected cats, clinical signs are rarely reported. Similarly, experimental infection often causes mild and transient clinical signs such as fever, lethargy, and lymphadenopathy in less than a third of infected cats. However, more severe manifestations have been reported from experimental studies, including mild neurologic signs (nystagmus, intermittent tremors, and focal motor seizures), epaxial muscle pain, reproductive failure, and severe myocarditis (respiratory distress, cardiac murmurs, and arrhythmias). As seen in dogs, *Bartonella* infection in cats can be associated with granulomatous lesions in several organs. Osteomyelitis (Figure 96.4), uveitis, hepatitis, gingivitis, and stomatitis, among other syndromes (Table 96.2), have been associated with natural *Bartonella* spp. infection in cats.

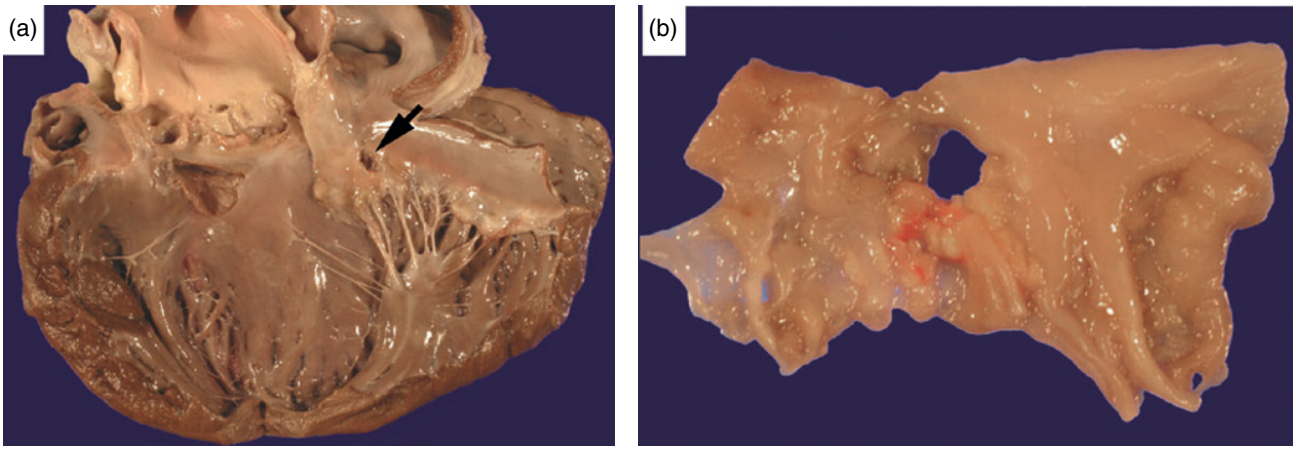


Figure 96.1 Endocarditis caused by *Bartonella vinsonii* subsp. *berkhoffii* in a dog. (a) Heart of a dog with mitral valve perforation (*black arrow*). (b) Close-up of the perforation in the supravalvular region of the mitral valve. *Source:* Chomel *et al*. (2009). Reproduced with permission of John Wiley & Sons.

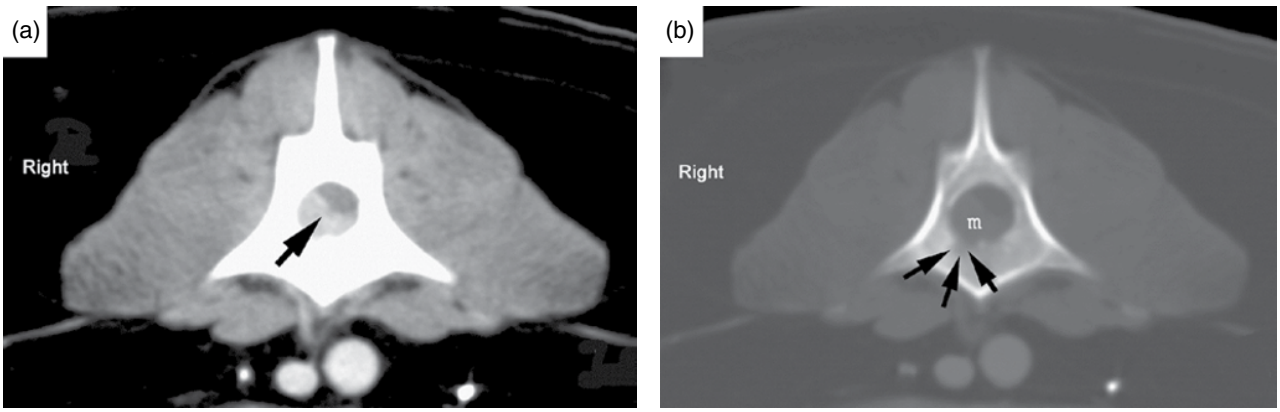


Figure 96.2 Computed tomography (CT) of spinal cord compression (a, *black arrow*) and vertebral bone reabsorption (b, *black arrows*) caused by an inflammatory granuloma (m, mass lesion) in a dog infected with *B. vinsonii* subsp. *berkhoffii*. *Source:* Cross *et al*. (2008). Reproduced with permission of John Wiley & Sons.

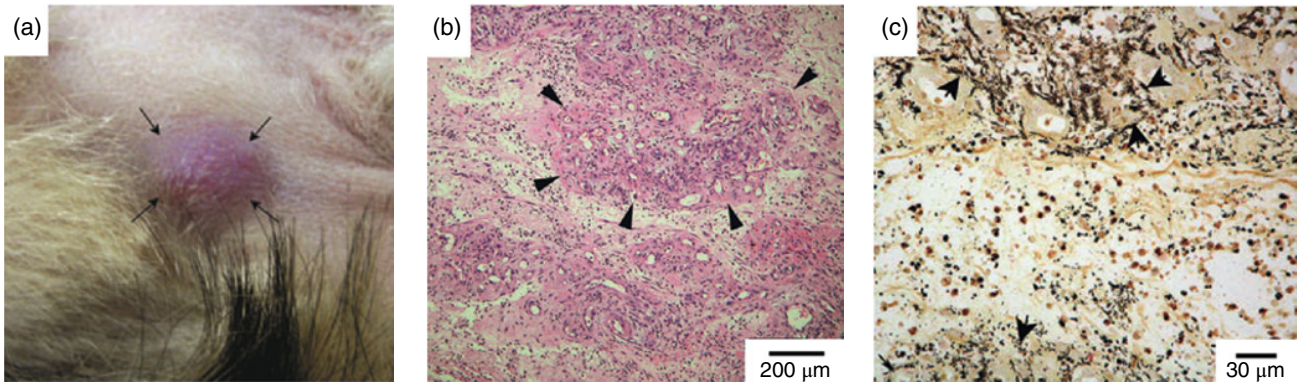


Figure 96.3 Bacillary angiomatosis in a dog. (a) Erythematous nodular skin lesion. (b) Proliferating capillaries (*arrowheads*) seen in skin nodules. (c) Bacteria present within the lesion, positively stained by Warthin–Starry. *Source:* Yager *et al*. (2010). Reproduced with permission of John Wiley & Sons.

Diagnosis

The most common laboratory abnormalities in dogs with endocarditis caused by *Bartonella* spp. are leukocytosis (78%), hypoalbuminemia (67%), thrombocytopenia (56%), and elevated liver enzymes (56%). Commonly, dogs infected with *Bartonella* spp. have laboratory abnormalities indistinguishable from other vector-borne diseases. Interestingly, although hyperglobulinemia occurs in dogs with bartonellosis, in one study, the presence of hypoglobulinemia was more frequent in *Bartonella*-infected dogs than dogs suspected of other vector-borne disease. In cats, laboratory abnormalities, when present, are limited to transient mild anemia, inflammatory leukogram, and/or eosinophilia in most cases. Hyperglobulinemia, particularly polyclonal gammopathy, is associated with *Bartonella* spp. in cats.

Because of the diversity of clinical presentations, the lack of an in-clinic rapid diagnostic test, and the limited diagnostic value of serology, diagnosis of canine or feline bartonellosis is a great challenge. For life-threatening illnesses such as endocarditis, myocarditis, and neurologic disease, clinicians should promptly investigate the presence of *Bartonella* spp. and presumptively treat for this infection, because specific antibiotic therapy is required for adequate management (see therapy section). The diagnostic approach of nonlife-threatening cases is based on ruling out other illnesses, including other vector-borne pathogens present in the area, submitting samples for microbiologic tests, banking samples, and evaluating response to antibiotic treatment, since laboratory test results may take weeks to months to become available. This author strongly recommend clinicians to bank samples at –20 °C (EDTA-blood, serum, plasma, tissues, etc.) collected prior to antibiotic therapy, which can be later tested by DNA and culture methods, because antibiotic therapy rapidly decreases the chances of detection of *Bartonella* spp. by these laboratory methods.

The microbiologic diagnosis of *Bartonella* infection is based on detection of *Bartonella* from whole blood,

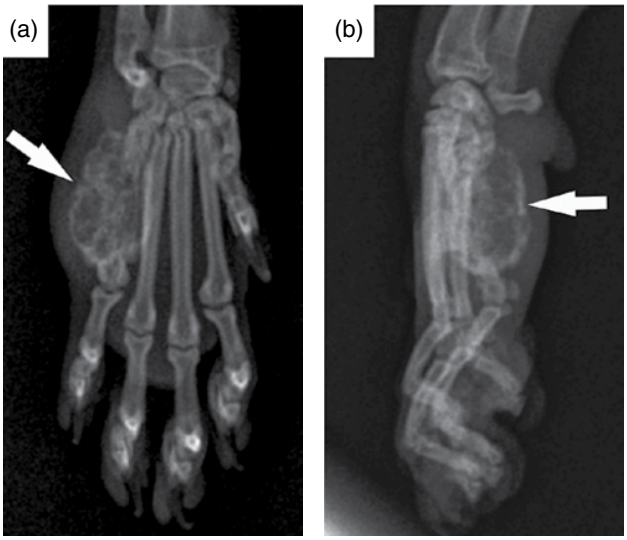


Figure 96.4 Radiograph images of the right forelimb of a cat with osteomyelitis due to *Bartonella vinsonii* subsp. *berkhoffii*. Dorsopalmar (a) and mediolateral (b) views show cortical bone destruction, irregular osteoproliferation and moderate thickening of the soft tissue (*white arrows*). *Source:* Varanat *et al.* (2009). Reproduced with permission of John Wiley & Sons.

Table 96.2 Average bacteremia level found in immunocompetent cats, dogs, and humans

	Cats	Humans	Dogs
Host type	Reservoir	Accidental	Accidental
Genome copies/μL	10^5–10^6	1–10	1–10
Bacteria per red blood cell (RBC)	1/10–100 RBC	$1/10^5$–$1/10^6$ RBC	$1/10^5$–$1/10^6$ RBC

Source: Breitschwerdt *et al.* (2010). Reproduced with permission of John Wiley & Sons.

other body fluids (cavitary effusions, synovial fluid, cerebrospinal fluid, etc.) or tissue specimens by specific polymerase chain reaction (PCR) assays or isolation by blood culture. While isolation remains the microbiologic gold standard, standard blood culture has limited diagnostic use because *Bartonella* spp. are fastidious bacteria that take months to grow in standard culture media. In addition, *Bartonella* bacteremia levels in dogs are very low (see Table 96.2) when compared to cats. Therefore, sensitivity of standard blood culture is very low in dogs. Consequently, preenrichment techniques are required in dog samples to increase the number of organisms to detection levels of PCR assays. Currently, the most sensitive diagnostic technique combines preenrichment culture in an insect-based liquid media (BAPGM) coupled with isolation in blood-based solid media and specific PCR testing of samples pre- and postenrichment culture, with DNA sequencing to confirm the species of *Bartonella* involved (so-called "enrichment PCR" platform). This approach is capable of detecting more than twice the number of infected dogs than the direct PCR from clinical specimens. In addition, using this platform allows initial results to be obtained as early as two weeks, with a number of new *Bartonella* species being detected in dogs. This assay is available at one commercial laboratory (www.galaxydx.com).

The direct detection of *Bartonella* DNA by PCR from blood, other body fluids or tissues is also available through commercial laboratories. Depending upon the assay design, this test may have high specificity but sensitivity is always limited by the magnitude of bacteremia (see Table 96.2). Therefore, direct PCR is a good diagnostic tool for feline samples, but it has limited sensitivity for canine samples. In a recent study, direct PCR from clinical specimens only detected 44.7% of dogs infected with *Bartonella* spp. Therefore, negative PCR results should never be used to rule out *Bartonella* spp. infection in dogs. It is important that clinicians choose a diagnostic laboratory that offers PCR testing for the entire *Bartonella* genus, not only for selected species, because a growing number of new *Bartonella* species has been described in sick and healthy companion animals recently.

Serology assays are available through veterinary laboratories, but have limited diagnostic use in dogs and cats because presence of antibodies does not correlate with infection. Only one-third to one-half of infected dogs and cats have detectable antibodies against *Bartonella* spp. Therefore, negative serologic testing does not rule out infection with *Bartonella* spp. Also, seropositivity does not indicate infection because only one-third of seropositive animals are bacteremic. When seropositive dogs are detected, serology may be helpful to monitor therapy progression, because many dogs that experience resolution of disease manifestation have decrease in antibody titers within 3–6 months following treatment. Serology has better diagnostic use in *Bartonella* endocarditis, which is usually associated with high antibody titers. There is some level of cross-reactivity among *Bartonella* spp. but multiple species-specific assays should be performed, including specific assays for *B. henselae*, *B. vinsonii* subsp. *berkhoffii*, *B. koehlerae*, and *B. clarridgeiae* (which cross-reacts with *B. rochalimae*).

Therapy

The optimal treatment protocol for *Bartonella* spp. infection in dogs and cats is unknown. Similar to other vector-borne infections, elimination of *Bartonella* may

not be achievable in all cases despite long-term use of antibiotics. Clinicians should focus on resolution of clinical abnormalities and monitor therapeutic success with serologic testing, PCR, and culture. Antibiotic therapy is recommended for two weeks past clinical resolution, which may require more than three months in some cases.

In dogs, while single therapy with doxycycline or azithromycin has been previously used with moderate success, rapid development of resistance has been documented. The current recommendation for clinically stable dogs is doxycycline at 5 mg/kg PO q12h for seven days, adding a second antibiotic such as a fluoroquinolone (enrofloxacin at 5 mg/kg PO q12h for 4–6 weeks) or rifampin (5 mg/kg PO p24h for 4–6 weeks). This stepwise approach is recommended in order to decrease the risk of Jarisch–Herxheimer reaction, which is caused by rapid death of bacteria and release of endotoxins with consequent increase of inflammatory cytokines in the bloodstream. Dogs that experience this reaction show lethargy, vomiting, and signs resembling bacterial sepsis that can last for a few days, and can be misinterpreted as an adverse drug event. Therefore, clinicians should not interrupt antibiotic therapy if a Jarisch–Herxheimer reaction occurs. Empirically, corticosteroids at antiinflammatory doses generally alleviate these signs.

Life-threatening diseases associated with *Bartonella* spp. infection in dogs (such as endocarditis, myocarditis, meningoencephalitis, etc.) should be treated with a combination of a fluoroquinolone or doxycycline with an aminoglycoside (amikacin at 15–20 mg/kg IV/IM/SC q24h), with constant monitoring of renal function. When discharged, these patients should receive doxycycline and enrofloxacin as described above.

In cats, administration of antibiotics generally limits bacteremia but does not eradicate the infection in all cats. The current recommendation from the American Association of Feline Practitioners (AAFP) is based on doxycycline at 5 mg/kg PO q12h or 10 mg/kg PO q24h for a minimum of four weeks. If a poor clinical response is observed in the first seven days of therapy, enrofloxacin at 5 mg/kg PO q24h or pradofloxacin at 3–5 mg/kg PO q24h should be used. It is currently unknown if these fluoroquinolones should be used in addition to doxycycline or as monotherapy in cats, as is recommended in dogs. Pradofloxacin has been shown *in vitro* to have superior activity against feline and human *Bartonella* isolates than enrofloxacin. Therefore, it is currently recommended for bartonellosis in cats. However, no information is currently available about the efficacy of pradofloxacin for canine bartonellosis.

Prognosis

Prognosis of bartonellosis in dogs and cats varies with the organ or system affected. For nonlife-threatening bartonellosis, anecdotal reports indicate moderate to good prognosis when adequate antibiotic therapy is instituted. *Bartonella* endocarditis has guarded prognosis, with dogs having shorter survival time than those with other causes of endocarditis.

Public Health Implications

Human bartonellosis ranges from benign self-limiting manifestation of cat scratch disease (CSD) to devastating hemolytic anemia seen in Oroya fever. The most common manifestation of human bartonellosis is cat scratch disease, followed by bacillary angiomatosis in immunocompromised patients and blood culture-negative endocarditis. Recent reports have associated *Bartonella* spp. infection with chronic neurologic disease, rheumatic signs, and small vessel syndrome. Direct transmission from infected dogs has not been documented, but they can be a reservoir for vector-mediated transmission to humans. Conversely, since *Bartonella* spp. can survive in flea feces for several days, cats can transmit *Bartonella* spp. to humans through scratching when cat claws are contaminated with infected flea feces.

The Centers for Disease Control and Prevention and the AAFP currently recommend the following steps to avoid human infection.

- Flea control should be initiated and maintained year round.
- If a family member is immunocompromised and a new cat is to be acquired, adopt a healthy cat >1 year of age and free from fleas.
- Immunocompromised individuals should avoid contact with cats of unknown health status.
- Be cautious about adding stray cats or cats from shelters to the household without controlling fleas.
- Cat claws should be trimmed regularly, but declawing of cats is generally not required.
- Scratches and bites should be avoided (including rough play with cats).
- Cat-associated wounds should be washed promptly and thoroughly with soap and water and medical advice sought.
- While *Bartonella* spp. have not been shown to be transmitted by saliva, cats should not be allowed to lick open human wounds.
- Keep cats indoors to minimize hunting and exposure to fleas and other possible vectors.

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97

Hemotropic *Mycoplasma*

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Etiology/Pathophysiology

The hemotropic mycoplasmas (hemoplasmas) are unculturable bacteria that parasitize red blood cells and can induce hemolysis, causing anemia. Commonly recognized feline and canine hemoplasma species are shown in Table 97.1. *Mycoplasma haemofelis* is the most pathogenic of the feline and canine species described, and can cause significant hemolytic disease in immunocompetent cats.

In cats, *Mycoplasma haemofelis* appears to be most pathogenic during acute infection, whereas chronic infection is not usually associated with significant anemia. *Candidatus* Mycoplasma haemominutum and *Candidatus* Mycoplasma turicensis infections are not usually associated with clinical signs, unless concurrent disease or immunusuppression exist in the host cat, such as feline leukemia virus (FeLV) infection, neoplasia. However, anemia due to these agents has occasionally been reported in immunocompetent cats. *Ca.* M. haemominutum has also been associated with the development of myeloproliferative diseases in cats with concurrent FeLV infection.

In dogs, *M. haemocanis* and *Ca.* M. haematoparvum infections are not often associated with hemolytic anemia unless infection occurs in a splenectomized host (particularly for *M. haemocanis*) or in association with concurrent disease or immunosuppression.

Asymptomatic carrier status can exist with all of the hemoplasma species, and so the detection of hemoplasma infection is not always indicative of clinical disease associated with that species.

Epidemiology

The prevalence of the commonly recognized feline and canine hemoplasma species is shown in Table 97.1; these vary considerably due to the differing populations of cats and dogs sampled in studies used to generate these data. Retroviral-infected cats are also usually found to be at increased risk in studies, although results are variable for FeLV and feline immunodeficiency virus (FIV). A recent study in the United States reported a low prevalence of canine hemoplasma infection in dogs.

The prevalence of feline hemoplasma infections is increased in cats that are male, non-pedigree and with access outdoors.

The natural route of transmission of hemoplasma infection in the field has not yet been determined but the clustered geographic distribution of infection in some studies supports the role of an arthropod vector in hemoplasma transmission. The cat flea, *Ctenocephalides felis*, has been implicated in feline hemoplasma transmission, but this has not been definitively proven in experimental studies, and transmission of *M. haemocanis* by the brown dog tick, *Rhipicephalus sanguineus*, has been suggested.

Studies have successfully transmitted feline hemoplasma infection via subcutaneous inoculation of blood containing low numbers of organisms, suggesting that transmission by aggressive interaction (e.g., fights) in the field is possible. Blood transfusion is another potential route of transmission, and blood donors should be screened for hemoplasma infection. Vertical transmission may also occur.

Signalment

Older cats are more likely to be infected with *Ca.* M. haemominutum whilst younger cats are more likely to show disease due to *M. haemofelis* infection. Canine hemoplasma infections appear to be more common in kennel-housed dogs, younger dogs, and dogs with mange.

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Table 97.1 Hemoplasma species, their prevalence and pathogenicity

Hemoplasma	Prevalence	Pathogenicity summary
Mycoplasma haemofelis	0.4–46.6%	Can result in hemolytic anemia in immunocompetent cats
Candidatus Mycoplasma haemominutum	8.1–46.7%	Can result in a drop in erythrocyte parameters but not usually severe enough to cause anemia unless cat has concurrent disease or is immunocompromised, e.g., retrovirus infection
Candidatus Mycoplasma turicensis	0.4–26%	
Mycoplasma haemocanis	0–45%	Hemolytic anemia primarily seen in splenectomized dogs, and occasionally in immunocompromised dogs (e.g., with neoplasia)
Candidatus Mycoplasma haematoparvum	0–33%	

History and Clinical Signs

When anemia results from hemoplasma infection, historical features can include lethargy, inappetence, pallor, weakness, pica, and weight loss. In immunocompromised hosts, evidence of concurrent disease is present. Dogs may have a history of splenectomy.

Clinical signs can include pyrexia, weakness, pallor, tachypnea, tachycardia (sometimes with a hemic murmur), bounding pulses, dehydration, cardiac murmurs, sometimes splenomegaly (in nonsplenectomized hosts) and, occasionally, jaundice.

Diagnosis

Acute hemoplasma infections are typically associated with a regenerative anemia with reticulocytosis, macrocytosis, polychromasia, and anisocytosis. However, the anemia may be nonregenerative if the animal is sampled early in the disease process (i.e., during the preregenerative phase) or if concurrent disease is present that inhibits regeneration (e.g., concurrent FeLV infection, neoplasia).

Acute *M. haemofelis* and *M. haemocanis* infections can be associated with the presence of persistent saline autoagglutination or positive Coombs' testing, indicating the presence of erythrocyte-bound antibodies. Autoagglutination may be noted on blood smear examination but the contribution of such antibodies to the development of hemoplasma-associated anemia has not been confirmed.

Serum biochemistry may reveal elevated liver parameters (ALT and AST) due to anemia-associated hypoxia, mild to moderate hyperbilirubinemia due to hemolysis, and prerenal azotemia due to dehydration. Hyperproteinemia may occur. Hemoplasmas are currently unculturable *in vitro*.

Cytologic detection of hemoplasma organisms on blood smears is occasionally possible but this is known to be very insensitive and shows poor specificity, and cytology cannot differentiate between hemoplasma species. When organisms are visible, they appear as small basophilic organisms on the surface of erythrocytes with Romanowsky-based stains (e.g., Wrights', Diff-Quik™). *M. haemocanis* has a tendency to form chains on the surface of erythrocytes, and so may be easier to differentiate from stain artifacts and other erythrocyte inclusions with which hemoplasmas are confused.

Polymerase chain reaction (PCR) assays are usually sensitive and specific, if designed appropriately, for the diagnosis of hemoplasma infection, and species-specific assays exist for both dogs and cats. EDTA-anticoagulated blood is usually the appropriate sample type for PCR. Real-time PCR (qPCR) assays are now increasingly used, and these allow for quantification of hemoplasma organism numbers (Figure 97.1), as well as detection of infection. Organism numbers in feline hemoplasma infections are often high during acute infection but it should be noted that large fluctuations in blood organism numbers can occur over time in some *M. haemofelis*-infected cats, meaning that qPCR results may not be correlated with anemia.

In addition, PCR results may be negative in an infected cat if a sample is obtained when the number of circulating organisms is very low, below the limit of detection of the PCR assay. Furthermore, the existence of asymptomatic carrier cats for all hemoplasma species means that the PCR results should always be interpreted in conjunction with the patient's clinical signs, the degree and nature of the anemia present, and any concurrent signs or diseases that could be contributing to the clinical presentation.

Therapy

Therapy for hemoplasmosis is required if infection is diagnosed in an animal with clinical signs and clinicopathologic changes consistent with hemoplasma infection. However, no treatment regime has yet been described that consistently eliminates hemoplasma infection with all species and the aim of most treatment protocols is resolution of clinical signs associated with infection.

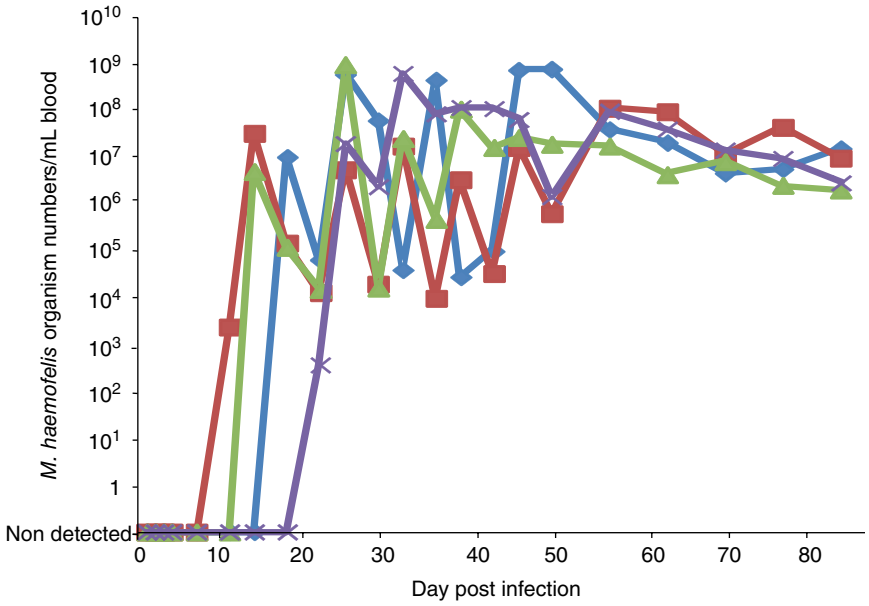


Figure 97.1 Hemoplasma organism numbers in the blood of four cats infected with 10^3 *M. haemofelis* organisms by subcutaneous inoculation on day 0 post infection. Cats infected with *M. haemofelis* often show marked fluctuations in blood organism numbers, especially during early infection. Such fluctuations, in the absence of treatment, should be considered when interpreting quantitative PCR results in *M. haemofelis*-infected cats. Longer term fluctuations in organism numbers in the blood are seen in some *M. haemofelis*-infected cats. In contrast, cats infected with *Ca.* M. haemomintum and *Ca.* M. turicensis do not show these blood organism number fluctuations at any stage of infection.

A number of antibiotics, notably tetracyclines (primarily doxycycline at 10 mg/kg once daily PO or 5 mg/kg twice daily PO; as some formulations have been associated with esophagitis following incomplete swallowing, all doses should be followed with food or water) and fluoroquinolones (e.g., marbofloxacin 2–5.5 mg/kg once daily PO, pradofloxacin 5 mg/kg once daily PO), have been shown to be effective in reducing feline hemoplasma (especially *M. haemofelis*) organism numbers and cause resolution of clinical signs. Courses of two weeks are usually recommended although some have suggested that longer treatment courses (up to six weeks) increase the likelihood of eliminating infection. Pradofloxacin may be more effective at clearing *M. haemofelis* than doxycycline. One recent study has suggested that clearance of *M. haemofelis* infection may be possible using 28 days of doxycycline followed by marbofloxacin for 14 days if the cats remained PCR positive.

Only limited information is available regarding the response of canine hemoplasma infections to antibiotic therapy. Tetracycline or fluoroquinolone treatments have both been associated with clinical improvement, but infection has sometimes persisted.

Ideally, response to antibiotic treatment in both cats and dogs should be monitored by qPCR to ensure organism numbers are decreasing with therapy but clinical improvement usually occurs within 2–3 days of effective treatment.

Affected dogs and cats may also require aggressive supportive treatment with crystalloids or blood products (blood transfusions).

Corticosteroids have been recommended as adjunct treatment for hemoplasmosis, to treat the immune-mediated component of anemia. However, the vast majority of hemoplasma-infected cats, including those that have erythrocyte-bound antibodies confirmed, respond to antibiotic treatment and supportive care alone without the need for corticosteroids. Indeed, immunosuppressive doses of corticosteroids have been used experimentally to exacerbate hemoplasma infection, so their routine use is not advised.

In view of the potential for vector transmission of hemoplasmas, control for fleas and ticks should also be instigated.

Prognosis

With prompt and appropriate therapy, the prognosis for feline and canine hemoplasmosis is good. However, the disease can be fatal if untreated, due to severe hemolytic anemia, collapse, and death.

Public Health Implications

Polymerase chain reaction methods have recently documented human hemoplasma infections and some have documented infection with veterinary hemoplasma species such as *Ca.* M. haematoparvum. In view of this, blood from potentially infected animals should be handled with care and vector control initiated. Future studies should evaluate the zoonotic potential and transmission of these emerging pathogens.

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98

Nonhemotropic *Mycoplasma*, *Ureaplasma*, and L-Form Bacteria

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Etiology

Mycoplasmas (general name for members of the class *Mollicutes*) are unusual bacteria representing the smallest and simplest self-replicating organisms. They are distinguished from ordinary bacteria by their complete lack of a cell, resulting in cellular pleomorphism and resistance to cell wall-inhibiting antimicrobials. The lack of a protective cell wall also makes mycoplasmas fragile outside their hosts. Due to their extremely small genome size, mycoplasmas possess limited anabolic and metabolic capabilities and maintain intimate parasitic lifestyles, depending on nutrients from their host cell environment. To keep this parasitic mode of life, mycoplasmas have developed sophisticated mechanisms to colonize their hosts and resist host defense. A highly dynamic, versatile membrane surface architecture appears to be crucial for their survival, and for establishing and maintaining a subtle relationship with their host. Certain mycoplasmas are capable of entry into nonphagocytic cells, providing them with the ability to resist host defenses or antibiotic treatment, which may contribute to chronic infection.

Nonhemotropic mycoplasmas usually exhibit a rather strict host and tissue specificity with predilection for mucous membranes of the respiratory and urogenital tract. Pathogenic mycoplasmas are not considered highly virulent and mostly cause mild, slowly progressive, chronic infections. Host cell damage and the resulting clinical manifestations appear to be mainly due to host immune reactions and inflammatory responses rather than to direct toxic effects of mycoplasma components.

Nonhemotropic mycoplasmas that have been isolated from cats and dogs include species within the genera *Mycoplasma*, *Ureaplasma*, and *Acholeplasma*. Some canine and feline mycoplasmas are considered mere commensals, but certain members are proven pathogens or play an etiologic role as opportunists in miscellaneous conditions (Table. 98.1).

Little is known about the virulence factors of canine and feline mycoplasmas so far. However, the availability of the complete genome of two canine *Mycoplasma* species (*M. canis, M. cynos*) will certainly increase understanding of their pathogenic properties in the future. Recently, a hemagglutinin that is probably involved in cytadherence to host cells has been identified and characterized in *M. cynos*. Furthermore, a secreted sialidase that presumably promotes colonization and tissue invasion has been proposed as a candidate virulence factor of *M. canis* and *M. cynos*. Its expression in canine mycoplasmas varies significantly among strains which may contribute to the variable spectrum of clinical manifestations and disease outcomes. Intracellular localization of *M. canis* has also been demonstrated which may contribute to chronicity of infection or perturbation of cell function and integrity.

L-forms are cell wall-deficient morphotypes of normal bacteria that resemble mycoplasmas. L-forms can be generated from many bacterial species by treatment with lysozyme or by exposure to beta-lactam antibiotics or host immune responses. Knowledge of the clinical significance of L-form bacteria is fragmentary and their role as a cause of disease is still under debate.

Epidemiology

Mycoplasmas are common inhabitants of the oropharynx and upper respiratory tract of dogs and cats wherein they are thought to be part of the normal bacterial flora. Mycoplasmas have been isolated from lungs of dogs and cats with pneumonia, are shown to be absent in the lungs

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Table 98.1 Nonhemotropic mycoplasmas frequently isolated from domestic dogs and cats

Species	Primary host	Primary colonization site	Diseases associated with or caused by mycoplasmas isolated from domestic dogs and cats
Mycoplasma cynos	Domestic dogs (canine mycoplasmas)	ONP, RT, UGT	CIRD, tracheobronchitis, bronchopneumonia, pyothorax
Mycoplasma canis		ONP, RT, UGT	Urethritis, epididymitis, orchitis in male dogs; endometritis, metritis, adverse pregnancy outcomes in female dogs
Mycoplasma edwardii		ONP, RT, UGT	Polyarthritis[a], meningoencephalitis[a]
Mycoplasma molare		ONP, UGT	ND
Mycoplasma maculosum		ONP, RT, UGT	ND
Mycoplasma opalescens		ONP, UGT	ND
Mycoplasma mucosicanis		ONP, RT, UGT	ND
Mycoplasma spumans		ONP, RT, UGT	Polyarthritis[a]
Ureaplasma canigenitalium		UGT	Infertility in male dogs[a]
Mycoplasma felis	Domestic cats (feline mycoplasmas)	C, ONP, RT	Conjunctivitis, keratitis[a], URTD, bronchopneumonia, pyothorax, polyarthritis, meningoencephalomyelitis[a]
Mycoplasma gateae		ONP, RT	Polyarthritis, bronchopneumonia[a]
Mycoplasma feliminutum		ONP, RT	ND
Ureaplasma felinum		ONP	ND
Ureaplasma cati		ONP	ND
Mycoplasma arginini	Various (ubiquitous mycoplasmas)	ONP, RT, UGT	ND
Acholeplasma laidlawii		UGT	ND

C, conjunctiva; ND, not defined, likely to be a commensal; ONP, oro- and nasopharynx; RT, respiratory tract; UGT urogenital tract.
[a] Single reports.

of healthy cats but can be isolated from the lungs of healthy dogs. Younger, group-living animals with syndemic viral/bacterial infections or underlying diseases that impair defense mechanisms are more likely to be infected by mycoplasmas. They are efficiently transmitted through oronasal contact with aerosolized respiratory secretions or contact with freshly contaminated fomites.

Mycoplasmas are among the recognized normal flora of the vagina and prepuce of dogs but are rarely isolated from the feline urogenital tract. They have been associated with canine urogenital diseases in subpopulations of colonized individuals. Reasons and risk factors for disease development and progression are unknown. Canine genital mycoplasmas may be transmitted via sexual intercourse, artificial insemination or orogenital contact. Mycoplasmas may also be transmitted vertically to fetus or offspring by ascending intrauterine infection, hematogenously acquired placental infection, or during passage through the birth canal.

Signalment

Younger, immunosuppressed dogs and cats are more likely to be affected by mycoplasmas and develop more severe diseases.

History and Clinical Signs

Ocular *Mycoplasma* Infections in Cats

Mycoplasma felis is considered a major pathogen in conjunctivitis of cats. The prevalence rate of the agent in ocular swabs taken from cats displaying conjunctivitis was 9.6% or 25% which is significantly higher than the respective rates of 2.3% or 0% present in clinically healthy cats. In contrast, *M. arginini* and *M. gateae* more often exist on the conjunctival surface of healthy cats. Experimental infections of *M. felis* have produced conjunctivitis only in young cats or when a large inoculation

dose was used. Natural *Mycoplasma* conjunctivitis predominantly occurs when infected cats are housed in groups or in kittens soon after weaning. The clinical signs observed may vary in severity and have been described as blepharospasm, conjunctival hyperemia, chemosis, and serous discharge followed by mucoid to sticky exudate. The cornea is usually not involved; however, *M. felis* and *M. gateae* have been occasionally associated with ulcerative keratitis and/or keratomalacia.

Respiratory *Mycoplasma* Infections in Cats

Mycoplasmas have been associated with chronic and acute feline upper respiratory tract disease (URTD) by epidemiologic evaluation, but available data are more inconclusive hypotheses than definite proofs of causality. Studies have also suggested that approximately 22% of cats with lower airway disease may have a concurrent *Mycoplasma* infection.

Experimental challenge with *M. felis* induced pneumonia in kittens, emphasizing its role as a primary pathogen in the lower respiratory tract. Naturally occurring infections with *M. felis* have been increasingly reported in the feline host associated with suppurative bronchitis and/or pneumonia. Radiographic or computed tomography (CT) findings may include diffuse interstitial pulmonary disease similar to that observed in adult human patients with *M. pneumoniae* pneumonia. Cats with concurrent pleural effusion show minimal signs of dyspnea and a nonodorous fluid is expected with uncomplicated *Mycoplasma* pyothorax.

Respiratory *Mycoplasma* Infections in Dogs

Mycoplasmas have been isolated from 78% of tracheobronchial lavages of younger dogs with pulmonary disease but may also be present in the lower respiratory tract of healthy individuals (20–25%). Consequently, the role of certain canine *Mycoplasma* species as pathogens in canine pulmonary disease is still a subject of controversy. Experimental infection with *M. canis*, *M. gateae*, and *M. spumans* failed to produce pulmonary disease. However, *M. cynos* has been consistently associated with canine respiratory diseases, including tracheobronchitis and bronchopneumonia, conditions that have been reproduced experimentally. A more recent study noted a correlation of *M. cynos* with canine infectious respiratory disease (CIRD) in younger dogs (<1 year). Dogs acquired infection during the first two weeks after being kenneled and seroconversion to *M. cynos* was correlated with the development of clinically respiratory disease. Further evidence of the primary pathogenic role of *M. cynos* was its isolation as sole pathogen from a litter of pups with severe respiratory disease. Clinical findings were fever, productive cough, and leukocytosis with a left shift. Radiographs featured alveolar and bronchointerstitial pulmonary densities and mild pleural effusion. Infection was fatal for some pups and necropsy findings were mucopurulent airway exudates and hemorrhagic fibrinous necrotizing bronchopneumonia. *M. cynos* was abundantly demonstrated at neutrophilic inflammatory sites using immunohistochemistry.

Urogenital *Mycoplasma* Infections in Dogs

Mycoplasmas are commonly present in the lower urogenital tract of dogs. They have occasionally been associated with canine reproductive diseases including poor conception rates, early embryonic death, fetal resorption, abortion, weak pups, and neonatal death. *M. canis* and *U. canigenitalium* are the species most consistently associated with canine genital mycoplasmosis. *Mycooplasma canis* has been isolated from dogs with urogenital disease and infertility, despite prolonged antibiotic therapy. It has also been cultured from the prostate, epididymis, and chronically inflamed bladder wall. Experimental infection with *Mycoplasma canis* produced urethritis, prostatitis or epididymitis in males and endometritis or metritis in females. In a single study, *U. canigenitalium* was associated with infertility in male dogs. Nevertheless, as conclusive evidence is lacking, further studies are required to establish whether *M. canis* or *U. canigenitalium* is linked to genital tract infections and infertility.

Arthritis in Cats and Dogs Caused by Mycoplasmas

Only a few cases of naturally occurring mycoplasma mono- and polyarthritis in cats (*M. felis*, *M. gateae*) and dogs (*M. edwardii*, *M. spumans*) have been documented so far. In most cases, predisposing factors such as immunosuppressive therapy, acquired immunodeficiency or traumatic bites have been identified. The pathogenic potential of *M. gateae* in cats, however, has been substantiated by intravenous injection resulting in polyarthritis.

Mycoplasma Central Nervous System Infections in Cats and Dogs

Mycoplasma felis has been isolated from brain and spinal cord sections of a young cat with meningoencephalomyelitis. A similar infection has been documented in a young dog with suppurative meningoencephalitis caused by *M. edwardii*, and a penetrating wound close to the skull was suspected as the source of infection.

Abscesses and Cellulitis in Cats Caused by Mycoplasmas and L-Form Bacteria

Abscess formations caused by mycoplasmas presumably introduced by bite wounds have been reported in cats. Nonodorous, nondegenerate, neutrophilic, gram stain-negative exudates are characteristic for *Mycoplasma* abscesses. L-form bacteria have been isolated from cats with persistently draining cellulitis and synovitis. Usual sources of infection with L-form bacteria have been penetrating bite wounds or surgical incisions. Spread of infection can occur manifested by polyarthritis or distant abscess formation.

Diagnosis

The fragile nature of mycoplasmas mandates careful attention to specimen collection, inoculation of transport medium, and proper transportation and shipping conditions. Laboratory diagnosis of canine and feline mycoplasmas is commonly achieved by cultivation (Figure 98.1) which also allows quantification or by polymerase chain reaction (PCR) if a particular *Mycoplasma* species is sought.

Cultivation is, however, expensive and requires specialized media and expertise not commonly available at all laboratories. Culture results are usually available within 2–4 days for most canine and feline mycoplasmas, but definitive species identification requires additional tests which traditionally include serologic methods depending on specific antisera to each individual *Mycoplasma* species. Such specific antisera are not readily available in most diagnostic laboratories and multiple cross-reactions may occur.

To circumvent the limitations of serologic differentiation methods, more accurate and rapid identification schemes employing PCR-restriction fragment length polymorphism (RFLP) of the 16S-23S intergenic region have been developed. Alternatively, PCR-denaturing gradient gel electrophoresis (DGGE) may be applied, enabling primary detection and differentiation of mycoplasmas in clinical material even if mixed infections occur. Recently, matrix-assisted laser desorption/ionization time of flight (MALDI TOF) mass spectrometry has become an excellent method for the identification and differentiation of animal mycoplasmas, representing a promising alternative to the currently practiced cumbersome diagnostics. No serologic assays for the detection of immune responses to canine or feline mycoplasmas have been standardized and made commercially available so far.

Therapy

In most diagnostic laboratories, susceptibility testing of mycoplasmas to antimicrobials is not available. As is known, mycoplasmas are inherently resistant to beta-lactam antibiotics. Treatment with nonbeta-lactams such as macrolides, tetracycline, chloramphenicol, clindamycin or fluoroquinolones should be effective against most canine and feline mycoplasmas providing that animals are treated for an extended period. For example, in cats with URTD, *M. felis* was eliminated with either pradofloxacin or doxycycline treatment for 42 days. No vaccines are currently available to prevent *Mycoplasma* infections in dogs and cats although they are successfully used in other animals.

Public Health Implications

Due to their rather strict host specificity, mycoplasmas of the dog and cat are not considered a major public health risk. Zoonotic infections have only been occasionally documented, predominantly involving immunosuppressed individuals.

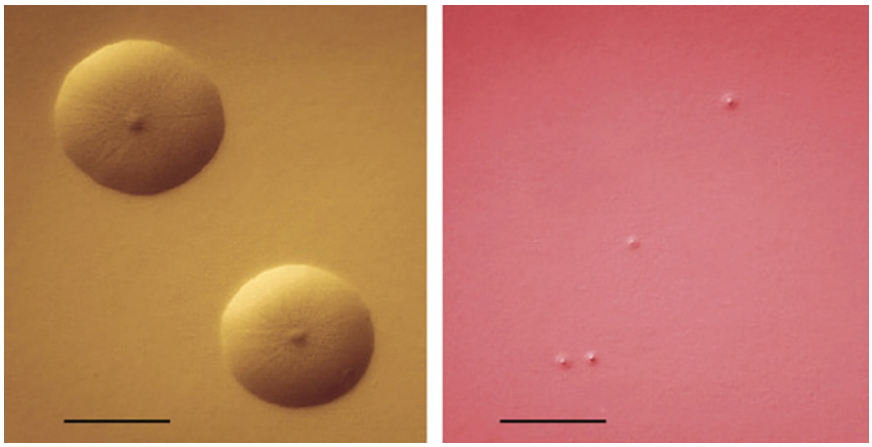


Figure 98.1 Cultivation.

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99

Spotted Fever and Typhus Group Rickettsia

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Etiology/Pathophysiology

Spotted Fever Group (SFG) and Typhus Group (TG) *Rickettsia* are alpha-proteobacteria belonging to the genus *Rickettsia*, family Rickettsiaceae, order Rickettsialis. There are over 20 species of SFG *Rickettsia*, whereas the TG *Rickettsia* include only *R. typhi* and *R. prowazekii*. The division of *Rickettsia* into groups is based on phenotypic and, more recently, genotypic characteristics.

One of the clinically important phenotypic characteristics that differentiates the SFG and TG *Rickettsia* is their vectors. Members of the SFG *Rickettsia* are primarily transmitted by ticks whereas *R. typhi* is transmitted by fleas, and *R. prowazekii* is transmitted by lice and other ectoarasites. Interestingly, *R. felis,* a *Rickettsia* that has characteristics of both TG and SFG, is transmitted by both fleas and ticks.

Spotted Fever Group *Rickettsia* have both pathogenic and nonpathogenic species. The two most pathogenic and well-studied members of the SFG *Rickettsia* are *R. rickettsii*, the cause of Rocky Mountain and Brazilian spotted fever, and *R. conorii*, the cause of Mediterranean spotted fever (MSF) in people. Infections with many other species of SFG *Rickettsia* have been described in people with spotted fever-type illness in recent years. Some of these new rickettsioses are caused by newly discovered species while others have been associated with species previously thought to be nonpathogenic endosymbionts of ticks. Discovery of the pathogenicity of atypical species has been greatly facilitated by advances in molecular biology that allow easy and accurate differentiation of species.

Illness caused by *R. rickettsii* is very well characterized in dogs and is quite similar to Rocky Mountain spotted fever (RMSF) in people. Recently, a spotted fever-type illness associated with *R. conorii* infection was also described in dogs. Many recent studies have shown that exposure to and infection with additional species of SFG *Rickettsia* occur in dogs. The ability for these additional species to cause illness has not been well characterized to date. However, it is important for practitioners to be aware of their potential as disease-causing agents.

The ability of SFG *Rickettsia* to cause disease in cats is not known. Antibodies to several SFG *Rickettsia* have been detected in cats and recently, DNA from some SFG *Rickettsia* species most closely resembling *R. massiliae* Bar29 and *R. conorii* has been amplified from naturally infected cats. Although antibodies to *R. rickettsii* are detected in cats in endemic areas, active infection and associated clinical signs have not been documented. Thus, whether RMSF occurs in cats is not known.

Rickettsia felis, a SFG *Rickettsia* transmitted by the cat flea (*Ctenocephalides felis*), is an important cause of illness in people. *Rickettsia felis* has been amplified from the blood of dogs and experimentally infected cats. Although the organism has been detected in the gingiva of naturally infected cats, bacteremia in naturally infected cats has not been documented. No association between infection or seropositivity and illness in cats or dogs has been documented.

The ability of TG *Rickettsia* to cause disease in cats and dogs is also not known. However, *R. typhi*, the cause of murine typhus in people, infects cat fleas and has been detected in the blood of cats and dogs. Cats and dogs in domestic areas commonly have antibodies to *R. typhi*. Whether the organism causes disease in dogs or cats remains to be determined.

Because it is well characterized and the most common cause of illness caused by *Rickettsia* species in small animals, canine RMSF caused by *R. rickettsii* is the focus of the remainder of this chapter. However, practitioners should keep in mind that infection and illness with other SFG and TG *Rickettsia* could occur in cats and dogs. Importantly, the flea and tick vectors that transmit these organisms must be controlled on pets to protect their human companions.

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Rickettsia rickettsii in Dogs

Rickettsia rickettsii is a tick-transmitted obligately intracellular coccobacillus that infects endothelial cells. Because it is endotheliotropic, vasculitis is a major clinical manifestation of infection. This results in disordered primary hemostasis, tissue edema, hypovolemia, and microthrombosis. Thrombocytopenia is common in dogs, and occurs due to vasculitis and antibody-mediated platelet destruction. Increased vascular permeability and associated edema and hypovolemia result from disruption of endothelial cell adherens junctions and endothelial cell death, and expression of inflammatory cytokines. Organisms also induce changes in platelet adherence to endothelium, increased tissue factor expression, and increased plasminogen activator inhibitor, and cause the release of von Willebrand factor, all of which likely contribute to microthrombosis.

Epidemiology

Rickettsia rickettsii is transmitted by several hard (ixodid) ticks including *Dermacentor variabilis* (American dog tick), *Dermacentor andersoni* (Rocky Mountain wood tick), *Amblyomma americanum* (Lone Star tick), *Amblyomma cajennense* (Cayenne tick), and *Rhipicephalus sanguineus* (brown dog tick). Historically, the geographic distribution of RMSF in the US has primarily followed that of its primary tick vectors, *D. variabilis* and *D. andersoni*. In endemic areas, most cases of canine and human RMSF are reported from April through October, months of peak tick activity. Dogs living outdoors, particularly those with access to shrubs and high grass, are at increased risk.

Increasing travel and the effects of climate change on tick populations and habitat are changing the geographic distribution of RMSF and other emerging infectious diseases. For example, a recent fatal outbreak of RMSF in people occurred in a nonendemic area of Arizona. The outbreak was caused by the ubiquitously distributed tick *R. sanguineus*. Retrospectively, it was shown that infection existed in the dog population before the fatal outbreak in people. *Rhipicephalus sanguineus* is the primary vector of *R. rickettsii* in Mexico. In South America, *Amblyomma* species are the main vectors. Recently, *A. americanum* was implicated in the transmission of *R. rickettsii* to a person in North Carolina. In fact, the importance of *D. variabilis* as a vector for RMSF in endemic areas of the US has recently come into question. Veterinarians should consider the possibility of transmission by novel vectors if dogs present with clinical signs of RMSF in nonendemic areas or at an unusual time of year.

Dogs are sentinels for spotted fever rickettsioses in people. RMSF in dogs can occur before, or coincide with, outbreaks of RMSF in people in the same household or community. Similarly, there is an increased risk of RMSF in people living near seropositive dogs in endemic areas. It is likely that as more species of SFG *Rickettsia* are shown to infect dogs, they will play a role as sentinels for these novel rickettsial infections as well.

Signalment

Young and pure-bred dogs are overrepresented in some but not other studies. Although some studies suggest male dogs may be at increased risk, no definitive sex predilection has been documented.

Diagnosis

Clinical Signs

The clinical signs and response to therapy for canine RMSF are very similar to RMSF in people. It is very important to be familiar with clinical signs of the disease because treatment must begin prior to diagnostic confirmation. RMSF is primarily an *acute* disease. Chronic infection has not been documented in naturally infected dogs. However, a recent experimental study documented an apparent relapse of clinical signs and bacteremia in a dog after treatment. Low numbers of SFG *Rickettsia* typically circulate in blood free or in detached endothelial cells for a short period of time after infection (13 days). This is the time when clinical signs are observed. Coinfection with other vector-borne agents is common and should be considered if the clinical presentation is atypical, there is an incomplete response to doxycycline therapy or clinical signs have been present chronically.

Because *R. rickettsii* infects endothelial cells, *vasculitis* is the major clinical sign associated with infection. However, due to variation in the extent and severity of vascular injury among dogs, a range of signs can occur and disease manifestations are initially mild and nonspecific. The nonspecific nature of the clinical signs makes diagnosis difficult. This is very important because a delay in diagnosis and appropriate antimicrobial therapy dramatically increases morbidity and mortality in people and dogs. Therefore, the clinician must have a high index of suspicion in order to correctly diagnose and treat this disease. This can be difficult because often there is no known history of a tick bite. Lethargy and anorexia are common, and may be the only clinical signs. Vomiting and diarrhea occur frequently. Melena may also occur. Central nervous system (CNS) abnormalities including

vestibular disease and seizures may be observed. Dramatic and rapid weight loss has been described.

On physical examination, fever and ocular abnormalities are common. Ocular signs may include mucopurulent discharge, scleral and conjunctival injection and hemorrhage, conjunctivitis, uveitis, retinal hemorrhage, and retinitis. Lymphadenomegaly, splenomegaly, nasal discharge, epistaxis, tachypnea, dyspnea, petechiae, ecchymosis, peripheral edema, hyperemia, and necrosis may occur. Cutaneous lesions are not always present in dogs or people. Orchitis and scrotal edema, hyperemia, and epididymal pain are common in intact male dogs. Generalized myalgia and arthralgia can be observed. CNS abnormalities can be focal or generalized and include paraparesis, tetraparesis, ataxia, hyperesthesia, central or peripheral vestibular signs, stupor, seizures, and/or coma. Arrhythmias may be noted. Microvascular hemorrhage, thrombosis, hypotension, oliguric renal failure, cardiovascular collapse, and brain death occur terminally. Thoracic radiographs may show an unstructured interstitial pattern.

Laboratory Testing

Complete blood count (CBC) commonly shows thrombocytopenia but it does not occur in all dogs with RMSF. Leukopenia or leukocytosis may be observed. Neutrophils may have toxic change. Nonregenerative anemia may be present. Serum biochemical abnormalities may include hypoalbuminemia, elevated alkaline phosphatase, hyponatremia, and mild hyperbilirubinemia. Prolonged activated partial thromboplastin time (APTT), prothrombin time (PT), and elevated fibrinogen and fibrin degredation products may occur. Disseminated intravascular coagulation (DIC) is uncommon. Urinalysis results are variable and may include proteinuria, hematuria, bilirubinuria, and pyuria. Granular casts can be observed. Cerebrospinal fluid (CSF) analysis may reveal a mixed cellular, neutrophilic, or lymphocytic pleocytosis. Arthrocentesis may reveal a neutrophilic polyarthritis. Cytologic examination of enlarged lymph nodes is consistent with reactive lymphoid hyperplasia.

Active infection with a SFG *Rickettsia* is confirmed in a patient with compatible and clinical signs and demonstration of the organism using polymerase chain reaction (PCR) or immunohistochemistry, or documentation of seroconversion. Importantly, serology and PCR can be negative at the time of testing because clinical signs can occur before seroconversion, and organisms circulate transiently in blood in low numbers. Repeat testing using PCR can increase sensitivity. Infection also cannot be definitively diagnosed by documenting a single positive titer because of cross-reactivity with nonpathogenic SFG *Rickettsia*, and the potential for long-lived antibody levels after infection. Therefore, documenting a fourfold change in titer is necessary to confirm acute infection with SFG *Rickettsia* using serology. That said, a single high titer in the context of acute and compatible clinical signs and an appropriate response to therapy is suggestive of infection.

Of note, most antibody-based diagnostic tests do not differentiate among species of SFG *Rickettsia*. Some PCRs can differentiate among species of infecting *Rickettsia* while others only amplify rickettsial DNA targets conserved among several species. Veterinarians should check with their laboratory regarding the sensitivity and specificity of a given PCR, keeping in mind that *in vitro* (absolute) sensitivity is higher than *in vivo* sensitivity due to low circulating copy numbers of *Rickettsia* in blood. Therefore, PCR can enable definitive diagnosis but a negative PCR does not rule out infection. It is also important to note that PCRs that specify that they target SFG *Rickettsia* may not detect TG *Rickettsia*.

Therapy

Appropriate antibiotic therapy must be instituted immediately based on clinical suspicion, before diagnostic tests confirm infection. Inappropriate or delayed antibiotic therapy may increase morbidity and mortality. Treating with an antibiotic that is not effective allows rapid progression. Some antibiotics such as trimethoprim sulfa may worsen disease in people. Doxycycline (5 mg/kg PO or IV q12h) is the treatment of choice. It is highly effective at eliminating *R. rickettsii*. Furthermore, it provides effective empiric therapy for *A. phagocytophilum*, *Ehrlichia* spp., and *Borrelia burgdorferi*, agents that are differential diagnoses or may co-infect patients with RMSF. Enrofloxacin has been shown to be effective against *R. rickettsii* in experimentally infected dogs. Chloramphenicol was effective in experimentally infected dogs but may be less effective in treating RMSF in people. The duration of therapy for RMSF is short, with 7–14 days being adequate in most cases. Treatment a few days past defervesence is recommended. A longer course of (doxycycline) therapy is recommended for patients co-infected with an *Ehrlichia* sp. or *B. burgdorferi*.

Many patients require hospitalization. Intravenous antibiotic therapy may be necessary in debilitated patients. Aggressive supportive care for complications such as thrombosis, CNS deficits, and gastrointestinal signs may be necessary. Due to the loss in vascular integrity, fluids should be administered with caution and colloids may be warranted in some cases. The use of corticosteroids in dogs with RMSF is controversial. Antiinflammatory and immunosuppressive doses did not affect overall outcome in experimentally infected dogs, but rickettsemia was prolonged in dogs concurrently treated with doxycycline and immunosuppressive

doses of corticosteroids. Antiinflammatory doses of corticosteroids have been used in dogs with severe CNS manifestations and may be necessary topically or systemically for treatment of ocular abnormalities.

Response to appropriate antibiotic therapy is very rapid (24–48 hours). Co-infection with *B. burgdorferi*, *Ehrlichia* spp., *Babesia* spp., and *Bartonella* spp. should be considered in dogs with severe or prolonged clinical signs and those that fail to respond to doxycycline. Residual CNS and other deficits may occur in severely affected patients. A convalescent serum sample should be drawn 2–3 weeks after the initial serologic sample in PCR-negative patients.

Prognosis

The prognosis is good to excellent if the disease is diagnosed and treated with appropriate antibiotics and supportive care early in the course of illness.

Public Health Implications

Rocky Mountain spotted fever is reportable in people in the US. It is also a reportable disease for dogs in some counties in the US. Because direct inoculation into blood or aerosolization can cause infection, all specimens should be handled with care and marked clearly as biohazards. Avoid needle sticks, contact with cuts in the skin, and aerosolization of rickettsemic blood.

It is important for veterinarians to communicate with owners and physicians that infection in a dog may precede tick-transmitted infection to owners or neighbors. Instruct clients to remove ticks properly and avoid crushing to prevent exposure to infected hemolymph. Refer to www.cdc.gov/ticks/removing_a_tick.html. Educating owners with regard to the importance of tick control and prevention for both people and pets and the environment is critical. In cases where *Rh. sanguineus* is the vector, environmental control is particularly important. The veterinarian should keep in mind that novel and well-characterized species of SFG *Rickettsia* are important causes of emerging infectious disease. Furthermore, *R rickettsii* is considered a potential bioterrorist agent. Because dogs are sentinels for infection, veterinarians can play an important role in detecting, defining, and preventing illness in their canine patients and their human companions.

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100

Lyme Borreliosis

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Etiology/Pathophysiology

Lyme borreliosis is caused by gram-negative spirochetes of the *Borrelia burgdorferi* sensu lato complex, including 21 species and at least 30 strains of *B. burgdorferi* sensu stricto in North America and Europe, and *B. afzelii*, *garinii*, and others in Europe. At least 52 *Borrelia* spp. exist; some 29 cause relapsing fever or rash in people, mimicking Lyme disease (e.g., *B. andersonii*, *B. hermsii*, *B. lonestari*, *B. miyamotoi*, *B. parkeri*, *B. recurrentis*, *B. turicatae*). Fever, lameness, anterior uveitis, splenomegaly, thrombocytopenia, and spirochetemia were associated with *B. turicatae* in dogs in Florida and Texas; *B. hermsii* was isolated in a febrile spirochetemic pancytopenic dog in Washington.

Lyme spirochetes are mainly transmitted via *Ixodes* tick bites after two days of host attachment, as outer surface protein A (ospA, the organisms's attachment to tick midgut) is downregulated and other antigens (e.g., ospC) become expressed. The organisms live extracellularly, associated with fibroblasts and collagen. Disease signs are due to immune-mediated reactions, not bacterial toxins or cellular damage by the organisms. Although many exposed people develop acute signs of illness (rash, flu-like signs) and later possible arthritis, neurologic, and/or cardiac manifestations, most exposed dogs and cats seroconvert without illness. The experimental model in 6–12-week-old beagle puppies showed no illness until 2–5 months after infected tick exposure. Carrier status and antigenic variation account for recurrent self-limiting episodes of anorexia, fever, and lameness. Only <5% of seropositive dogs in the field show Lyme arthritis. In some endemic areas, 70–90% of healthy dogs are seropositive. Canine Lyme nephritis is rare (<2% of those exposed), even among seropositive retrievers (predisposed breeds). Other manifestations in dogs are not well documented. Lyme arthritis is rare in seropositive cats; signs may be due to co-infection with *Anaplasma phagocytophilum*.

Lyme nephritis in dogs is not due to spirochetal renal invasion but rather Lyme-specific antigen–antibody complex deposition and immune-mediated glomerulonephritis, with secondary changes of tubular necrosis/regeneration and interstitial nephritis. There is no experimental model of Lyme nephritis, but genetic predisposition appears to play a role.

Epidemiology

Ixodes ticks are the main vector of *B. burgdorferi*. The main reservoirs are mice, small mammals, and birds. In the US, 95% of human cases are seen in the Northeast, MidAtlantic, and Midwest states. Bird migration and climate changes are extending the habitat of infected ticks to adjacent areas.

Signalment

Most affected dogs are middle-aged, large-breed dogs with outdoor lifestyles exposing them to field ticks questing in leaf litter, hedges, bushes, and tall grasses. Lyme nephritis can occur in any breed, but Labrador and golden retrievers appear predisposed.

History and Clinical Signs

Lyme Arthritis

The experimental tick exposure model shows that dogs seroconvert and become nonclinical carriers of spirochetes for many years, based on positive spirochetal cultures and polymerase chain reaction (PCR) tests of skin and subcutis biopsies from tick bite sites. Very young (6–12 weeks old) puppies showed signs of illness 2–5

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months after infected tick exposure, starting with a four-day episode of self-limiting anorexia, fever, lameness, and local lymphadenopathy in the leg closest to tick attachment, followed sometimes by several additional short episodes in the same or different leg(s) every two weeks, resolving without treatment. Older exposed puppies (13–26 weeks old) showed fewer signs and episodes, and adult dogs (>26 weeks old) seroconverted without illness. Antibiotic therapy cleared 85–90% (but not all) experimental dogs, based on skin biopsy culture and PCR test results.

In clinical cases in the field, dogs with suspected Lyme arthritis may show lameness in one leg with a hot swollen painful joint and joint effusion. Dogs with polyarthropathy (e.g., hocks/carpi) may have co-infections, immune-mediated arthritis or perhaps had multiple tick attachment sites affecting multiple limbs/joints. Dogs with Lyme arthritis typically respond quickly (within 1–2 days) to antibiotics, and if they do not, other causes of signs should be sought. Response to treatment may be coincidental, due to responsive co-infections (e.g., anaplasmosis), or due to the antiarthritic, antiinflammatory properties of doxycycline.

Lyme Nephritis

There is no experimental model for Lyme nephritis so the incubation, progression, best treatment, or whether Lyme vaccine prevents or promotes aggravates the illness are unknown. It is suspected to be a chronic manifestation, since it is associated with seropositivity and circulating immune complexes at presentation. Retriever dogs are predisposed, so an underlying genetic immunodysregulation and/or podocytopathy may exist. Dogs with early or mild glomerulonephritis may have occult proteinuria; more severely affected dogs present with signs of protein-losing nephropathy (PLN), such as edema/effusions, thromboembolic events (e.g., pulmonary, saddle, portal, neurovascular), hypertensive damage (e.g., blindness, epistaxis, neurovascular events), and eventually renal failure (e.g., anorexia, weight loss, emesis, polyuria/polydipsia, and potentially oliguria/anuria).

Diagnosis

Serology

The organism migrates interstitially (exception: *B. mayonii*, a cause of Lyme borreliosis in humans, may travel hematogenously) and is difficult to find by cytology with special stains, culture, or PCR testing, so serologic testing is used for antibodies directed against natural exposure antigens. Older tests such as whole-cell enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence assay (IFA), immunoglobulin (Ig) G, IgM, and western immunoblot show cross-reactivity with antibodies from vaccines and other infections, and are no longer preferred.

The C_6 peptide antibody test is sensitive and specific for natural exposure antibodies against part of the VlsE antigen, which is only expressed by the spirochete after infecting the host and is not in Lyme vaccines. Antibodies against the C_6 peptide rise 3–5 weeks after infection and persist in carriers. Qualitative in-house C_6 peptide testing is combined with tests for heartworm antigen and antibodies against multiple *Anaplasma* and *Ehrlichia* spp. (e.g., SNAP-4Dx Plus, IDEXX Reference Laboratories). Quantitative C_6 peptide antibodies (Lyme Quant C_6, IDEXX) usually wane 50% by six months post treatment. The new baseline result is useful for comparisons should future signs of illness suggest relapse or reinfection. The AccuPlex®4 test (Antech Diagnostics Reference Laboratories) tests for heartworm antigen and antibodies against *Anaplasma phagocytophilum* and *Ehrlichia canis*; its qualitative Lyme antibody test uses an algorithm comparing the magnitude and responses to five markers, including those usually found in vaccinates (ospA) vs after natural exposure (ospC, VlsE, ospF), and for recent exposure (ospC antibody rises 2–3 weeks post exposure and wanes within 3–5 months) vs past/chronic infection (ospF antibody rises 6–8 weeks post exposure and persists). The Multiplex test (Cornell University) quantitates ospA, ospC, and ospF antibodies. The in-house Abaxis/Zoetis qualitative tests for only Lyme (VetScan) or for Lyme/*A. phagocytophilum*/*E. canis*/heartworm (FLEX4) tests for Lyme antibodies directed against proprietary antigens mimicking VlsE, ospC, and p41 (flagellin).

Compromised interpretation of the Lyme test results above may be due to ospA antibodies possibly present in nonvaccinates after natural exposure (acutely or in carriers), ospC antibodies induced by new Lyme vaccines (bacterins and chimeric recombinant), and cross-reacting flagellin antibodies from other infections/vaccines. The magnitude of any natural exposure Lyme antibody titer does not predict illness, but may validate exposure.

Lyme Arthritis

Many causes for lameness or inability to rise need to be considered. Overdiagnosis is a problem; one study showed that 40% of Lyme arthritis cases were misdiagnosed and signs were due to other causes – for example, Lyme seropositivity was coincidental. Blood tests (complete blood count [CBC]/biochemical profile) are not abnormal but other tick-borne or other illnesses may cause changes such as cytopenias, hypoalbuminemia, hyperglobulinemia, azotemia, etc. All seropositive dogs

should be checked for proteinuria. Joint tap cytology shows a neutrophilic inflammatory response without bacteria, but morulae may be seen due to co-infections.

Lyme Nephritis

Abnormalities may include elevated blood pressure measurement, proteinuria/cylindruria, ± glucosuria, ± decreased concentrating ability, hypoalbuminemia, hypercholesterolemia, azotemia, hyperphosphatemia, anemia, thrombocytopenia, and abnormal (hypercoagulable) thromboelastography. Diagnostic work-up of PLN also includes screening for other infectious, inflammatory, genetic, and neoplastic diseases that cause proteinuria (e.g., serologic testing, urine culture, chest radiographs, abdominal ultrasonogram). Renal imaging is usually unremarkable. Renal biopsy by experienced personnel with thin section light microscopy, special stains, immunofluorescence, immunohistochemistry, and transmission electron microscopy shows immune-complex glomerulonephritis (staining techniques for Lyme-specific complexes are not validated), and possible secondary tubular necrosis/regeneration and interstitial nephritis.

Therapy

Therapy for nonclinical nonproteinuric dogs is not warranted. For Lyme arthritis signs, doxycycline (10–20 mg/kg/day for 30 days) or minocycyline is recommended because of possible responsive co-infections. Other antispirochetal antibiotics include amoxicillin, erythromycin, azithromycin, cefovecin, and ceftriaxone. Management for Lyme nephritis includes longer antibiotic regimes (perhaps until the Quant C_6 result has waned), a modified low-protein diet, renin-angiotenin-aldosterone system inhibitors (e.g., angiotensin-converting inhibitors and/or angiotensin receptor blockers), omega-3 fatty acids, antithrombotics, antihypertensives, drugs for renal failure (e.g., antiulcer medications, phosphate binders), and possibly immunosuppressives if renal biopsy shows glomerular immune-complex deposition or, in rapidly progressive cases, even without biopsy confirmation (compassionate care). The best protocol is unknown but may include single or combined mycophenolate, cyclophosphamide, steroids, chlorambucil, cyclosporin, and/or azathioprine.

Prognosis

The prognosis for Lyme arthritis is excellent as the course is self-limiting or responsive to antibiotics within 1–2 days. If unresponsive, consider other causes. The prognosis for Lyme nephritis is guarded to poor if the dog presents in renal failure, but may be better in earlier stages. Monitoring abnormalities frequently with treatment adaptation is essential.

Prevention

Tick control year round (ticks are active when temperature is >40 °F or 4 °C) is most important, since ticks in Lyme-endemic areas may transmit borreliosis as well as anaplasmosis, babesiosis, ehrlichiosis, mycoplasmosis, and Rocky Mountain spotted fever, and possibly bartonellosis. Some of these are transmitted within the first day of tick attachment so products which prevent tick attachment (e.g., permethrins or amitraz) or kill ticks fast after attachment (e.g., isoxazolines) are preferred.

There are five Lyme vaccines available: three killed adjuvanted bivalent bacterins (LymeVax, Zoetis; Duramune Lyme, Elanco; Nobivac Lyme, Merck Animal Health) including ospA and ospC, a nonadjuvanted recombinant subunit ospA vaccine (Recombitek Lyme, Merial), and a chimeric recombinant adjuvanted vaccine which includes ospA plus ospC from seven strains (Vanguard crLyme, Zoetis). Even in endemic areas, Lyme vaccination is controversial because:

- tick control is important to protect dogs from other tick-borne diseases in these areas
- most exposed dogs do not become ill or they respond quickly to commonly used antibiotics
- Lyme vaccines may interfere with some diagnostic tests
- Lyme vaccines are costly, have inconsistent efficacy, produce weaker/shorter duration of immunity that may require six-month boostering, and cause more postvaccinal adverse events than other canine vaccines.
- the most serious forms of Lyme disease have an immune-mediated pathogenesis, so theoretically it may not be a good idea to introduce Lyme antigens to genetically predisposed dogs, lest sensitization or aggravation of immune-complex deposition in glomeruli or joints may occur.

These last possibilities may not appear temporally associated with vaccination and are difficult to study without an experimental model of Lyme nephritis. Most concerns are anecdotal and theoretical, and because owner compliance to using adequate tick control may be problematic, many veterinarians recommend Lyme vaccinations in addition to tick control.

Public Health Implications

A seropositive dog has exposure to wildlife, may be a carrier for infection with other tick-borne diseases or leptospirosis, and is a sentinel for Lyme exposure in the environs. Educate owners about landscaping, tick prevention on their pets and themselves, and that physicians in Lyme-endemic areas may prescribe humans a single day's preventive dose of doxycycline to be taken within 72 hours of removing an engorged *Ixodes* tick.

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101

Leptospirosis

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Etiology/Pathophysiology

Leptospirosis is a zoonotic bacterial disease affecting the health of animals and humans throughout the world. In small animals, clinical leptospirosis is a significant problem in dogs, but the role of leptospires in feline disease is still poorly understood. Leptospiral organisms are typically divided into serovars, based on antibody responses to surface proteins. Serovars are further classified into antigenically related serogroups. Canine leptospirosis is caused by several serovars of the pathogenic species *Leptospira interrogans* sensu latu. Examples of serovars that have been implicated in canine disease include Grippotyphosa (serogroup Grippotyphosa), Pomona (serogroup Pomona), and Bratislava (serogroup Australis).

Leptospiral organisms enter the host through intact mucosal surfaces or damaged skin. During the first week of infection, organisms multiply and spread throughout the vascular space, leading to vascular damage and invasion of many organs and tissues. During this initial leptospiremic phase, organisms can be isolated from the blood. The immune phase of infection begins in the second week, with the appearance of serum antibodies. This leads to clearing of leptospires from the blood and many organs; however, organisms may be protected from the systemic antibody response in sites such as the renal tubules and the eye. Leptospiruria develops in the second week after infection and can persist for days to months, depending on the species of the mammalian host and the infecting serovar.

Pathologic changes associated with leptospirosis include vasculitis and endothelial cell damage. The precise mechanisms by which leptospires cause tissue damage and disease are not well understood, but several toxins and enzymes produced by the organisms likely contribute to disease pathogenesis. The pathogenicity of leptospires may also be related to their motility and their ability to adhere to, and penetrate, cells.

Epidemiology

Pathogenic leptospires are maintained in the environment through the shedding of organisms in the urine of a wide variety of endemically infected mammalian reservoir hosts. These reservoir hosts usually do not develop clinical disease, but serve as a source infection for incidental hosts, such as dogs and humans. In some locations, there appears to be an increased incidence of leptospirosis in late summer and fall, perhaps associated with weather conditions and wildlife behavior. Leptospires survive, but do not replicate, in warm and wet environments, whereas freezing, ultraviolet radiation, and dehydration all reduce survival. Transmission to incidental hosts is usually indirect, through exposure to contaminated water, soil, food or bedding, although direct contact through ingestion, bite wounds, or direct contact with urine is possible.

Reservoir hosts that likely contribute to environmental contamination include the raccoon, opossum, fox, skunk, mouse, rat, vole, squirrel, and deer. Clinicians should note that many of these reservoirs co-exist with humans in urban, suburban, and periurban environments, thus leptospirosis is not confined to large-breed, working, predominantly outdoor dogs or rural dogs. Many clinicians routinely diagnose leptospirosis in small-breed indoor dogs. Indeed, two different recent studies have demonstrated that dogs in some urban areas are at increased risk for leptospirosis, and that small dogs (<15 lb) were more likely to be diagnosed with the disease. Case reports and serologic surveys have demonstrated both clinical leptospirosis and subclinical exposure to the organisms in dogs from many locations in the US and Canada, and it is likely that only desert regions are truly free of the disease. Unfortunately, it is difficult to determine which serovars predominate in different geographic regions, as diagnosis is usually based on antibody titers, and these cannot identify the infecting serovar. Further studies are needed to

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isolate and genetically type the organisms in order to better understand the epidemiology of leptospirosis in different hosts and regions of the world.

Signalment

Any age, breed, and sex of dog is susceptible to leptospirosis, and the diagnosis should not be ruled out on the basis of signalment. A recent study of the Veterinary Medical Database demonstrated signalment changes in canine leptospirosis from 1970 to 2009. In the most recent decade studied, the highest prevalence of disease was in the 7–9.9 year age group, and in dogs <15 lb. The terrier group had the highest prevalence in this decade, and Yorkshire terriers had the highest prevalence among small breeds. Other sources have suggested an increased susceptibility in German shepherd dogs, although this has not been rigorously evaluated.

There are few reports of clinical leptospirosis in cats, but it has been shown that cats can seroconvert to leptospiral organisms, and there is some evidence that cats may shed leptospires in the urine. However, it has not been clearly demonstrated that leptospirosis is a significant clinical problem in domestic cats.

History and Clinical Signs

The manifestations of leptospirosis in dogs range from peracute disease to subclinical infection, and include sudden death, acute kidney injury (AKI), liver disease, vasculitis, and uveitis. Because this is a zoonotic disease, it is essential that veterinarians maintain a high index of suspicion for this infection, particularly in cases with atypical clinical signs.

Typical clinical signs in acute or subacute leptospirosis include lethargy, anorexia, fever, muscle pain, abdominal pain, signs of shock, dehydration, vomiting, diarrhea, bleeding, jaundice, polyuria, oliguria, and anuria. While AKI has been the most common presentation for canine leptospirosis in recent years, affected patients may also present with a combination of renal and hepatic disease, or hepatic disease alone.

Acute kidney injury in leptospirosis may be anuric, oliguric, or polyuric. Dogs that survive AKI due to leptospirosis may progress to chronic kidney disease (CKD). Acute kidney injury may be undetected in subclinically infected animals, and those patients may eventually be diagnosed with CKD of unknown cause. Leptospirosis should also be considered in any dog with previously diagnosed CKD that develops unexplained "acute-on-chronic" kidney disease. Other manifestations of renal disease in canine patients with leptospirosis include glucosuria in the absence of hyperglycemia, nephrogenic diabetes insipidus, and renal tubular acidosis. Liver disease associated with leptospirosis is predominantly cholestatic in nature, with minimal histopathologic changes.

Clinicians should be aware that patients with leptospirosis may present with unusual signs, including respiratory distress, bleeding disorders, effusions, and uveitis. Pulmonary disease in dogs with leptospirosis is probably more common than previously suspected, and has been attributed to pulmonary hemorrhage, a known serious complication of leptospirosis in people. Bleeding disorders may manifest as petechiae, epistaxis or gastrointestinal bleeding, and are most likely due to vasculitis, although the mechanisms are poorly understood.

Diagnosis

Common but nonspecific laboratory findings in dogs with leptospirosis include azotemia, hyperphosphatemia, metabolic acidosis, hyper- or hypokalemia, hyperbilirubinemia, increased serum alkaline phosphatase (ALP) activity, and increased serum alanine aminotransferase (ALT) activity; the latter is usually less markedly increased than ALP activity. Mild to moderate thrombocytopenia is relatively common, although the platelet count is seldom low enough to directly cause spontaneous bleeding. Urine specific gravity can be hyposthenuric in patients with nephrogenic diabetes insipidus; it may also be isosthenuric or concentrated, depending on the extent of renal involvement. Urinalysis may reveal hematuria, cylindruria, proteinuria, or glucosuria.

Imaging findings are also nonspecific, and may include reticulonodular pulmonary interstitial or alveolar opacities on radiographs, and ground-glass nodules or diffuse opacity and peribronchovascular interstitial thickening on thoracic computed tomography (CT). Abdominal ultrasound examination has been reported to reveal renal and hepatic changes, perirenal and peritoneal effusions, intestinal wall thickening, and lymphadenopathy.

Diagnostic tests for leptospirosis rely on detection of the organism, or detection of an antibody response in the infected patient. It is recommended that both types of tests be utilized to maximize the chance of diagnosing this zoonotic disease. It is essential that the results of any diagnostic test be interpreted in light of the patient's clinical signs, clinicopathologic findings, and vaccination history.

The microscopic agglutination test (MAT) is still the most widely used antibody detection test for the diagnosis of leptospirosis. Advantages of this test are that it is widely available and provides a numerical titer that allows

comparison of paired acute and convalescent titers. Most authors recommend that an initial titer of ≥1:800 is consistent with a diagnosis of leptospirosis in an unvaccinated dog. If initial titers are low, or the patient has an unknown vaccine history, convalescent titers can provide further information. Although a 2–4-week period between acute and convalescent titers is often recommended, it is not always necessary to wait that long. When performing paired acute and convalescent titers, a fourfold change (usually an increase) in titer supports the diagnosis of leptospirosis. Most laboratories that perform the MAT will test patient sera against multiple serovars (representative of serogroups) and often report seropositivity to more than one serogroup, due to significant cross-reactivity. For this and other reasons, it should be noted that MAT results cannot identify the infecting leptospiral serovar in an individual patient. However, for most clinicians this is of little importance, as there is currently no evidence that clinical signs, treatment, or prognosis are serovar or serogroup specific. When paired titers are performed, the MAT is a highly sensitive and specific test for leptospirosis.

More recently available serologic tests for the diagnosis of canine leptospirosis include an enzyme-linked immunosorbent assay (ELISA) test that detects antibodies to the lipoprotein LipL32 found on the surface of pathogenic leptospires, available both at a reference laboratory and as a point-of-care test (SNAP® Lepto Test, IDEXX), and a patient-side lateral flow device test that detects IgM antibodies to a whole-cell antigen from Grippotyphosa and Bratislava serovars (WITNESS® Lepto, Zoetis). These tests give qualitative positive or negative antibody results, with proposed advantages including lower cost and shorter turn-around time, compared to the MAT. In one study, SNAP Lepto demonstrated similar performance to the MAT for the detection of antibodies to *Leptospira* spp., with agreement being greater in MAT-positive samples with higher titers. In a more recent study comparing MAT, SNAP Lepto, and WITNESS Lepto in experimentally infected dogs, the WITNESS test detected seroconversion to common leptospiral serovars in all 32 dogs by day 10 after infection, the MAT detected seroconversion in 30 of 32 dogs by day 14, and the SNAP test detected antibodies in only three of 32 dogs in the 14-day follow-up period. However, it is important to note that the challenge infection in these dogs did not result in clinical illness, and the comparative performance of these tests may be different in a clinical setting in which patients are sick and potentially presented later in the course of infection.

Advantages of the point-of-care tests include that they potentially allow earlier diagnosis of leptospirosis, thus facilitating early institution of safe patient handling protocols and appropriate medical therapy. However, these tests cannot reliably distinguish vaccinal titers from natural infection, and they do not provide numerical titers to allow comparison of acute and convalescent titers. These disadvantages are particularly important in dogs with low initial titers, vaccinated dogs, or dogs with an unknown vaccination history.

If a negative result is obtained on either point-of-care test, additional serum samples should be obtained for acute and convalescent MAT titers (or the point-of-care test can be repeated in 1–2 weeks), polymerase chain reaction (PCR) testing should also be performed (see later), and leptospirosis should not be ruled out unless an alternate diagnosis is confirmed, or acute and convalescent serologic tests are negative. If a positive result is obtained on a point-of-care test and the patient is vaccinated, or has an unknown vaccine history, acute and convalescent MAT titers should be performed to distinguish between vaccinal titers and natural infection.

Bacterial culture of pathogenic leptospires is very rarely used as a diagnostic test in dogs, because it is technically demanding, of limited availability, and requires several months of incubation. Dark-field microscopy and fluorescent antibody tests have been used to demonstrate the presence of organisms in urine samples but sensitivity is poor, and these tests have largely been replaced by PCR-based assays. Blood or urine samples from canine patients can be tested by PCR for the presence of DNA from pathogenic leptospires.

A variety of different PCR tests are available, with quantitative tests such as real-time PCR likely to be more sensitive. Despite the wide availability and frequent use of PCR-based assays, there are relatively few published studies that evaluate their sensitivity and specificity. Potential causes of false-negative results include low leptospire numbers in the sample collected, intermittent shedding of organisms in the urine, or the presence of PCR inhibitors in the sample. False-positive results on the PCR assay may be due to sampling from a subclinically affected carrier, the presence of dead organisms, or contamination of the sample during collection, handling, or processing in the laboratory. If leptospirosis is suspected, obtaining both blood and urine samples for PCR testing may increase the chances of detecting the organism. Positive or negative results from the PCR should be further followed up with acute and convalescent MAT titers, and should always be interpreted in light of the patient's clinical signs.

Therapy

There are no prospective studies that provide data regarding the best antibiotic protocols for treatment of leptospirosis in dogs. There are many studies that address

antibiotic therapy in other species, including experimental models of leptospirosis, and large animals such as pigs and cows. Antibiotics used to treat leptospirosis should terminate leptospiremia and eliminate the carrier state. Doxycycline is often used as it is generally believed to achieve both of these goals. Doxycycline is also used prophylactically in humans who have a high risk of exposure to leptospirosis. Penicillins are often used to clear leptospiremia, which should also reduce the risk of organ damage. Penicillin, ampicillin, and amoxicillin all appear to be effective.

The choice of antibiotic to be used in the acute phase of the disease is generally dictated by the clinical status of the patient. In general, injectable antibiotics are used in acutely ill patients that are vomiting or not eating. Patients that tolerate oral medications may be started on amoxicillin and then changed to oral doxycycline, or oral doxycycline may be used as the sole therapy if the patient tolerates it. Again, there are no published data that address the duration of antibiotic therapy in dogs with leptospirosis. Most clinicians treat with a penicillin for 1–2 weeks, followed by doxycycline for two weeks, or treat with doxycycline alone for 2–3 weeks.

For dogs with AKI due to leptospirosis, supportive care is essential for a successful outcome. Patients with leptospirosis that remain oliguric or anuric are candidates for extracorporeal therapies such as hemodialysis.

Prognosis

The prognosis for dogs with leptospirosis likely depends on which body systems are affected, and the extent and severity of organ damage. If suspected or diagnosed promptly, and appropriate specific and supportive therapy is initiated, the majority of dogs with leptospirosis will recover from the disease. The prognosis is expected to be guarded for patients with oliguric or anuric AKI, unless renal replacement therapy is initiated. Patients with less severe AKI may progress to CKD or return to normal. In a recent German study of 99 dogs with leptospirosis, dogs that did not survive were more likely to have severe dyspnea, oliguria, azotemia, hyperbilirubinemia, and severe radiographic pulmonary changes, with the latter being specifically associated with high mortality.

Vaccination

Most of the canine leptospirosis vaccines currently used in the US include the serovars Icterohaemorrhagiae, Canicola, Pomona, and Grippotyphosa. It is not known whether these vaccines protect against additional serovars. Contemporary vaccines are purified by subunit technology or microfiltration processes, and they appear to be associated with fewer vaccine reactions compared to the whole-cell cultures that were commonly used in the past.

Vaccination against canine leptospirosis continues to be an area of controversy, despite a growing body of work regarding vaccine efficacy in dogs. In particular, it has been convincingly shown in several studies that vaccination against leptospirosis confers protection against challenge for at least one year, and also confers significant protection against urine shedding. It should be noted that there is little correlation between protection against clinical disease and antibody titers in vaccinated dogs. Postvaccination MAT titers generally fall by four months after vaccination, and rarely persist for one year. This should be kept in mind when interpreting MAT titers in vaccinated dogs. It has been shown that vaccination does not cause false-positive results in a PCR-based assay for canine leptospirosis.

As noted above, leptospirosis is not a disease that is confined to large-breed, outdoor, rural, or working dogs. This author recommends that the risks and benefits of vaccination against leptospirosis be discussed with every dog owner. It is important to bear in mind that leptospirosis is one of the most commonly diagnosed causes of canine AKI, and that the disease can be seen in dogs of any age, breed, sex, or lifestyle. It is also important to bear in mind that currently available vaccines appear to be both safe and efficacious.

Public Health Implications

Leptospirosis is a zoonotic disease. It is essential that veterinary personnel understand how the organism is spread and that infection can occur through damaged skin or intact mucus membranes. In this author's opinion, all dogs with unexplained acute azotemia (including acute-on-chronic) should be treated as leptospirosis suspects until an alternate diagnosis is obtained. It is not necessary to place these dogs in isolation, but it is essential to avoid human and animal contact with the urine of suspects. Direct contact with blood should also be avoided. Leptospirosis suspects should have a urinary catheter placed, or should only urinate in a dedicated area that can be cleaned and disinfected. Dogs that urinate in their cages should have a urinary catheter placed with a closed collection system. This is also often a valuable procedure in the management of AKI patients. If placement of a urinary catheter is not possible, for example in a small dog, absorbent pads can be used in the cage to collect urine. These can also be weighed to monitor urine output.

All personnel nursing a dog with leptospirosis should wear gowns, gloves, and shoe covers while handling the patient. Immunosuppressed individuals should not handle leptospirosis suspects. Facemasks and eye protection should be worn when cleaning cages or runs, or handling wet bedding. Laboratory personnel should wear gloves and a mask when handling body fluids from a leptospirosis suspect. Gloves should always be worn when handling canine urine, as dogs can be asymptomatic carriers of leptospirosis. Fortunately, leptospires are sensitive to most detergents and disinfectants, and are also killed by drying and sunlight. Owners of dogs with leptospirosis should be advised to avoid contact with the dog's urine. If the dog urinates in the house, they should wear gloves and use household detergents or disinfectants to clean up the urine. How long these dogs will shed leptospires is unknown, but appropriate antibiotic therapy should reduce the risk. Owners should contact their own physician with questions about human leptospirosis.

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102

Yersiniosis

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Etiology/Pathophysiology

Yersinia pestis is the agent of a rare, highly contagious, and often fatal zoonosis. Known since ancient times as plague or "black death," *Y. pestis* devastated medieval Europe with widespread epizootics. Today, *Y. pestis* is enzootic in some foci in the Americas, Africa, the Middle East, and Asia.

Yersinia pestis is a gram-negative, facultatively anaerobic coccobacillus that belongs to the family *Enterobacteriaceae*. The bacterium can survive for weeks in the environment as it is resistant to low temperatures and freezing. However, it is sensitive to high temperatures and desiccation. *Yersinia pestis* is a vector-borne pathogen transmitted by many flea species. *Xenopsylla cheopis* (Oriental rat flea) and some other flea species such as *Oropsylla montana* (the ground squirrel flea) are very efficient vectors whereas others, such as the dog and cat fleas (*Ctenocephalides* spp.), are much less efficient. Fleas acquire the organism from bacteremic mammals. *Yersinia pestis* can infect a wide range of mammals, including humans. Host species have variable susceptibility to development of the disease due to various factors. Less susceptible hosts such as mice, rats, squirrels, and prairie dogs usually develop prolonged bacteremia and therefore act as natural reservoirs. Due to high flea infestation rates and a communal lifestyle, burrowing mammals facilitate transmission of the organism by fleas to a high number of hosts.

Within the flea midgut, the bacterium replicates. Aggregates of the organism block the digestive tract, which causes the flea to suck blood with increased effort and regurgitate organisms into the bite wound it inflicts on subsequent hosts. Cats and dogs can acquire the infection from fleas but they may also become infected by ingesting infected prey. Although less common, transmission through aerosolization or contact with mucous membranes or skin wounds also occurs.

In susceptible mammalian hosts like the cat, *Y. pestis* is able to evade host innate immune defenses. It can infect macrophages wherein it abundantly multiplies inside phagolysosomes, causing cell lysis. In more resistant hosts such as dogs, *Y. pestis* is susceptible to macrophage killing inside phagolysosomes. When transmitted by a flea bite, the bacterium is carried by mononuclear cells to regional lymph nodes where it causes a suppurative lymphadenitis with a marked lymph node swelling (the bubo). Fistulae drain thick purulent exudate from the affected lymph nodes. When transmission occurs via ingestion of infected prey, mandibular and retropharyngeal lymph nodes are involved. Clinical disease characterized by lymphadenitis is called bubonic plague. Dissemination via lymphatic vessels or the bloodstream can follow lymphadenitis. After bacteremia, other lymph nodes, the lungs, and many other organs and tissues can be affected. Abscesses, hemorrhagic and necrotic lesions may occur in many organs. Sepsis may also occur. Bacteremia and multiple organ involvement is referred to as septicemic plague. Dissemination occurs more quickly after ingestion of infected prey or inhalation of the organism from contaminated aerosol droplets. The pulmonary form, known as pneumonic plague, can occur in cats due to hematogenous spread or inhalation of organisms.

It has been established that cats are the domestic species most susceptible to plague. Reinfection is possible and seropositive cats are not protected from bacteremia or death but may have a more prolonged course of the disease.

Similar to the presentation in cats, three different clinical forms of plague are described in humans: bubonic, pneumonic, and septicemic. Bubonic plague is the consequence of flea transmission while pneumonic plague develops after inhalation of the bacterium or hematogenous spread. Septicemic plague may arise from the other two forms.

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Epidemiology

One of the oldest diseases known to man, plague is still endemic in many natural foci in the Americas (western USA, Peru, Brazil, Argentina, Ecuador), Africa (Algeria, Libya, Congo, Madagascar, Malawi, Mozambique, Uganda, Tanzania, South Africa) and Asia (China, Mongolia, Vietnam, India, Indonesia, Kazakhstan, Iran). Recent outbreaks have occurred in previously endemic areas after prolonged periods of absence. Countries belonging to the World Health Organization are obliged to notify officials when plague is diagnosed in humans, but underreporting likely occurs.

Each endemic focus is linked to the presence of a specific mammalian reservoir and flea vector. Variability in annual incidence is linked to climatic variability, specifically to rainfall because humidity favors both flea reproduction and increased food availability for rodent hosts. Enzootic hosts of *Y. pestis* are resistant to the development of disease and have prolonged bacteremia, thereby maintaining the flea–host–flea cycle in the wild. In endemic areas, outbreaks of recurrent or sporadic plague epizootics rapidly involve individuals of a particularly susceptible (epizootic) host species. These animals are easily infected when a highly competent flea vector species is more abundant.

Most cases of human plague result from exposure to fleas or activities that result in contact with reservoir hosts, such as skinning rabbits. Exposure to domestic cats accounts for approximately 10% of human plague cases. Veterinary staff and owners of free-roaming cats are at increased risk for *Y. pestis* infection in endemic areas. In some cases, human patients reported being bitten or scratched by infected cats but sometimes just handling or caring for a sick cat was the only contact reported. In one human case, the infecting scratch was obtained by a healthy cat which had fought with a cat suffering from bubonic plague. Importantly, human infection from cats commonly results in the pulmonary form of the disease (pneumonic plague) which is associated with rapid progression and a higher fatality rate.

Dogs rarely develop clinical signs. Infection results in people primarily due to contact with the *Yersinia*-infected fleas they carry. Dogs and other carnivores may serve as sentinels for *Y. pestis* because infection results in the transient production of antibody, peaking 3–4 weeks post exposure and lasting 4–8 months.

Signalment

Yersiniosis is diagnosed in dogs much less frequently than in cats. The disease is reported in cats (3 months to 15 years old) and dogs (1–14 years) of any age, but it seems to be more frequent in adults. No gender or breed predilection is known.

History and Clinical Signs

Free roaming in rural areas and hunting activity are the main risk factors for dogs and cats in endemic areas. In experimental infections, the incubation period lasts 24–48 hours but after natural exposure it may be up to a few days.

Fever, lethargy, and anorexia occur in cats associated with the development of the "bubo," a swollen painful lymph node. This swelling can be confused with abscesses that commonly arise from cat fights. Buboes may involve any superficial lymph node but mandibular and retropharyngeal nodes are more frequently affected because infection is commonly acquired by the oral route as a result of predation. Ulcerative or necrotic lesions may be observed on lips or oral mucosa. The white blood cell count is usually elevated with increased neutrophils and bands. In benign cases, drainage of the primary bubo is followed by resolution of fever and progressive recovery. In other cases, fatal septicemia rapidly occurs and may evolve to distributive shock and multiple organ dysfunction syndrome (MODS). MODS associated with *Y. pestis* is manifested by persistently high fever, depression, hypotension, rapid capillary refill time (CRT), bradycardia, hypodynamic peripheral pulses, hypoalbuminemia, hypoglycemia, and increased bilirubin, liver enzymes, blood urea nitrogen (BUN), and creatinine. Oliguria and metabolic acidosis are also observed. Disseminated intravascular coagulation (DIC) may also occur and is responsible for a hemorrhagic diathesis. Suspicion of DIC is increased in patients with thrombocytopenia, prolongation in activated partial thromboplastin time (APTT) and prothrombin time (PT), increased fibrin degradation products (FDPs) and/or D-dimer, and decreased antithrombin. In some septicemic cases a primary bubo is not found.

Primary pneumonic plague is not a typical presentation in cats because infection is rarely caused by inhalation. Pulmonary involvement is usually due to dissemination from a bubonic primary lesion. Cough and dyspnea represent the clinical manifestation of a pulmonary disease and thoracic radiographs may show the presence of poorly defined focal patchy and coalescing opacities due to pulmonary abscessation. Pleural effusion may also be found.

Few case reports of plague in dogs have been documented. Clinical signs include mild to severe hyperthermia, lethargy, anorexia, stomatitis, painful enlargement of the superficial lymph nodes (mandibular, retropharyngeal, superficial cervical or inguinal), vomiting, diarrhea,

respiratory signs, and abscesses. Leukocytosis and neutrophilia are often recorded.

Diagnosis

In endemic areas, bubo-like lesions and hyperthermia should immediately prompt consideration of *Y. pestis* in free-roaming or hunting cats and dogs. Public health officials should be notified immediately. Standard operating procedures for handling potentially infectious animals or materials should always be followed. Such procedures include isolation of the patient, and wearing surgical masks, gloves, and eye protection when performing physical examination and any clinical or laboratory procedures. Laboratories should be contacted for proper collection and submission protocols prior to collecting and submitting samples from an animal suspected of being infected.

Cytologic evaluation on both Gram- and Giemsa-stained smears from draining lesions may quickly show the presence of a large number of monomorphic Gram-negative (Gram staining) organisms with a bipolar safety pin shape (Giemsa staining). The diagnosis is confirmed by culture, direct fluorescent antibody test (DFA) or polymerase chain reaction (PCR). The DFA is performed by approved laboratories on tissue imprints on slides, smears of lymph node aspirate, or samples from draining pharyngeal or cutaneous lesions. Isolates can be made from cultures of oral swabs, blood or swollen lymph nodes if samples are obtained before starting antibiotic therapy. However culture can be insensitive, and takes several weeks. It should be noted that culture of *Y. pestis* can only be performed at approved laboratories due to its zoonotic potential, and public health authorities should be contacted to obtain information on collection and submission guidelines. Molecular diagnostic methods from clinical samples are also available from select laboratories. Negative immunofluorescence assay (IFA), culture or PCR does not rule out infection.

Diagnosis can also be confirmed by serologic methods. Antibodies against the organism's F1 capsular antigen can be detected many days after the onset of clinical signs and last many months after the infection. Dogs and cats may test seronegative at presentation, as illness may occur prior to seroconversion. A fourfold or more rise in antibody titer against F1 antigen (15 days minimum apart) or a single titer of 1:32 or more by hemagglutination in a cat or dog with signs suggestive of plague is diagnostic. ELISA tests or semiquantitative rapid lateral flow immunochromatographic tests using recombinant antigens have also been developed for humans and mammal reservoirs. Tests for antigen detection in mammals, fleas, and environmental samples are also available.

Therapy

Rapid appropriate therapy should be started as soon as possible without waiting for the confirmatory test result when infection is suspected. Strict isolation measures and personal protection measures should be followed and antiflea treatment applied. Public health authorities should be contacted immediately for notification and guidelines. Treated cats and dogs are considered noninfectious after three days of therapy when fever wanes and clinical recovery occurs but a minimum of three weeks of therapy is required. Many antibiotics have *in vitro* efficacy or are effective in experimental mouse studies. Gentamicin is a first-choice antibiotic for dogs and cats at a dose of 6–8 mg/kg q24h IM, SC or IV. Doxycycline is a second choice for less severe cases. Oral administration of this antibiotic poses a higher risk for caretakers and should be avoided in the initial treatment period. Draining of buboes is recommended (adopting the appropriate operating procedures for avoiding infection as explained earlier). Chlorhexidine is used for flushing fistulae.

Prognosis

In an experimental trial which reproduced oral transmission, 37% of 16 infected cats died. A minority of cats (19%) experienced a subclinical infection and 44% recovered after a clinical disease. Poor prognosis was associated with persistently high fever (≥40 °C, 105 °F). None of the cats in this experimental trial were treated with antibiotics or other measures and in natural disease a fatal course is observed in about half of feline clinical cases. Most cats promptly treated with antimicrobial drugs survive and drainage of cutaneous abscesses improves prognosis. Conversely, abscess development in the lung is considered a negative prognostic factor in cats.

Experimental studies show that dogs have only a mild febrile syndrome and a benign course with no fatality, and this appears to be the case in naturally infected dogs as well. Co-infection with other agents such as *Ehrlichia canis* may result in more severe clinical manifestations. In treated dogs, clinical cure is obtained in 1–21 days.

Prevention

Several types of vaccines have been produced for use in people at risk who are exposed to *Y. pestis* due to professional activities. However, these vaccines are no longer available in the US. Under experimental conditions, vaccination with a killed vaccine did not protect cats from

infection or death. This is consistent with the fact that after infection, seropositive cats are not protected from bacteremia or death.

Doxycycline (10 mg/kg SID PO for seven days) is administered to exposed animals to prevent development of disease.

Public Health Implications

Humans can acquire *Y. pestis* from cats through bites, scratches or aerosolization of respiratory secretions. Fleas on pets also expose humans to the disease. Personnel working in veterinary practices where plague is enzootic should be aware that plague occurs in cats and dogs. Veterinary staff handling potentially infectious animals or materials should be adequately protected from *Y. pestis* infection by wearing a well-fitted surgical mask, gloves, and eye protection. Exudates should be considered infectious, and any material used for treating suspect cats should be disinfected, autoclaved, or incinerated.

In plague-affected areas, owners should be advised to prevent their cats and dogs from roaming freely and to strictly follow flea control programs. Other general advice includes avoiding sleeping with pets, avoiding handling sick or dead animals without adequate protection, and preventing rodent infestations by eliminating food sources and available shelter. Owners of an animal diagnosed with plague should be instructed to contact their physician immediately for prophylactic antibiotics and other treatment as indicated.

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103

Tularemia

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Etiology/Pathophysiology

Tularemia is a rare but severe zoonotic illness caused by *Francisella tularensis*, a small gram-negative non-spore-forming, aerobic coccobacillis bacterium. The organism infects a number of mammals although some, such as rabbits and hares, rodents, cats and sheep, appear to be particularly susceptible to disease. The organism is classified into subspecies (also referred to as types), with *F. tularensis tularensis* (type A) and *F. tularensis holarctica* (type B) causing most disease in cats and people. Disease caused by type A appears to be more severe and is diagnosed more commonly in cats and people than that caused by type B.

Francisella tularensis is very stable in the environment and is transmitted to people and other mammals by a number of mechanisms. These include through biting flies, mosquitoes, fomites, aerosols, and water. Aquatic protozoa may also play a role in transmission. Fleas are considered potential but inefficient mechanical vectors. Several tick species also transmit *F. tularensis.* Transstadial and transovarial transmission have been documented in ticks so they are true biologic rather than mechanical vectors.

Francisella tularensis readily infects macrophages and cells of the reticuloendothelial system. It can also infect hepatocytes and other cells. In macrophages, it survives by inhibiting phagolysosomal fusion and the respiratory burst. After replicating, it induces a form of apoptosis known as pyroptosis. This releases the bacterium and allows it to be taken up by other phagocytic cells. Severe inflammatory responses in the host can cause serious morbidity.

After cutaneous infection, the bacteria may replicate locally and then migrate to local lymph nodes. Further dissemination and septicemia can follow. Lesions in the lungs, spleen, liver, lymph nodes, and skin may result. Systemic infection may also occur without prior localized infection. Pulmonary infection may also result directly from aerosolization. Infection may also be introduced by the oral or gastrointestinal route.

Immunity is T cell mediated, and natural killer cell secretion of interferon-gamma and subsequent activation of macrophages appears important in immunity.

Epidemiology

Type A occurs in North America, whereas type B occurs throughout the northern hemisphere. Types A and B cause disease in both cats and people. Type A is subdivided into types I and II, which appear to have relatively distinct geographic distributions and differences in pathogenicity, with type I causing more severe disease. *F. tularensis* is a reportable disease in the US, occurring in every state except Hawaii. The prevalence of the disease in people is highest in the south central US, the Pacific Northwest, and Massachusetts (Figure 103.1). The incidence of tularemia has been decreasing overall in the US in recent years.

In people, tularemia has classically been referred to as rabbit fever, because many reports of the disease have been associated with contact with rabbits. These include an outbreak associated with aerosolization of the organism while skinning rabbits after a hunt, and running over a rabbit nest with a lawn mower, among others. Recently, however, the importance of cats as a source of human infection has been illustrated. Due to predation on rabbits and rodents, and exposure to environmental sources such as water and ticks, free-roaming cats are believed to be at particular risk for exposure. In one serosurvey in the US, 12–24% of cats were seropositive. Alarmingly, it was recently reported that 48% of human cases in Nebraska were cat associated.

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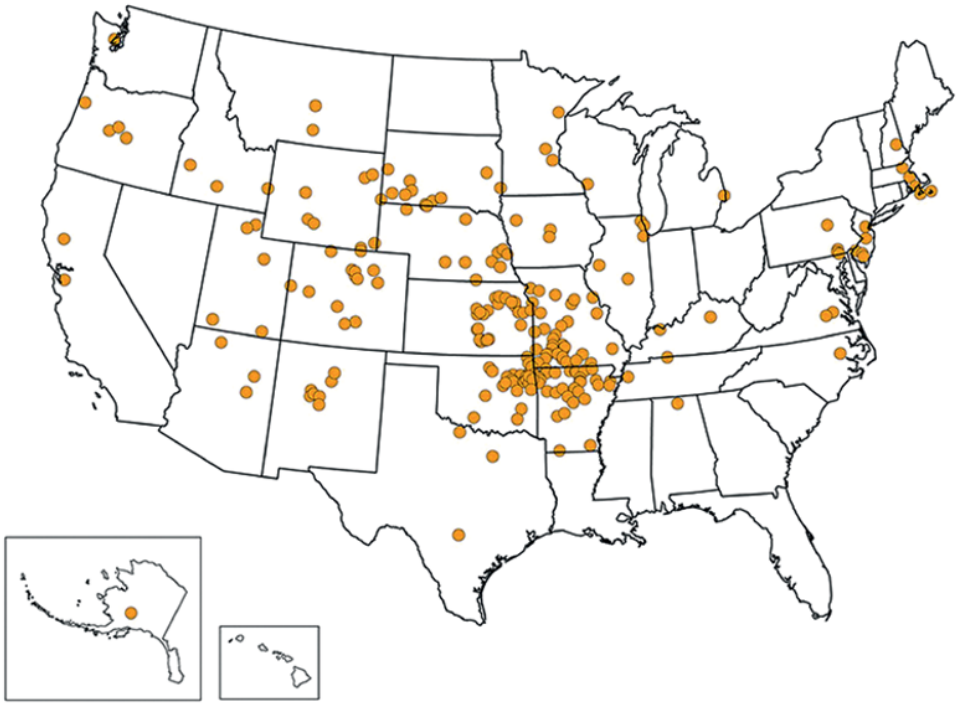


Figure 103.1 Reported tularemia cases in the United States, 2016. *Source:* www.cdc.gov/tularemia/statistics/map.html.

Because of its pathogenicity, the potential for aerosol transmission and other factors, *F. tularensis* is considered a Tier 1 bioterrorism agent. This is important for veterinarians to consider, as cats and possibly dogs could potentially serve as sentinels if such an attack were to occur.

Signalment

Infection in young adult cats and dogs has been reported most frequently, with natural infection in cats reported much more commonly than in dogs.

History and Clinical Signs

Clinical signs can range from minimal to severe disease and death. Severity of illness is likely determined by type and subtype of the organism and host immunity. Different clinical categories of disease, including ulceroglandular, glandular, pneumonia, and tonsillitis or pharangitis with cervical lymphadenopathy, are described in people. These disease manifestations are determined in part by route of inoculation.

Manifestations in cats appear to be similar to those found in people. In cats, clinical findings may include a more localized form that includes chronic subcutaneous draining abscesses, or generalized severe disease. In the severe form of the disease, fever, depression, lethargy, jaundice, splenomegaly, lymphadenomegaly, and hepatomegaly occur. Oral and lingual ulcerations may be present and might indicate ingestion as a route of infection. Embolic pneumonia associated with oral or gastrointestinal exposure has been described. Fever, lethargy, anorexia, lymphandenopathy, ocular changes, and tonsillitis have been described in dogs.

Diagnosis

Tularemia should be a differential diagnosis in cats with fever of unknown origin, chronic draining lesions/abscesses, lymph node enlargement and hepatosplenomegaly and oral ulcerations. Free roaming and hunting behaviors, especially predation of rabbits or rodents, should increase the index of suspicion for infection. Plague is an important differential diagnosis for tularemia.

Guidelines have been established by the European Advisory Board on Cat Diseases (www.abcdcatsvets.org/) for tularemia in cats. They state:

> When handling animals with suppurative or draining skin or lymph node lesions in endemic areas, gloves and goggles should be worn. Gloves should

also be worn when there is any direct contact with the oral mucosa. Handling of diagnostic samples by laboratory staff should follow biosafety procedures.

In addition to taking in-clinic precautions, laboratories and couriers should be warned that tularemia is a differential diagnosis before diagnostic specimens are submitted and appropriate precautions taken. Veterinarians should notify and consult public health authorities for guidance when tularemia is suspected.

Complete blood count may reveal thrombocytopenia, leukocytosis or leukopenia. Toxic change may be present in neutrophils. Serum chemistry may reveal elevations in alanine aminotransferase (ALT), alkaline phosphatase (ALP), and bilirubin. Lymph node aspiration may show reactive changes, pyogranulomatous inflammation or neutrophilic inflammation.

Pathologic findings include multiple foci of necrosis in lymph nodes, spleen, liver, and lung. Fibrinosuppurative to granulomatous inflammation may be present in many organs. It is difficult to demonstrate the organism in tissues with routine staining.

A fourfold increase in titer demonstrates acute infection, although it is important to note that animals may be seronegative early in the course of disease. Therefore, a negative titer does not rule out infection. Because antibody can be long-lived, a single positive titer is not diagnostic for active infection.

Antibodies may be used to directly demonstrate the presence of the organism in lymph node aspirates and tissue samples using direct immunofluorescent antibody assays. PCR verifies active infection. Culture is also a diagnostic method that demonstrates the presence of the organism. The laboratory must be notified that tularemia is a differential to protect laboratory workers and because the organism is fastidious and requires special media to grow. A negative result for immunofluorescent antibody assays, PCR or culture does not rule out infection.

Therapy

Aminoglycosides are the treatment of choice. Doxycycline and fluoroquinolones are also effective treatments but may be associated with relapse, which may be ameliorated with a longer course of treatment (three rather than two weeks).

Prognosis

Specific information about prognosis in dogs and cats has not been published.

Public Health Implications

Public health authorities should be notified immediately when tularemia is suspected. Infected cats may transmit tularemia by bites, scratches or contact with or aerosolization of fluids or tissue specimens or potentially fur. Veterinary and laboratory personnel should take appropriate precautions as detailed earlier. To prevent tularemia, owners should be advised to keep cats from roaming and hunting, provide appropriate ectoparasite control and to seek medical care if they feel ill or if they have been scratched or bitten by a cat with suspected infection.

According to the US government, "an urban cluster of tularemia cases among persons with a common natural exposure could be the first sign of a bioterrorist attack." Cats may serve as sentinels for such an attack due to their apparent disease susceptibility and exposure to environmental sources of the organism. Veterinarians should be vigilant in considering tularemia as a differential diagnosis in cats or dogs with compatible clinical signs.

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104

Q Fever

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Etiology/Pathophysiology

Q fever is caused by the gram-negative bacterium *Coxiella burnetii*. *Coxiella burnetii* is a gamma-proteobacteria currently classified in the order Legionellales. The organism exists in two forms: a large-cell variant that is the metabolically active form, and a small-cell variant which is spore-like. The small-cell variant is released into the environment where it is very resistant to destruction by chemicals, light, and desiccation, and can survive for long periods of time. The target cell of this obligately intracellular organism is the macrophage. Host factors may contribute to its ability to survive intracellularly as interleukin (IL)-10, an antiinflammatory cytokine, appears to inhibit phagosome maturation, while intracellular killing appears to be facilitated by interferon (IFN)-gamma. Cell-mediated immunity is important in controlling infection. Granulomatous inflammation occurs in infected hosts. In animals, the uterus and mammary glands are the most common sites of infection. The organism concentrates in the placenta during parturition, and large numbers of the organism are aerosolized from these membranes and also carried by dust and other environmental sources once contamination has occurred.

Epidemiology

Coxiella burnetii has a worldwide distribution. Many species of mammals, birds, and arthropods, including ticks, can be infected. Infection of mammalian hosts may occur through aerosolization, oral (ingestion) or tick transmission. In mammals, the organisms concentrate in placenta and are excreted in milk, urine, saliva, and feces. Cattle, sheep, and goats are the most important reservoirs for the organism. Serosurveys suggest free-roaming rural cats and dogs are at increased risk. Exposure to raw meat, particularly raw kangaroo meat, has been implicated as a possible risk factor in cats. Recently, infections have been identified in United States soldiers returning from Iraq where Q fever is endemic. In a recent serosurvey, 5% of wild canines in Iraq were seropositive, while no military working dogs (MWDs) in the region were seropositive. Diligent use of flea and tick control, and the fact that the MWDs in this study did not have access to local farm animals or food were hypothesized to contribute to the discrepancy. Serosurveys have shown that exposure in cats is common in many areas of the world, ranging from 2% to 61%. Interestingly, polymerase chain reaction (PCR) failed to amplify DNA from the organism from the vaginas of 50 intact female Colorado shelter cats while 4/47 uterine biopsy samples from client-owned cats were positive. A follow-up study showed a similar PCR-positive prevalence rate of 8.1% in the uterine tissues of cats with and without reproductive abnormalities.

Coxiella burnetii is primarily of importance in small animal medicine due to its zoonotic potential. Clinical disease in dogs and cats is not commonly recognized. Multiple reports of infection in people after exposure to periparturient cats and dogs have been described. Despite these reports, a study on pet ownership was not associated with increased risk of antibody formation in people. Cats and neonatal kittens have been reported as a source of infection in people more often than dogs. A recent report of an outbreak in a small animal veterinary hospital was associated with a female cat undergoing C-section; 8/9 infected personnel working at the veterinary hospital worked the day of the C-section while the ninth person cleaned equipment the morning after.

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Signalment

Because infection is usually asyptomatic, a study on signalment of naturally infected cats and dogs has not been described. Most cases in the literature describe intact female dogs and cats undergoing parturition as a source of exposure. MWDs deployed in Iraq may be at increased risk for infection especially if they have exposure to farm animals.

History and Clinical Signs

Disease is usually subclinical in dog and cats. Fever, anorexia, and lethargy have been described in experimental infection. Abortion or neonatal death has been associated with infection but the organism's role in causing reproductive abnormalities in dogs and cats is not fully elucidated. In one report, lesions in affected kittens included granulomatous myocarditis, hepatitis, nephritis, and pneumonia.

Diagnosis

Serology has been used to document exposure, while isolation, histopathology, immunohistochemistry, fluorescence *in situ* hybridization (FISH), and PCR can document infection. Public health authorities should be contacted for guidance on sample submission for suspected cases. Animals may be seronegative in the acute phase of disease prior to seroconversion. Sensitivity also varies depending on the serologic assay, and assays are species specific. The inability to demonstrate the organism using PCR, culture, FISH, and histologic methods does not rule out infection. Because the organism is highly infectious to people and stable in the environment, taking precautions to prevent infection in clinical and laboratory workers and owners is important.

Therapy

Studies investigating efficacy of treatment in cats and dogs have not been reported. Doxycycline is the treatment of choice in people with acute infections. Doxycycline in combination with hydroxychloroquine is recommended for chronic infections in people. Doxycycline and chloramphenicol are suggested for treating cats by the European Advisory Board on Cat Diseases (www.abcdcatsvets.org/coxiellosis-q-fever/).

Prognosis

Because naturally infected dogs and cats are asymptomatic, prognosis for survival in these species is thought to be good. The possibility of chronic asymptomatic infection and reservoir potential should be considered.

Public Health Implications

Q fever is a reportable disease in the United States. Humans are very susceptible to Q fever. Farm workers, laboratory workers, and veterinarians are at increased risk. Acute and chronic infections occur in people and are associated with significant morbidity and mortality. Exposure to parturient cattle, sheep, and goats, and aerosolization of the organism from environmental contamination by their fluids and tissues has historically been the primary route of infection in people, although exposure to periparturient cats has been the primary risk in some studies. Human infection associated with exposure to cats and dogs is usually in the context of aerosolization of high concentrations of organisms in placental tissues during parturition.

Guidelines for prevention and management of *C. burnetii* in cats have been established by the European Advisory Board on Cat Diseases (www.abcdcatsvets.org/coxiellosis-q-fever/). *Wearing gloves and masks during parturition of ALL cats and dogs,* diligent use of tick control and preventing cats and dogs from roaming have been recommended. Direct mouth-to-mouth resuscitation of kittens and puppies after C-section should be avoided. More extensive guidelines to prevent infection in people, which include additional recommendations such as avoiding the consumption of raw milk or raw milk products, are available from the United States Centers for Disease Control and Prevention (www.cdc.gov/qfever/).

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105

Brucellosis

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Etiology/Pathophysiology

Canine brucellosis is caused by the aerobic, gram-negative, coccobacillus species *Brucella*. The most clinically relevant infection in dogs is caused by *Brucella canis*, although reports exist of infection with *B. abortus*, *B. melitensis*, and *B. suis* in individual animals. The bacterium is highly contagious, and often spreads rapidly in breeding kennels. Transmission is also possible via frozen semen and artificial insemination as the bacterium is resistant to cryopreservation.

The organism is best known for being venereally transmitted via vaginal and seminal secretions in sexually mature animals. Transmission also occurs *in utero*, at parturition, or during abortion through oronasal, conjunctival, or transdermal contact of aborted fetal tissues, placental tissues, urine, milk, or vulvar discharge. Aborted tissues are highly infectious, containing high numbers of organisms, and abortion often results in persistent vaginal discharge that can last for 4–6 weeks. Infection can also occur via artificial insemination with infected semen, and via fomites such as contaminated food and water bowls, equipment, and clothing. The bacterium is highly stable and can survive for months in moist soil in the environment.

Following contact, invading bacteria are able to survive phagocytosis and are taken up by lymphatic and genital organs where they rapidly reproduce. Bacteremia occurs 1–4 weeks post infection and can persist for up to six months. Bacteria can be intermittently detected in tissues and secretions for up to 64 months post infection. While the bacteria reproduce best in reproductive tissues, a variety of clinical signs can manifest as a result of hematogenous transmission to the eye, kidneys, and vertebrae.

Epidemiology

Canine brucellosis is widespread in domestic and feral dog populations throughout the southern United States, in Central and Southern America, and Asia. It is unclear how important wild canids or stray dog populations are in disease transmission. Sporadic cases have been reported in Europe. Recently, the disease has become more prevalent in breeding kennels due to their growing number, ease of buying/selling and trading infected dogs, and increased international semen shipment.

Signalment

There are no current recognized breed or age predispositions. As venereal transmission is most significant, sexually intact, reproductively mature dogs are most likely to become infected, but the disease has been readily identified in both neutered and intact individuals. There has been a case report of a child becoming infected as a result of contact with an infected 8-week-old puppy and thus, the disease is zoonotic, especially in immunocompromised individuals.

History and Clinical Signs

The majority of individuals infected with *B. canis* are asymptomatic. Fever is uncommon and there are no clinical signs that are pathognomonic. The classic clinical sign is late-term abortion in bitches, with abortion occurring at 45–55 days gestation. Deceased pups are often autolysed, and surviving pups are often weak, have peripheral lymphadenopathy, and may die months later as a result of bacteremia. A greenish-gray vulvar

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discharge may persist in aborting bitches for up to six weeks. Some bitches may have perceived infertility due to early embryonic loss.

Males develop a characteristic epididymitis approximately five weeks after infection. Increased presence of neutrophils and teratozoospermia with sperm agglutination is often seen 18 weeks post infection. Over 90% of sperm are morphologically abnormal by week 20 post infection. The enlarged epididymis is often painful and scrotal dermatitis may also be seen due to increased licking of the scrotum because of discomfort. Chronic infection often leads to testicular atrophy. Concurrent prostatitis is common.

Dogs with systemic infection may also present with clinical signs outside the reproductive tract, depending on the site of infection. Discospondylitis, lymphadenitis, lameness, ataxia, recurrent anterior uveitis, and low-grade meningitis have all been reported in *B. canis*-infected animals.

Diagnosis

Direct detection of the organism in culture remains the only definitive diagnostic method available; however, the slow growth rate, intracellular location, and previous antibiotic therapy may affect the results. Therefore, a negative culture does not rule out disease. Positive blood cultures may occur starting at 2–4 weeks post infection up to several years following infection due to intermittent shedding of the organism. Placenta, fetus, lymph nodes, bone marrow, prostate, spleen, urine, vaginal discharge, and semen may all be potential sites for culture of organisms.

Due to the difficulty in growing the organism in culture, serology can be a helpful screening tool for the disease. Antibodies can be detected 3–4 weeks post infection and serology is most accurate as a screening test 8–12 weeks post infection. Serologic testing is highly sensitive, but has low specificity due to cross-reactivity with other bacterial species. Serologic tests include the rapid slide agglutination test (RSAT), which is available as a commercial, cage-side screening test, with or without the addition of 2-mercaptoethanol (2-ME). If a sample tests positive with the RSAT test, 2-ME should be added to prevent cross-reactivity with IgM antibodies to other bacteria species and increase the specificity of the test. A second serologic test, the tube agglutination test (TAT), is similar but is quantitative. Titers less than 1:200 should be retested approximately two weeks later. Any positive agglutination test should be validated with ancillary testing before the animal is considered to be truly positive.

Agar gel immunodiffusion (AGID) assays are frequently used as the confirmatory test of choice for other serologic assays, although positive cross-reactions are common. Enzyme-linked immunosorbent assays (ELISAs) detect antibodies to the organism and may be more rapid and specific than agglutination or AGID assays. Positive dogs can be detected within 30 days of infection using this test, but current availability of this test is limited commercially.

Most recently, real-time polymerase chain reaction (PCR) testing has become available as a rapid, sensitive, and specific assay for *Brucella* species. It also has the benefit of being able to directly detect *Brucella canis* DNA in blood and tissues. It is likely that PCR will be the diagnostic test of choice in the future as it becomes more widely available.

Therapy

Due to the intracellular location of *Brucella* bacteria, antimicrobial treatments are challenging. There is no vaccine currently available. While it is possible for aborting females to subsequently carry and produce litters without treatment, infection is likely to be transmitted to offspring and infected dogs remain a risk to other dogs and humans.

Infected animals should be quarantined and removed from the breeding population via surgical sterilization. In kennel situations where infected animals are identified, euthanasia may be recommended to prevent transmission of disease and resident animals should be tested monthly. New animals introduced to the kennel should be isolated until two negative screening tests are obtained at least 30 days apart. Breeding animals should be screened serologically every six months prior to breeding.

No single antimicrobial protocol has been shown to consistently eliminate the disease long term. Many believe that permanent cures may not be possible even with surgical sterilization and antimicrobial treatment. Combination protocols with aminoglycosides and tetracyclines (gentamicin 5 mg/kg SC q24h for seven days, repeated every three weeks for three months, and doxycycline 10 mg/kg orally q12h), or tetracyclines and streptomycin (tetracycline 30 mg/kg orally q12h for 28 days and streptomycin 20 mg/kg IV q24h for 14 days) show the most success, but even with treatment, titers may reappear much later after infection, especially during times of stress. A protocol using twice-daily oral enrofloxacin

(5 mg/kg q12h for 30 days) has been described as successful in preserving fertility in a kennel outbreak situation, although some dogs had persistently elevated antibodies and subsequent treatments were required.

Prognosis

As infected dogs rarely show clinical signs, prognosis for survival is excellent. However, since infected dogs remain a potential source for infection for other dogs and immunocompromised humans, they should be kept in isolation from these individuals. Infected dogs should not be used for breeding and infection may be devastating to a breeding kennel due to its rapid spread.

Public Health Implications

Due to zoonotic concern, *B. canis* is a reportable disease in most states. Human case reports are often limited to laboratory workers and immunocompromised individuals. Most infections in people are mild although serious illness can occur. The disease may be underreported in humans due to varying clinical symptoms, which may mimic other diseases. Krueger and workers showed in a 2014 study that based on serologic testing, kennel employees and dog breeders are most likely to be exposed and many may have experienced *Brucella*-associated illness without diagnosis. Fortunately, humans respond well to antibiotic therapy and the disease is cleared when treated appropriately long term.

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106

Tetanus and Botulism

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Tetanus

Etiology and Pathophysiology

Tetanus results from the effects of tetanus toxin (tetanospasmin) which is released by the anaerobic bacillus *Clostridium tetani*. Spores of *C. tetani* are ubiquitous, survive in soil, and can contaminate and infect wounds. Thus, tetanus is a true toxicoinfection in which the toxin is produced and released within the infected wound. Following binding to peripheral nerve surface ganglioside receptors, the toxin (L-chain of tetanospasmin) is internalized into the peripheral nerve terminals. Tetanospasmin undergoes retrograde axonal transport to the spinal cord or brainstem, where it migrates transsynaptically to its site of action, inhibitory interneurons which utilize glycine or gamma-aminobutyric acid (GABA) as neurotransmitters. Tetanospasmin acts as a metalloproteinase which cleaves and inactivates a vesicle-associated membrane protein (VAMP) called synaptobrevin. Synaptobrevin mediates fusion of vesicles with the neuronal membrane and release of neurotransmitter into the synaptic cleft. Interference with the release of glycine from inhibitory neurons in the spinal cord and brainstem results in stimulus-sensitive muscle rigidity and spasticity worsened by touching, stretching or noise.

Tetanus can be localized or generalized. With localized tetanus, the toxin migrates only to the inhibitory interneurons in the spinal cord segments which are closest to the injury site and there is no hematogenous spread to distant synapses or further transsynaptic migration as in generalized tetanus.

Epidemiology

Tetanus occurs in a worldwide distribution. Dogs are less sensitive to the effects of tetanus toxin than horses or humans, and cats are more resistant than dogs. Consequently, localized tetanus is more frequently reported in cats than in dogs.

Signalment

Any dog or cat of any breed or age can be affected, but younger animals appear to be more susceptible.

History

Many patients have a history of an infected wound within the previous 10 days (up to three weeks). Draining wounds, tracts or wounds of the feet are frequent causes. Rarely, tetanus may occur following non-sterile surgical procedures, intraabdominal (female reproductive tract) or dental infections. Occasionally, the initial site of infection may not be detectable. Previous paw wounds may be diifucult to detect and only mild swelling may be evident despite ongoing infection. Radiographs of the paws are often indicated to identify foreign bodies and ongoing osteomyelitis which may require surgical management.

Clinical Signs

Localized tetanus presents with rigidity or stiffness, often resulting in rigid extension of one or both limbs, usually the ones next to the infection site or injury. Generalized tetanus causes signs of generalized muscle stiffness and rigidity, which are exacerbated by excitement, touch, or noise. Generalized tetanus is always associated with characteristic head muscle spasms resulting in trismus, erect ears, which are drawn together, excessive wrinkling of the forehead, drawn-back muzzle (risus sardonicus), and episodic prolapse of the third eyelid. Initially, only salivation, miosis, enopththalmos, risus sardonicus, erect ears or trismus may be present (severity class I), but these may progress to severe trismus, dysphagia, and generalized extensor rigidity

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presenting as a stiff gait and sawhorse stance (severity class II), or recumbency with rigid extension of all limbs, muscle fasciculations, spasms, seizures, and opisthotonus (severity class III). Severity class IV involves autonomic dysregulation of heart rate and blood pressure. Mental status is usually normal unless severe hyperthermia or a seizure develops. Trismus, pharyngeal and laryngeal muscle spasms impair food and water intake and increase the risk for aspiration pneuomonia. Complications in severely affected animals are respiratory distress and aspiration pneumonia, hyperthermia, gastrointestinal ulceration, multiple organ failure, and autonomic failure. Hiatal hernia, megaesophagus, and urethral sphincter spasms may occur. Autonomic failure results in bradyarrhythmias and blood pressure variability.

Diagnosis

Tetanus is one of the rare diseases in which diagnosis is solely based on a combination of characteristic clinical signs and history. Attempts to culture *C. tetani* from the wound are often not successful and do not prove toxin production. Real-time polymerase chain reaction (PCR) for detection of the neurotoxin gene fragments of *C. tetani* has been used to support the diagnosis in humans. Continuous motor unit activity in antagonistic flexor and extensor muscles and repetitive discharges following peripheral nerve stimulation during electromyography may suggest tetanus but these findings are not specific.

Therapy

Routine first line management consists of application of tetanus antitoxin, metronidazole TID, sedatives and thorough investigation for an infected wound, especially on the paws. Equine tetanus antitoxin (median dosage 100–300 U/kg IV, range up to 1000 U/kg, higher dose given to smaller patients, not to exceed 20 000 units) should be given once immediately upon hospital admission slowly over 5–10 minutes and also prior to any wound management. Tetanus antitoxin will neutralize any free unbound toxin in the circulation but is not effective against the toxin once it has been internalized. Intravenous administration of equine tetanus antitoxin is preferred to intramuscular application of human tetanus immunoglobulin. Intravenous administration achieves a rapid increase in circulating antitoxin, but is associated with risk of anaphylaxis. An intradermal or subcutaneous test dose is routinely recommended but its predictive value is poor. The antihistamine diphenhydramine may be given prior to tetanus antitoxin administration. Tetanus antitoxin (500–1000 units) should also be injected locally proximal and around the wound and prior to any surgical exploration. Intrathecal injection into the subarachnoid space (1000 units preservative-free antitoxin) has been beneficial in human patients.

Metronidazole 10 mg/kg TID IV is the preferred drug for treatment of clostridial infection. Penicillin G is also an appropriate choice, although the fact that it is a GABA antagonist should be considered. Antimicrobial treatment should be continued for 7–10 days. Surgical wound debridement may be necessary.

It is of the utmost importance to keep the animals in a quiet noise-protected environment and to avoid any unnecessary manipulations. Ear plugs should be considered. Diazepam, acepromazine (0.005 - 0.02 mg/kg/h CRI or repeated injections as needed), chlorpromazine or methocarbamol (5 - 10 mg/kg/h CRI or 30 - 60 mg/kg QID IV) alone or in combination may achieve sufficient muscle relaxation and sedation in milder affected cases (class I). Dexmedetomidine CRI (25 µg/m2/h) is very effective to provide a continuous state of sedation. Diazepam or midazolam constant rate infusion (CRI) and phenobarbital CRI, or even general anesthesia may be necessary to achieve muscle relaxation in severe generalized tetanus. Propofol or pentobarbital CRI may also be used. Magnesium sulfate CRI has been beneficial as an adjunctive treatment. Pain should be addressed aggressively. Opioids are preferred to non-steroidal analgesics e. g. butorphanol (0.1 - 0.2 mg/kg/h CRI) or fentanyl CRI. Rescue therapy in humans consists of intrathecal baclofen, anesthesia with neuromuscular blockade, and positive pressure ventilation.

Management of severe generalized tetanus requires intensive supportive care in the intensive care unit for up to three weeks. This is an essential part of the management of generalized tetanus and needs to be communicated to the clients. Parenteral nutrition or an esophagostomy tube may be necessary to address caloric needs and keep the animal hydrated if trismus develops. Urinary catheterization may be necessary. Patients need to be closely monitored for signs of autonomic failure (heart rate, blood pressure regulation) including life-threatening bradyarrhythmias and signs of aspiration pneumonia.

Glucocorticoids are contraindicated in the management of tetanus.

Prognosis

Patients can completely recover within 4–6 weeks. Published survival rates are from 50% to 80%. Prognosis varies with tetanus severity classification. Sleep disturbances are reported following recovery from tetanus.

Public Health Implications

Body fluids and tissues, urine, and feces should be handled with care and appropriately labeled before submitting to the laboratory as they may contain toxin. Animals with tetanus have the potential to cause bite wounds as well.

Botulism

Etiology and Pathophysiology

Botulism results from ingestion of spoiled food or dead carcases which have been contaminated with bacteria of the species *Clostridium botulinum*. Clinical signs of botulism are due to the effects of *C. botulinum* neurotoxins which are already present in the food. Unlike tetanus, botulism is a true intoxication, in which the preformed toxin is ingested with the food, rather than an infection. Up to now, seven types of neurotoxin have been identified (botulinum toxins A–G). In people, types A and B are identified in most intoxications, while type C remains the most commonly reported toxin in dogs and also in one case series describing occurrence of botulism in cats. Toxicoinfection, in which the toxin forms secondary to bacterial growth in the gut or a wound, is recognized in people (wound botulism in drug abusers) but has not been described in dogs.

Once the ingested toxin passes the gastrointestinal (GI) barrier and gains access to the systemic blood circulation, it binds to surface ganglioside receptors on the peripheral nerve endings of motor nerves, which utilize acetylcholine as the neurotransmitter. Following internalization, the L-chain of botulinum neurotoxin remains in the presynaptic motor nerve terminals. Unlike tetanospasmin, botulinum neurotoxin does not undergo retrograde axonal transport. Each type of botulinum toxin (L-chain) targets specific proteins of the SNARE protein family, which mediate neurotransmitter release in the synaptic cleft. Thus, all types of botulinum toxins result in a similar functional deficit, namely impaired release of acetylcholine into the synaptic cleft in response to arriving action potentials and influx of calcium. Functionally, botulism represents a presynaptic neuromuscular transmission disorder.

Epidemiology

Botulism can occur worldwide. Groups of animals may be affected if they share feeding habits, such as several dogs eating from a large animal carcase or when spoiled contaminated food is fed to several dogs. Outbreaks may also occur around polluted lakes when dogs ingest dead waterfowl harboring *C. botulinum* in their guts. Nevertheless, isolated cases of botulism may also occur

Signalment

Any dog of any age can be affected. There is only one report of botulism in cats.

History and Clinical Signs

A thorough dietary history is essential. Botulism is considered if ingestion of dead fish, dead waterfowl, other animal carcases or rotten meat is reported. Feeding a raw food and bones diet should be considered a risk factor.

Botulism has a rapid onset of action. Intoxicated animals present with acute onset of generalized lower motor neuron paresis or paralysis. In many cases, peak paralysis will be reached within a day. Uncommonly, a more protracted onset over several days has been reported. Neurologic examination shows normal mentation, flaccid generalized lower motor neuron paresis or paralysis with absent spinal reflexes of all limbs. Additional cranial nerve signs such as mydriasis, facial nerve paralysis, and/or tongue paralysis may occur in more severely affected dogs. Respiratory movements may be impaired due to diaphragmatic or intercostal muscle paralysis. Laryngeal paralysis may co-exist. There is no evident hyperesthesia on palpation of the spine or muscles. In people, prolonged autonomic impairment following recovery from botulism is a concern but has not been described in dogs.

Diagnosis

Clinical suspicion of botulism is based on the neurologic signs of acute lower motor neuron paresis or paralysis and a history suggestive of possible toxin uptake in the absence of other causes such as polyradiculoneuritis, raccoon bites, tick paralysis, myasthenia gravis (crisis), coral snake poisoning, and ionophore toxicity. Confirmation is obtained by the detection of botulinum neurotoxin (direct evidence) or botulinum toxin producing Clostridia (indirect evidence) in the serum or feces by mouse bioassay. Toxin-specific enzyme-linked immunosorbent assays (ELISAs) or PCR are increasingly available for toxin detection, but their sensitivity may be lower than the mouse bioassay. Serum antibodies against botulinum neurotoxins may appear during the recovery phase. Unless seroconversion or a significant rise in titers is demonstrated, they can only be considered as a rather nonspecific indicator of exposure because antibody may also be present in normal dogs. Notably, results of confirmatory tests (toxin assays, toxin-specific antibodies) are usually obtained with a significant time delay for up to seven days or more, and thus offer little help for the initial emergency management of the patient.

Electrodiagnostic examinations may facilitate diagnosis , because they offer a readily available bedside test. When performed within the first days after onset, EMG will be remarkably unremarkable. Distal peripheral nerve stimulation results in a compound action potential of normal morphology but with a reduced amplitude and area. Nerve conduction is commonly normal. In contrast to polyradiculoneuritis there is no temporal dispersion. Repetitive stimulation may show a decrement or increment or be normal. Consequently, high-frequency repetitive stimulation has been recommended. However, examination in normal dogs showed variable results,

limiting the value of this test due to a lack of specificity. Botulism may result in mild spontaneous electric activity from denervation in the second week after onset and also a mild decrease in nerve conduction velocity, but electrodiagnostic examination is rarely performed at that time due to the early disease peak followed by gradual recovery starting at day 5–7 after onset.

Therapy

The focus of therapy is to provide supportive care to the patient. Clinicians should not be reluctant to provide ventilator support if there is obvious respiratory impairment. Especially during the first two days after onset, the dog's respiration needs to be carefully monitored.

The use of botulinum antitoxin is controversial. First, botulinum antitoxin needs to be directed against the specific toxin type, which suggests that antitoxin CD should probably be used in dogs. There is a risk for anaphylaxis but this appears to be low. A subcutaneous test dose may be applied 30–45 minutes prior to IV application and pretreatment with diphenhydramine considered. Botulinum antitoxin will only be able to neutralize the free unbound fraction of toxin in the systemic circulation but not the bound and internalized toxin which is responsible for the observed clinical signs. Consequently, the goal behind the application of toxin type-specific botulinum antitoxin is to prevent further progression of the paralysis and specifically to avoid respiratory paralysis and the need for ventilatory support in cases with large amounts of circulating unbound toxin or ongoing GI absorption.

Supportive care should include adequate bedding, frequent turning, and intravenous fluids. Nutritional support is also needed if the dogs are unable to eat or drink on their own. Application of an eye lubricant is indicated if facial movements and lid closure are impaired. Any dog with botulism needs to assessed carefully for the presence of megaesophagus. Prolonged autonomic dysfunction as a consequence of botulism is a concern in humans, thus bladder emptying and GI motility should be closely monitored. Drugs that can impair neuromuscular transmission (clindamycin, aminoglycosides, neuromuscular blocking agents) and glucocorticoids should be avoided. In severely affected animals with respiratory distress, early intubation and ventilation should be considered as a life-saving tool.

Prognosis

Most dogs recover from botulism within 2–3 weeks if they do not die from respiratory arrest at the peak of the paralysis.

Public Health Implications

Botulism cannot be transmitted directly from dogs and cats to people but body fluids and tissues, urine, and feces should be handled with care and appropriately labeled before submitting to the laboratory as they may contain toxin.

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107

Anthrax

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Etiology/Pathophysiology

Anthrax is a life-threatening infectious disease that normally affects animals, especially ruminants (such as goats, cattle, sheep, and horses). Both the dog and cat appear to be relatively resistant to the inhalational and cutaneous forms of anthrax, but clinical disease associated with ingestion of contaminated carcases is reported. Because dogs and cats may theoretically act as sentinels for infection in people during bioterrorist attacks, familiarity with the disease is important for the small animal clinician.

The agent of anthrax is a bacterium called *Bacillus anthracis* and it possesses three known virulence factors: an antiphagocytic capsule and two protein exotoxins, called the *lethal* and the *edema* toxins. The role of the capsule in pathogenesis was demonstrated in the early 1900s, when anthrax strains lacking a capsule were shown to be avirulent. The capsule is composed of a polymer of poly-D-glutamic acid, which confers resistance to phagocytosis and may contribute to the resistance of anthrax through lysis by serum cationic proteins.The anthrax toxins, like many bacterial and plant toxins, possess two components: a cell-binding, or B, domain necessary for entry into the host cell, and an enzymatically active, or A, domain that has the toxic and, usually, the enzymatic activity. The two toxins are unusual in that the B protein, called *protective antigen* (molecular weight [MW] 83 000), is shared by both toxins. Thus, the lethal toxin is composed of the protective antigen combined with a second protein, which is known as the *lethal factor* (MW 90 000). The lethal toxin is lethal for experimental animals and also has been shown to possess similar structure and activity to metalloproteases, although no direct enzymatic activity has yet been discovered.

The edema toxin, consisting of the same protective antigen together with a third protein, *edema factor* (MW 89 000), causes edema when injected into the skin of experimental animals. The edema factor is a calmodulin-dependent adenylate cyclase, which elevates intracellular cyclic adenosine monophosphate, and which is likely to be responsible for the marked edema often present at the site of bacterial replication.

Each of the three toxin proteins – the B protein and both A proteins – individually is without biologic activity. The critical role of the toxins in pathogenesis was established when it was shown that deletion of the toxin-encoding plasmid or the protective antigen gene alone attenuates the organism. The lethal toxin also appears to be more important for virulence in a mouse model than the edema toxin.

Anthrax can infect humans in three ways. The most common is infection through the skin, which causes an ugly sore that usually goes away without treatment. Humans and animals can ingest anthrax from carcases of dead animals or contaminated soil/plant materials that have been contaminated with anthrax. Ingestion of anthrax can cause serious, sometimes fatal disease. The most deadly form is inhalation anthrax. If the spores of anthrax are inhaled, they migrate to lymph nodes in the chest where they proliferate, spread, and produce toxins that often cause death. Interestingly, the dog is quite resistant to inhalational anthrax. Experimental studies have shown it required over 150 times the dosage in dogs as compared to humans. Likely it is the long nose of the dog which serves as an effective filtration system in preventing the usual fatal inhalational form of anthrax.

Infection is initiated with the introduction of the spore through a break in the skin (cutaneous anthrax), through entry through the mucosa (gastrointestinal anthrax), or inhalation of spores 1–2 μm in diameter. After ingestion by macrophages at the site of entry, germination to the vegetative form occurs, followed by extracellular multiplication and capsule and toxin production. In the lungs, the

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anthrax spores are deposited in alveolar spaces and from there are transported by lymphatics to regional lymph nodes where germination occurs up to 60 days later.

Signalment

Anthrax occurs throughout the world. *B. anthracis* exists in the soil as a spore. The question remains unsettled as to whether its persistence in the soil is due to significant multiplication of the organism in the soil or if it is due solely to cycles of bacterial amplification in infected animals whose carcases then recontaminate the soil. The form of the organism in infected animals is the bacillus. Only when the organism in the carcass is exposed to oxygen does sporulation occur.

Anthrax is most common in agricultural regions where it occurs in animals. It is primarily a disease of herbivores (Table 107.1); carnivores and humans are incidental hosts. Animals, domestic or wild, become infected when they ingest spores while grazing on contaminated land or eating contaminated feed. Environmental conditions such as drought, which may promote trauma in the oral cavity during grazing, are thought to increase the chances of acquiring anthrax. It is spread from animal to animal by mechanical means and biting flies. Spread from one environmental site to another appears to occur via nonbiting flies, rodents, and carrion-eating birds. Free anthrax spores can also be spread by water and wind.

Human anthrax victims can also theoretically spread anthrax spores that landed on their clothing and external body surfaces. Therefore, each victim should be decontaminated and issued new clothes *before* leaving the scene. Estimates have shown that ~90% of anthrax will be on the clothes of a person exposed to an anthrax aerosol. Affected clothing should either be destroyed or can be washed using a 0.5% hypochlorite solution. Wounded or discharged victims will create a possible vector if they are not properly decontaminated. Anthrax does not readily transfer from one person to another unless the spores are in the clothing/shoes and there is some method of moving the spores to another person. Once a rescuer walks in the anthrax, then the threat of "movement" to other areas is very real.

Bodies that are not immediately recoverable pose little threat. Anthrax doesn't "jump up and bite you or me"! As long as the bodies are not disturbed and/or wind movement is low, the anthrax will stay inside the bodies or in the clothing.

History and Clinical Signs

Anthrax in veterinary species may be peracute, acute or subacute, or chronic. The peracute form most frequently affects cattle, sheep, and goats. The acute or subacute form is common in cattle, sheep, and horses. Chronic anthrax is most often seen in less susceptible species such as swine but may also be seen in cattle, horses, dogs, and cats. Suspicions of anthrax are raised when livestock are found dead, bloated, and without rigor mortis. Blood is usually evident at body orifices.

Dogs and Cats

Both the dog and cat appear to be relatively resistant to anthrax. Dogs are supposedly 500–1000 times more resistant to anthrax infection than humans. The gastro-

Table 107.1 Anthrax severity in potentially affected species

Dogs	Horses	Cattle	Sheep	Goats	Pigs	Cats	Birds	Other animals
D	**S**	**S**	**S**	**S**	**D**	**D**	Resistant	**S** Wild herbivores and carnivores camels, antelope, guinea pigs

Source: Wingfield *et al.* (2009). Reproduced with permission of John Wiley & Sons.
D, moderate; S, severe.

intestinal form is most common. In most cases, consumption of tissue from infected livestock is considered the source of the infection. Inhalational and cutaneous anthrax have not been reported in dogs and cats. Their longer noses and dense hair coats are possible reasons for this.

Clinical signs of anthrax include respiratory distress and dysphagia resulting from swelling of the neck secondary to regional lymphadenopathy, hemorrhagic and ulcerative inflammation of the oral cavity and pharynx, hemoptysis, lingual swelling, enteritis, and enlargement of the kidneys, spleen, and liver. Sudden death with few premonitory signs has also been reported. The incubation period in naturally infected carnivores is often difficult to determine, but it is believed to be approximately 3–7 days with a range of 1–14 days.

Pets exposed to anthrax will likely be subject to the gastrointestinal problems listed above but may complicate matters for their owners/rescuers with their thick fur harboring *B. anthracis* spores. When petted or handled, these spores can be aerosolized and expose the pet owner or rescuer. Additionally, dogs and cats "wash" their feet/bodies with their tongue, which transfers the anthrax directly into the pet (possibly initiating either pharyngeal or gastrointestinal anthrax). These facts would seem to favor early decontamination and quarantine of exposed animals.

Birds

Birds are usually highly resistant to anthrax. Buzzards, vultures, and other carrion-eating birds may transmit the spores on their talons and beaks.

Humans

People are infected with anthrax in three ways: cutaneous, gastrointestinal, and inhalational.

Diagnosis

Bacillus anthracis is a large, gram-positive, encapsulated, spore-forming, nonmotile bacillus (1–1.5 µm × 3–10 µm), grows readily on sheep blood agar aerobically, and is nonhemolytic under these conditions. The colonies are large, rough, and grayish-white, with irregular, curving marginal outgrowths. Both *in vitro* in the presence of bicarbonate and carbon dioxide, and in tissue *in vivo*, *B. anthracis* forms a prominent capsule. In tissue, the encapsulated bacterium occurs singly or in chains of two or three bacilli. The organism does not form spores in living tissue; sporulation occurs only after the infected body has been opened and exposed to oxygen. Remember that samples are highly infectious! Extreme caution should be taken in collecting, preparing for shipment, or transporting any material suspected of being contaminated with this bacterial agent. Contact your state public health service for specific instructions. The spores are oval and occur centrally or paracentrally. They are very resistant and may survive in the environment for *decades* in certain soil conditions. Bacterial identification is confirmed by gram stain and culture techniques, immunofluorescence assays (IFA), enzyme-linked immunosorbent assays (ELISA), or polymerase chain reaction (PCR). Each of these tests has limitations, with the standard still being the direct identification of the organism.

Therapy

Anthrax is a reportable disease. That means that local or state health agencies must be notified if a case of anthrax is diagnosed in dogs, cats, and other veterinary species.

Treatment for anthrax in small animals is undocumented at this time. Natural strains of *B. anthracis* are usually susceptible to several antibiotics; most but not all natural strains are susceptible to penicillin (dogs: penicillin G potassium 20 000 U/kg IV, IM, SC q4h). Some strains, particularly those used in bioterrorist attacks, may be resistant to penicillin. For this reason, the Centers for Disease Control and Prevention (CDC) recommends other antibiotics (Table 107.2) as the initial treatment, particularly for systemic disease, until antibiotic

Table 107.2 *In vitro* antimicrobial susceptibility of *B. anthracis*

Susceptible	Resistant
Ciprofloxacin	Cefuroxime
Ofloxacin	Cefotaxime
Levofloxacin	Ceftazidime
Tetracyclines	Aztreonam
Chloramphenicol	Trimethoprim
Macrolides	Sulfamethoxazole
Doxycycline	
Aminoglycosides	
Clindamycin	
Imipenem	
Rifampin	
Vancomycin	
Cefazolin	
Other first-generation cephalosporins	

susceptibility has been determined. Antibiotics are effective only against the vegetative stage of *B. anthracis*, and not against spores. Treatment is continued for at least 60 days in people with inhalational anthrax, as spores may remain dormant in the lungs and germinate during that time.

The pulmonary form of anthrax in people is a medical emergency. Early and continuous intravenous therapy with antibiotics may be life-saving and ventilator support is often required. In a bioterrorism attack, humans exposed to anthrax will be given antibiotics before they become sick. A vaccine exists but is not yet available to the general public. Most experts think that the vaccine will also be given to exposed individuals who are victims of a bioterrorist attack. Supportive therapy may also be necessary, particularly for the inhalational and gastrointestinal forms.

Effective treatment depends on early recognition of the symptoms. Treatment for cutaneous anthrax is usually effective, but the inhalational and gastrointestinal forms are difficult to recognize early and the mortality rates are higher.

Public Health Implications

Anthrax in humans is associated with agricultural, horticultural, or industrial exposure to infected animals or contaminated animal products, and as a weapon of mass destruction disseminated by terrorists. In less developed countries, primarily in Africa, Asia, and the Middle East, anthrax occurs from contact with infected domesticated animals or contaminated animal products. This includes handling contaminated carcases, hides, wool, hair, and bones, and ingesting contaminated meat. Cases associated with industrial exposure are rarely seen today but may occur in workers processing contaminated hair, wool, hides, and bones. Direct contact with contaminated material leads to cutaneous disease, while ingestion of infected meat gives rise to oropharyngeal or gastrointestinal forms of anthrax. Inhalation of a sufficient quantity of spores, usually seen only during generation of aerosols in an enclosed space, is associated with processing contaminated wool or hair, or opening anthrax-laced letters, giving rise to inhalational anthrax.

In mail-handling sites, *B. anthracis* spores may be aerosolized during the operation and maintenance of high-speed mail-sorting machines, potentially exposing workers and other mail. In addition, these spores could get into heating, ventilating, or air-conditioning systems.

Unreliable reporting makes it difficult to estimate with accuracy the true incidence of human anthrax. It was estimated in 1958 that worldwide between 20 000 and 100 000 cases occurred annually. In more recent years, anthrax in animals has been reported from 82 countries, and human cases continue to be reported from Africa, Asia, Europe, and the Americas. In the United States, the annual incidence of human anthrax had steadily declined, from about 127 cases in the early years of this century to about one per year over the past 10 years. The vast majority of cases were cutaneous. Under natural conditions, inhalational anthrax is exceedingly rare, with only 18 cases having been reported in the United States in the 20th century.

Outbreaks of Weaponized Anthrax

Weaponized anthrax has caused two outbreaks of disease (key points from each are outlined in the sections below).

Sverdlovsk Outbreak – 1979

This outbreak in the Union of Soviet Socialist Republics resulted from accidental release of anthrax spores from a military microbiologic facility where weaponized anthrax was being produced.

Seventy-seven human cases were reported and 66 of the patients died, for a case–fatality rate of 86%; 75 cases were inhalational and two were cutaneous (one on the back of the neck and one on the shoulder). A recent statistical analysis of available data suggests that 250 cases with 100 fatalities may actually have occurred. The mean patient age for males was 42 and for females was 55 years, and interestingly no cases were reported in children.

United States – 2001

This outbreak predominantly involved direct exposure to mail that was deliberately contaminated with anthrax spores. Several contaminated letters were sent and one was reported to contain 2 g of powder, with 100 billion to 1 trillion anthrax spores per gram.

Twenty-two cases (11 inhalational and 11 cutaneous) were identified. Five of the patients with inhalational anthrax died, for a case–fatality rate of 45% among that group. The outbreak demonstrated several important points about weaponized anthrax: mail can be an effective vehicle for disseminating anthrax spores; cross-contamination of mail likely can occur within postal facilities; and persons who handle or process unopened contaminated mail are at risk of acquiring anthrax. Substantial environmental contamination can occur in facilities handling contaminated mail or in offices where contaminated mail is opened.

Prevention

Public health measures to prevent contact with infected animals are invaluable. There is a vaccine available for

people at high risk (such as veterinarians, laboratory technicians, employees of textile mills processing imported goat hair, and members of the armed forces). The Department of Defense and the Centers for Disease Control and Prevention are working hard to prevent a bioterrorist attack and to be prepared to deal with the consequences if one occurs. For anthrax, vaccines with greater efficacy and fewer side-effects are under development. Currently, most vaccines are given by injection. Early studies in experimental animals are showing promise for an oral vaccine for anthrax.

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108

Actinomycosis, Nocardiosis, and Mycobacterial Infections

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Actinomyces, *Nocardia*, and *Mycobacteria* belong to the order Actinomycetales. All are bacilli that form branching filaments and cause pyogranulomatous infections. However, differences in antimicrobial susceptibility patterns, zoonotic implications, and prognoses make an understanding of how the organisms are differentiated clinically important.

Actinomycosis

Etiology/Pathophysiology and Epidemiology

Actinomyces spp. are facultatively anaerobic or microaerophilic, Gram-positive, nonacid-fast, nonsporulating, and nonmotile bacilli. These opportunistic pathogens are commensals of the mucous membranes, especially the oral cavity but also the gastrointestinal and genitourinary tracts. *Actinomyces* are often involved in polymicrobial infections that enhance their pathogenicity. *A. viscosus*, *A. hordeovulneris*, *A. bowdenii*, *A. canis*, *A. catuli*, *A. turicensis*, *A. weissii*, and *A. odontolyticus* have been isolated from canine infections. *A. viscosus*, *A. meyeri*, *A. odontolyticus*, *A. hordeovulneris*, and *A. bowdenii* have been isolated from infections in cats. *Actinomyces pyogenes* was recently reclassified based on 16S rRNA gene sequencing to be included in the genus *Arcanobacterium*. This organism has been reported to produce actinomycosis-like infections in both dogs and cats.

Actinomyces cause disease following inoculation of body tissues, frequently in conjunction with other bacteria. Portals of entry include oral mucosa damaged by chronic gingivitis and periodontal disease, foreign body migration, subcutaneous inoculation via bite wounds or plant material, and aspiration of oropharyngeal material or grass awns. Infections occur primarily in immunocompetent individuals.

Actinomyces form histopathologic lesions characterized by pyogranulomatous inflammation with areas of central necrosis surrounded by macrophages, neutrophils, and plasma cells. Subacute and chronic infections result in granulation tissue formation, extensive fibrosis, and sinus tracts. Exudates and effusions are often malodorous. *Actinomyces* may form bacterial colonies in infected body fluids, commonly referred to as "sulphur granules," that grossly appear tan or white.

Signalment

Young, male, large-breed outdoor dogs are overrepresented. Hunting and working animals are often affected, particularly with soft tissue abscesses or pyothorax associated with plant material foreign bodies. Young, male cats are also at increased risk from aggressive interactions involving scratches and bite wounds resulting in inoculation of oral bacteria.

History and Clinical Signs

In both dogs and cats actinomycosis is most commonly associated with subcutaneous and soft tissue abscesses and intrathoracic disease. Clinical findings may include pneumonia, lymphadenopathy, intra- or extrapulmonary masses or pyothorax. Central nervous system (CNS), periodontal, ocular, peritoneal, urinary bladder, cardiac, and orthopedic infections have also been reported in dogs. In cats, less common presentations include abdominal granulomas, intracranial/spinal empyema, and cholecystitis.

Cervicofacial actinomycosis occurs in both cats and dogs associated with extension of oral bacteria into the soft tissues of the head and neck secondary to periodontal

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disease, oral trauma, and bite wounds. Lesions most commonly develop around the jaw and neck.

Cutaneous and subcutaneous actinomycosis manifests as flocculent to firm masses often with draining sinus tracts typically on the thoracic wall, flanks or limbs. These lesions in dogs are often secondary to migrating grass awns. In cats, they are associated with bite wounds.

Thoracic actinomycosis can present as pneumonia, lymphadenopathy, intra- or extrapulmonary masses or pyothorax. Thoracic actinomycosis in cats occurs secondary to aspiration of oral flora whereas canine infections are secondary to inhalation and migration of grass awns. Clinical signs may be nonspecific, such as lethargy and weight loss, or can include tachypnea, dyspnea, and coughing. Foreign bodies in dogs can migrate further into the retroperitoneum, resulting in abscessation in this area.

Abdominal, visceral, and central nervous system infections can develop from extension of subcutaneous infections, foreign body migration or hematogenous spread. Osseous infections can result from extension from other locations or contamination of orthopedic implants.

Diagnosis

A provisional diagnosis of actinomycosis is based on the identification of Gram-positive, nonacid-fast filamentous organisms on cytologic examination of fluid or tissues from suspicious lesions using a modified Ziehl–Neelson (Kinyuon) method. A definitive diagnosis requires either isolation and phenotypic identification of the causative agent using biochemical methods, chemotaxonomy, and serology or identification using molecular methods. Molecular methods, most commonly 16S rRNA gene sequencing, are now the diagnostic techniques of choice for identifying the infecting species as they provide accurate and rapid results. It is important to note that culture and polymerase chain reaction (PCR) can be negative in some cases. Furthermore, culture or detecting organisms using PCR without compatible clinical signs may not be clinically significant since *Actinomyces* are commensals.

Therapy

The combination of surgery and antimicrobial treatment is generally superior to antimicrobial treatment alone in resolving *Actinomyces* infections in which a foreign body is suspected. Thoracotomy and debridement are recommended in dogs with pyothorax, while cats generally require only tube thoracostomy in addition to medical therapy. This likely reflects the difference in etiologies in which canine infections generally result from foreign body migration and feline infections are caused by aspiration of oral flora. Prolonged antimicrobial therapy for several months is often required to resolve infection. *Actinomyces* spp. are susceptible to high doses of penicillins as well as other antibiotics (Table 108.1). As actinomycosis often occurs as a component of a mixed bacterial infection, identification, susceptibility testing, and treatment of the co-infectious agents are also imperative for resolution.

Prognosis

The prognosis for dogs and cats with subcutaneous and soft tissue actinomycosis and for cats with pyothorax is generally good when treated for sufficient time. However, reported survival rates in dogs with thoracic disease are variable and CNS actinomycosis is invariably fatal.

Table 108.1 Antimicrobials used to treat *Actinomyces* and *Nocardia* infections

	Canine	Feline
Actinomyces spp.	Penicillins • Ampicillin (10–20 mg/kg IV/IM/SC q6–8h) • Amoxicillin (10–30 mg/kg IM/SC/PO q12h) Macrolides/Lincosamides • Clindamycin (5 mg/kg IV/IM/SC/PO q12h) • Erythromycin (10 mg/kg PO q8h) Chloramphenicol* (50 mg/kg IV/IM/SC/PO q8h)	Penicillins • Ampicillin (10–20 mg/kg IV/IM/SC q6–8h) • Amoxicillin (10–30 mg/kg IM/SC/PO q12h) Macrolides/Lincosamides • Clindamycin (5 mg/kg IV/IM/SC/PO q12h) • Erythromycin (10 mg/kg PO q8h) Chloramphenicol* (50 mg IV/IM/SC/PO/cat q12h)
Nocardia spp.	Sulfonamides • Trimethoprim-sulfonamide* (30 mg/kg PO q12h) Amikacin (10–30 mg/kg IV/IM/SC q24h)* Imipenem-cilastatin (3-10 mg/kg slow IV q8h) Cefotaxime (25–50 mg/kg IV/IM/SC q6h)	Sulfonamides • Trimethoprim-sulfonamide* (30 mg/kg PO q12h) Amikacin (10–15 mg/kg IV/IM/SC q24h) Imipenem-cilastatin (3-10 mg/kg slow IV q8h) Cefotaxime (22 mg/kg IV/IM/SC q6–8h)

* Potential severe adverse drug effects.
For all medications please consult comprehensive formularies for potential adverse drug effects, interactions, and contraindications.
Please see text for further information regarding treatment protocols.
IM, intramuscular; IV, intravenous; PO, by mouth (*per os*); SC, subcutaneous.

Public Health Implications

Humans bitten by dogs or cats can develop actinomycosis. However, there have been no reports of transmission from infected animals to humans.

Nocardiosis

Etiology/Pathophysiology and Epidemiology

The genus *Nocardia* consists of filamentous, branching, Gram-positive, variably acid-fast, catalase-positive, nonmotile aerobic bacilli. Unlike commensal *Actinomyces*, *Nocardia* species are ubiquitous soil saprophytes, involved in plant decomposition. Pathogenic species have been isolated from house dust, garden soil, beach sand, swimming pools, and tap water in different geographic regions. Pathogenic *Nocardia* species in dogs include *N. caviae*, *N. asteroides*, *N. abscessus*, *N. otitidiscaviarum*, *N. brasiliensis*, *N. cyriacigeorgica*, and *N. veterana*, while those in cats include *N. tenerifensis*, *N. africana*, *N. nova*, *N. farcinica*, *N. cyriacigeorgica*, *N.brasiliensis*, and *N. elegans*. The virulence of *Nocardia* spp. varies with the phase of growth associated with changes in composition of the cell wall.

Infection with *Nocardia* species occurs after inhalation of aerosolized environmental organisms or inoculation via puncture wounds. The host T cell response is essential in limiting dissemination of nocardial infection following inoculation, but it is also responsible for the development of the characteristic suppurative to granulomatous lesions of nocardiosis.

Nocardiosis is less common than actinomycosis and in contrast to *Actinomyces*, *Nocardia* infections are most common in immunosuppressed patients.

Signalment

Localized infections, particularly abscesses of the subcutaneous tissues, are most frequently seen in young outdoor dogs secondary to foreign body migration and inoculation during puncture wounds. Similarly, cats of any age with outdoor access more commonly develop superficial lesions.

Disseminated or systemic nocardiosis develops in young and immunosuppressed dogs and cats. The increasing use of immunosuppressive medications in veterinary patients has resulted in an increase in the incidence of such infections.

History and Clinical Signs

Nocardiosis is typically classified as subcutaneous, pulmonary and systemic, or disseminated. In immunocompetent companion animals, especially cats, disease most commonly manifests as cutaneous and pulmonary lesions. Disseminated disease, often involving the CNS, has been reported more commonly in young and immunosuppressed dogs. *Nocardia* spp. have been isolated sporadically from cases of hepatitis and cystitis.

Cutaneous nocardiosis is the most common manifestation of disease in cats, associated with inoculation via scratches from cat fights and punctures from plant material.

Dogs and cats with disseminated or systemic disease typically have a history of immunosuppressive disease or administration of immunomodulating drugs. In particular, nocardiosis has been shown to occur currently with canine distemper virus infection in endemic areas.

Pulmonary nocardiosis may occur in isolation associated with wound inoculation or foreign body migration, or as a component of disseminated disease. In dogs, the most common clinical signs of pneumonia include dyspnea, nasal discharge, fever, weight loss, and anorexia.

Diagnosis

A presumptive diagnosis of nocardiosis may be made based upon macroscopic and microscopic examination of clinical specimens. Organisms on Gram-stained slides will appear as Gram-positive, thin filamentous organisms within a background of lymphocytes and macrophages. Acid-fast stains may be used to demonstrate acid-fastness in samples that have revealed filamentous organisms with Gram staining. However, this reaction is unreliable in direct clinical samples and may be dependent on the growth media used and age of culture samples. Species identification has traditionally been performed based on biochemical methods, chemotaxonomy, and serology. Molecular methods, most commonly 16S rRNA gene sequencing, are now used preferentially for bacterial identification as these provide accurate and rapid results.

Due to the ubiquitous nature of *Nocardia* spp., the significance of isolation of these organisms from clinical samples should be assessed in light of the clinical findings. Identification of the sample organism in multiple samples also aids in determining significance.

Therapy

Treatment of nocardiosis relies upon debridement and drainage of the lesion and prolonged antimicrobial therapy. Most *Nocardia* spp. are susceptible to sulfonamide antimicrobials and these often form the basis of medical therapy. However, species differences in susceptibility have been reported and *in vivo* response to treatment does not always reflect *in vitro* results. In humans, a range of other antimicrobials (see Table 108.1) are efficacious

with protocols based on established species-specific susceptibility patterns advocated for treatment of persistent or disseminated infections. Six to 12 months of antimicrobial therapy is required in most cases for optimal results. Alternatives to sulfonamides should be considered for prolonged treatment of nocardiosis to minimize the risk of adverse drug reactions.

Prognosis

While cases of superficial nocardiosis may show initial response to treatment, most patients are euthanized due to deterioration or disease recurrence. Disseminated nocardiosis, especially with CNS involvement, has a grave prognosis. The poor outcome for these patients is likely associated with the underlying immunosuppressive disease.

Public Health Implications

There have been no cases of acquired infection from infected animals, but cat scratches have caused cutaneous nocardiosis in people. Immunocompromised individuals should take special precautions when interacting with infected dogs or cats.

Mycobacteriosis

Etiology/Pathophysiology

Members of the genus *Mycobacterium* are intracellular, aerobic, acid-fast, nonspore-forming, environmentally resistant bacilli. *Mycobacteria* spp. are generally saprophytic and nonpathogenic, but several are primary or opportunistic pathogens in dogs cats, and humans. Infecting bacteria are phagocytosed by host macrophages within which the organism replicates. Infected macrophages produce proinflammatory mediators and attract monocytes and other inflammatory cells to the site of infection, resulting in focal or disseminated granulomatous to pyogranulomatous disease.

Mycobacterial infections are recognized increasingly in companion animals because of improved diagnostic techniques and increased use of immunosuppressive medications. Recent evidence suggests that the prevalence of mycobacteriosis in companion animals, particularly in the United Kingdom, is underestimated due to nonspecific signs, a low index of suspicion, and difficult antemortem diagnosis.

The mycobacteria that cause companion animal infections are generally divided into tuberculous, saprophytic or opportunistic, and lepromatous groups. Generally, the tuberculous group includes members of the *Mycobacterium tuberculosis* (MTB) complex, the saprophytic group includes members of the *M. avium* complex (MAC) and other nontuberculous bacteria, and the lepromatous group includes bacteria that cause feline leprosy and canine leproid granuloma syndromes (Table 108.2). However, there is much overlap in these categories since different organisms cause similar clinical lesions and there is disagreement in the grouping of organisms. Organisms from all groups can cause cutaneous lesions whereas systemic or disseminated disease results from infection with tuberculous or saprophytic/opportunistic agents.

Epidemiology

Tuberculosis is caused by infection with members of the MTB complex, all of which are obligate pathogens (see Table 108.2). The prevalence of disease within a region and the causative agent are dependent on the presence of the primary host species. Humans are the reservoir host for *M. tuberculosis* so the incidence of *M. tuberculosis* infection in dogs follows the distribution reported for people, and includes areas of the US, Africa, France, and Switzerland. *M. bovis* infections in people occur in Great Britain and New Zealand and consequently most feline infections are also reported in these regions.

Mycobacterium tuberculosis infection typically results from close contact with infected humans. Disease transmission occurs via inoculation, ingestion or inhalation. Organisms in sputum and respiratory secretions are aerosolized and inhaled or ingested by in-contact pets. However, due to the chronicity of disease and potential for hematogenous dissemination, the route of infection may not be identifiable at the time of diagnosis. Although there are minimal reports of transmission of *M. tuberculosis* from pets to their owners the zoonotic potential of infected animals is of major concern, particularly for immunocompromised owners.

The primary reservoir of *M. bovis* is domestic cattle, with transmission to dogs and cats thought to be due to ingestion of contaminated meat or milk. Cats and dogs are considered to be potential amplifier hosts of *M. bovis* in endemic areas, meaning that they may act as a source of infection for other animals and people. Rodents, feral pigs, wild deer, badgers, and opossums are established reservoir hosts for *M. bovis* and/or *microti*.

The occurrence of peripheral primary cutaneous lesions in cats suggests that some infections may develop following inoculation of organisms via bite wounds. Hunting and catching small rodents are risk factors for *M. microti* infection in cats.

The saprophytic mycobacteria are the most common causes of mycobacteriosis in cats and dogs. This group includes the rapid-growing mycobacteria (RGM) and

slow-growing mycobacteria (SGM) groups, including the *M. avium-intracellulare* complex (see Table 108.2). The saprophytic mycobacteria are widely distributed in the environment. They have variable geographic prevalence likely associated with environmental factors such as warmer temperatures that support their growth. Infection with RGM usually follows cutaneous, pulmonary or gastrointestinal inoculation. Disseminated disease may develop in immunosuppressed animals.

Canine and feline leproid syndromes are characterized by discrete cutaneous lesions. The causative agents are fastidious and cannot be cultured readily. Feline leprosy results from infection with one of a number of saprophytic species (see Table 108.2). *M. lepraemurium* infection is thought to be transmitted to cats by rodent bites. Insect vector transmission has also been proposed but is unverified.

It is not clear whether canine leproid granuloma syndrome results from infection with one or more species. Partial characterization using gene sequencing has shown that genetically identical organisms have been associated with the disease worldwide; however, the causative species remains incompletely defined due to inability to culture it in the laboratory. Transmission of the canine agent via insect vectors seems likely. Case clusters of disease in related foxhounds suggest additional environmental or genetic factors may be involved.

Signalment

Younger animals tend to be more commonly affected by mycobacteriosis, particularly cutaneous forms of the disease. This may be associated with increased exposure to environmental organisms and precipitating injuries that allow infection. Patients that develop disseminated disease are often suspected to be immunocompromised although supportive evidence for this may not be apparent. Tuberculosis is most commonly observed in animals with prolonged close contact with an infected primary host. Adult nonpedigree cats with outdoor access are most commonly affected, although Siamese cats are also overrepresented. Feline leprosy is most common in young cats and in older cats that are immunosuppressed. Canine leproid granuloma syndrome is most common in large-breed, short-haired dogs, especially boxers. Bassett hounds, schnauzers, and Abyssinian cats are overrepresented in disseminated saprophytic mycobacteriosis, suggesting genetic immunodeficiencies in these breeds.

Table 108.2 Mycobacteria spp. and their manifestations in dogs and cats

		Canine	Feline
Tuberculous		*M. bovis*[DCP] *M. tuberculosis*[DCL] *M. microti*[D]	*M. bovis*[CD] *M. microti*[CDL] *M. tuberculosis*[CD]
Saprophytic	Rapid growing	*M. fortuitum*[LC] *M. goodii*[CP] *M. smegmatis*[CP] *M. chelonae-abscessus*[L]	*M. fortuitum*[PCL] *M. smegmatis*[PD] *M. chelonae-abscessus*[PC] *M. alvei*[P] *M. goodii*[D] *M. thermoresistibile*[PL] *M. phlei*[P] *M. mucogenicum*[C] *M.* massilence[C]
	Slow growing	*M. avium* complex[D] *M. ulcerans*[C] *M. kansasii*[L]	*M. avium* complex[CDL] *M. ulcerans*[C] *M. terrae*[C] *M. xenopi*[PD] *M. simiae*[D] *M. celatum*[D] *M. malomense*[C] *M. heckeshornense*[D] *M. kansasii*[D]
Leproid syndromes		Unclassified species[C]	*M. lepraemurium*[C] *M. visibile*[C] *Canditatus 'M. tarwinense'*[C] *Canditatus 'M. lepraefelis'*[C,D] Unclassified species[C]

C, cutaneous lesions; D, disseminated disease; L, pulmonary disease; P, panniculitis.

History and Clinical Signs

Cutaneous lesions in mycobacteriosis vary. Leproid granulomas can be single or multiple nodules with or without ulceration and frequently occur on the head and limbs. The most common manifestation of tuberculosis and saprophytic mycobacterial infections in cats is the cutaneous form that results in the development of subcutaneous masses, often with draining sinuses and a regional lymphadenopathy. Skin lesions are usually mobile, firm, raised, moist, and without odor. The saprophytic mycobacterial agents have a predilection for adipose tissue and often cause a panniculitis of the ventral abdomen and inguinal area in cats (Figure 108.1). Ocular lesions are frequently reported in cats with the leproid syndrome. Pulmonary, gastrointestinal or disseminated granulomatous lesions can result from infection with tuberculous and saprophytic group organisms. Abdominal and pleural effusions often develop with progressive disease.

Diagnosis

Clinical pathologica results are generally nonspecific, and may include a neutrophilia with a left shift, nonregenerative anemia, decreased albumin:globulin ratio, and hypercalcemia. Where there is systemic involvement, diagnostic imaging findings are consistent with nonspecific infiltrative disease of the abdominal and/or thoracic cavities with possible organ and lymph node mineralization. Tuberculin intradermal testing in dogs and cats is generally unrewarding. However, immunodiagnostic assays for diagnosis of *M. bovis* in cats, including semiquantitative interferon-gamma production and point-of-care qualitative antibody detection tests, have shown positive results, although further evaluation is required.

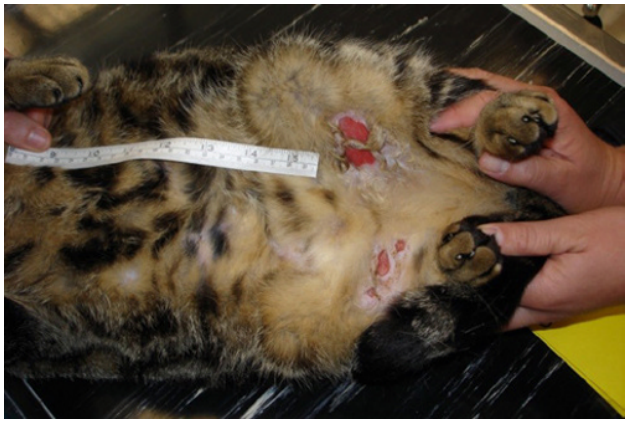


Figure 108.1 Inguinal panniculitis in a cat.

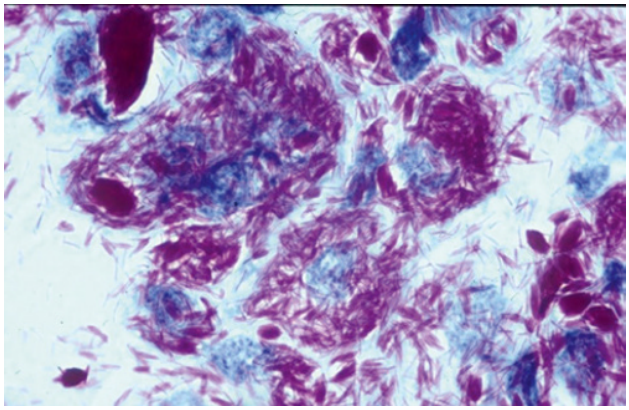


Figure 108.2 Acid-fast bacilli in a sample from a cat with feline leprosy.

Suspicion of mycobacteriosis should be raised in animals with consistent presenting signs whenever pyogranulomatous inflammation is identified on cytologic or histopathologic examination. Provisional diagnosis is based on the identification of acid-fast bacilli within tissue samples, exudates or blood smears (Figure 108.2). Definitive diagnosis requires organism identification and is imperative in mycobacterial infections in connection to their treatment and zoonotic potential. Like acid-fast staining, culture for mycobacteria must be specifically requested from the laboratory.

While RGM are often difficult to identify cytologically due to the scant number of organisms seen, they can generally be cultured within seven days. Conversely, SGM may be abundant on tissue cytology but cannot be cultured readily, if at all. Molecular techniques, particularly 16S rRNA sequencing, provide rapid and accurate identification of mycobacteria which is of particular importance in potential zoonotic infections. However, bacterial culture and susceptibility testing should still be attempted to determine appropriate antimicrobial therapy.

Therapy and Prognosis

The zoonotic potential and implications of treating infected animals must be considered before treatment (see later). Recommendations for treatment of tuberculous and saprophytic infections include triple agent antimicrobial therapy (a fluoroquinolone, a macrolide, and rifampicin) for three months followed by continued administration of two of these agents for an additional six months (see Table 108.3). Other antimicrobials, including doxycycline, aminoglycocides, third-generation cephalosporins, and chloramphenicol, have been reported to have been used in combination protocols or

Table 108.3 Antimicrobials used to treat mycobacterial infections

		Canine	Feline
Tuberculous mycobacteriosis		Rifampicin* (10–15 mg/kg, max 600 mg/day, PO q24h) Enrofloxacin (5-10 mg/kg IV/IM/SC/PO q24h) Macrolides • Clarithromycin (5–15 mg/kg PO q12h) • Azithromycin (5–15 mg/kg PO q24h) Isoniazid* (10 mg/kg, max 300 mg/day, PO q24h) Pyrazinamide* (15–40 mg/kg PO q24h)	Rifampicin* (10–20 mg/kg PO q24h) Fluoroquinolones • Marbofloxacin (2 mg/kg PO q24h) • Moxifloxacin (10 mg/kg PO q24h) Macrolides • Clindamycin (125 mg/cat PO q24h) • Azithromycin (5–15 mg/kg PO q24h) Isoniazid* (10–20 mg/kg PO q24h) Pyrazinamide* (15–40 mg/kg PO q24h)
Saprophytic mycobacteriosis	Rapid growing	Enrofloxacin (5-10 mg/kg IV/IM/SC/PO q24h) Rifampicin* (10–15 mg/kg, max 600 mg/day, PO q24h) Clarithromycin (5–15 mg/kg PO q12h) Doxycycline (5–10 mg/kg PO q12–24h) Amikacin* (10–15 mg/kg IV/IM/SC q24h) Cefotaxime (25–50 mg/kg IV/IM/SC q6h)	Gentamicin* (peri-op.) (5–8 mg/kg IV/IM/SC q24h) Amikacin* (peri-op.) (10–15 mg/kg IV/IM/SC q24h) Fluoroquinolones • Marbofloxacin (2 mg/kg PO q24h) • Moxifloxacin (10 mg/kg PO q24h) • Pradofloxacin (5 mg/kg PO q24h) Doxycycline (5–10 mg/kg PO q12–24h) Clarithromycin (62.5 mg PO q12h) Cefotaxime (22 mg/kg IV/IM/SC q6–8h)
	Slow growing	Clarithromycin (5–15 mg/kg PO q12h) Clofazamine (4–12 mg/kg PO q24h) Rifampicin* (10–15 mg/kg, max 600 mg/day, PO q24h) Doxycycline (5–10 mg/kg PO q12–24h)	Clarithromycin (62.5 mg PO q12h) Moxifloxacin (10 mg/kg PO q24h) Clofazamine (8 mg/kg, max 25 mg) PO q24h) Rifampicin* (10–20 mg/kg PO q24h) Doxycycline (5–10 mg/kg PO q12–24h)
Leproid syndromes		Rifampicin* (10–15 mg/kg PO q24h) Clarithromycin (5–15 mg/kg PO q12h) Clofazamine (4–8 mg/kg PO q24h) Doxycycline (5–10 mg/kg PO q12–24h)	Rifampicin* (10–15 mg/kg PO q24h) Clarithromycin (62.5 mg PO q12h) Clofazamine (8 mg/kg, max 25 mg) PO q24h) Doxycycline (5–10 mg/kg PO q12–24h) Fluoroquinolones • Marbofloxacin (2 mg/kg PO q24h) • Moxifloxacin (10 mg/kg PO q24h) Amikacin (10–15 mg/kg IV/IM/SC q24h)

* Potential severe adverse drug effects.
Please see text for further information regarding treatment protocols and drug combinations.
For all medications please consult comprehensive formularies for potential adverse drug effects, interactions, and contraindications.
IM, intramuscular; IV, intravenous; PO, by mouth (*per os*); SC, subcutaneous.

have been shown to have *in vitro* efficacy. However, these are not recommended as first-line therapies. Similarly, protocols including isoniazid and pyrazinamide have been reported for treatment of resistant infections but should be used with care due to potential toxicities. It is important to note that *M. bovis* has natural resistance to pyrazinamide. While superficial infections hold a guarded prognosis for long-term resolution, the prognosis for systemic infections is grave.

Treatment of the leproid syndromes is not always required as spontaneous remission has been reported, especially in dogs. Refractory lesions should be treated with surgical resection with prolonged, dual or triple antimicrobial therapy comprising a combination of rifampicin, clarithromycin, and/or clofazamine (Table 108.3).

Public Health Implications

Although the risk of transmission from dogs and cats to humans is low, members of the tuberculosis complex and MAC have zoonotic potential. Infected animals may excrete organisms in sputum and respiratory secretions that are aerosolized and can be inhaled or ingested by humans in close contact. Euthanasia or aggressive treatment of

dogs and cats infected with these organisms is imperative to eliminate the risk of zoonotic transmission.

Infection of veterinary personnel with *M. tuberculosis* has been reported following necropsy of infected dogs. In one case, the organism may have been aerosolized during use of an electric saw. Cutaneous inoculation of mycobacterial bacilli has also been reported associated with needle sticks contaminated by laboratory and patient samples. Care should be taken in specimen handling and appropriate personal protective equipment must be worn to avoid aerosolization, inhalation, and inoculation of organisms.

Tuberculosis is reportable or notifiable in a number of countries. Regional and national health authorities should be consulted when tuberculous infections are suspected or diagnosed in dogs and cats to allow thorough epidemiologic investigation.

Further Reading

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109

Fungal Infections

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General Features of Fungal Infections

Etiology/Pathophysiology

Fungal infections can be classified as *superficial* (*cutaneous) mycoses* or *deep mycoses*. Superficial mycoses are limited to the skin and include dermatophytosis and *Malassezia* infections. Deep mycoses can be caused by:

- organisms that exist as molds (hyphal forms) in the environment, the conidia (spores) of which are typically inhaled by mammalian hosts and then transform into replicating yeasts in tissues (*dimorphic fungi*)
- organisms that exist as spore-producing molds in the environment, are inhaled by mammalian hosts and then continue to grow as molds in tissues, such as *Aspergillus*
- *Candida*, which is a commensal of mucous membranes and invades opportunistically.

With the exception of *Sporothrix*, infections caused by dimorphic fungi and molds are acquired from the environment, and disease transmission from one affected animal to another does not occur. Incubation periods are often several weeks to months in duration, because of the slow replication rate of many fungi.

Epidemiology and Signalment

In general, dogs and cats of any age, breed, and sex can develop deep mycoses, but dogs are often young adult, pure-bred dogs, suggesting that genetic factors predispose to infection. Most cats with deep fungal infections test negative for retroviruses, but some animals have concurrent diseases such as malignancy or a history of treatment with immunosuppressive drugs, including chronic low-dose glucocorticoid therapy. Some dogs and cats have evidence of concurrent opportunistic infections such as toxoplasmosis, neosporosis or papillomavirus. Cats housed exclusively indoors can develop soil-borne fungal infections such as histoplasmosis or cryptococcosis.

History and Clinical Signs

Many infections with dimorphic fungi are probably subclinical. Animals that develop systemic disease are often evaluated for vague signs such as lethargy, weight loss, inappetence, weakness, and low-grade fever, together with signs of respiratory involvement and/or dissemination to sites that commonly include the skin, bone, eye, and brain. Findings on routine hematologic and biochemical testing are also nonspecific and include nonregenerative anemia, mild leukocytosis, hypoalbuminemia, and hyperglobulinemia. In a smaller proportion of dogs with systemic mycoses, hypercalcemia secondary to granulomatous inflammation may be present. Although most infections are acquired through inhalation, radiographic evidence of pulmonary involvement can be absent in some dogs and cats with disseminated disease.

Diagnosis

Persistent disease in the face of antibacterial therapy, or progression in the face of glucocorticoid therapy, should raise suspicion for a fungal infection. Definitive diagnosis is based on clinical suspicion combined with cytology and/or histopathology, fungal culture, antibody or antigen testing, and/or real-time polymerase chain reaction (PCR) assays. Cytology and histopathology have variable sensitivity and specificity and a limited ability to identify fungal pathogens. The use of special stains such as periodic acid–Schiff or Gomori's methenamine silver can

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highlight fungal elements in tissues. Most fungi grow within seven days in the laboratory, but occasionally several weeks elapse before growth occurs. Some dimorphic fungi (*Blastomyces*, *Histoplasma*, *Coccidioides*) grow as a mycelial form in the laboratory, which represents a laboratory health hazard. For these pathogens, culture should only be performed if a diagnosis cannot be established through other methods, and the laboratory should be warned that infection with a dimorphic fungus may be present, so that appropriate precautions are taken. Culture also allows antifungal susceptibility testing, although at this time, the clinical relevance of susceptibility test results is unclear for many fungi.

Antigen testing can be helpful for diagnosis and therapeutic monitoring of histoplasmosis (urine), blastomycosis (serum), cryptococcosis (serum or cerebrospinal fluid [CSF]), and disseminated aspergillosis (serum), although serologic cross-reactivity with other fungal pathogens is common with all assays except those for cryptococcosis. Serum antibody testing is helpful for diagnosis of coccidioidomycosis and pythiosis. At the time of writing, more information is needed on the clinical sensitivity and specificity of real-time PCR assays that are available for detection of fungal pathogens, but these may be useful when a fungal pathogen is suspected but cannot be detected or identified using other diagnostic tests.

Therapy

Treatment of fungal infections most often involves the use of orally administered azole antifungal drugs such as itraconazole capsules (usually 5 mg/kg PO q24h for dogs) or fluconazole tablets (5–10 mg/kg PO q24h). In general, fluconazole is less active than itraconazole, and itraconazole is preferred as first-line treatment for most infections, with the exceptions of *Cryptococcus* and *Candida*. Most molds are resistant to fluconazole. Topical antifungal drug preparations that contain azole drugs may be sufficient for treatment of the superficial mycoses. Liver enzyme activities should be monitored monthly during systemic treatment with azole antifungals in order to monitor for hepatotoxicity. Itraconazole solution (10 mg/mL) has higher bioavailability than the capsules and is administered at a lower dose (3 mg/kg PO q12h) and on an empty stomach. If itraconazole capsules are used, they should be administered with food. Compounded formulations of itraconazole should be avoided.

If clinical signs do not improve with azole treatment, measurement of serum drug concentrations could be considered. Serious systemic infections may require treatment with intravenous amphotericin B, with careful monitoring for evidence of nephrotoxicity before each infusion. Lipid complex amphotericin B preparations are not necessarily more effective than deoxycholate amphotericin B but are less nephrotoxic. Deoxycholate amphotericin B is administered to dogs at 0.5 mg/kg in 250–1000 mL of 5% dextrose over 4–6 hours on a Monday-Wednesday-Friday basis; the dose for cats is 0.25 mg/kg, which is given in 30 mL of 5% dextrose over one hour. Administration of 0.9% NaCl at 1.5–2 times maintenance for one hour prior to and after administration is recommended. Electrolytes cause amphotericin to precipitate so the line must be flushed with D5W prior to administration of the drug. Lipid complexed amphotericin B is administered to dogs at 3 mg/kg and cats at 1 mg/kg over two hours.

Voriconazole or posaconazole could also be considered for treatment of refractory deep fungal infections if client finances permit their use. Voriconazole (4–5 mg/kg PO q12h) has excellent central nervous system (CNS) penetration and so represents an option for dogs with fungal meningoencephalomyelitis. However, virtually all cats do not tolerate voriconazole due to gastrointestinal, neurologic, and cardiac adverse effects, so until a safe dose is known, voriconazole should not be administered to cats.

Other treatments that may be required for dogs or cats with serious pulmonary infections with or without dissemination are supplemental oxygen, nebulization and coupage, fluid therapy, and, in some cases, mechanical ventilation. Initially, clinical signs may worsen with treatment, possibly as a result of organism death and an associated inflammatory response. Nonsteroidal antiinflammatory drugs such as carprofen could be considered to control pyrexia, and systemic glucocorticoids may be required to control brain inflammation and edema in dogs and cats with CNS infections, although this is controversial. Topical antiinflammatory and antiglaucoma agents may be indicated if ocular involvement is present. In animals with endophthalmitis, enucleation may be necessary to control ocular pain and eliminate infection. Surgery may also be required for treatment of refractory fungal osteomyelitis (amputation) or large pulmonary granulomas (lung lobectomy).

Prognosis

Most fungal infections require several months of treatment at a minimum. Typically, treatment is continued until there is no evidence of disease remaining based on serial physical examinations, imaging, and antigen or antibody testing. Animals with disseminated fungal infections often require more than a year of treatment, or lifelong therapy. The prognosis is often poor when severe immunosuppression and dissemination are present at the time of diagnosis, but if immunosuppression can be

reversed and aggressive antifungal drug treatment is initiated promptly, complete recovery is possible.

Public Health Implications

Direct inoculation of yeast forms of fungi can potentially cause infection. The mycelial form of dimorphic fungi can pose significant zoonotic risk, although these are typically only present when the organisms are cultured in the laboratory. Appropriate precautions such as avoiding needle sticks and other traumatic wounds when working with animals that have deep fungal infections should be followed. Caution when performing necropsies, and cremating, rather than allowing burial of deceased patients are also important to prevent zoonosis from mycelial forms.

Dermatophytosis

Etiology/Pathophysiology

Dermatophytosis is caused by fungi that belong to the genera *Microsporum*, *Trichophyton* or *Epidermophyton*. These organisms secrete proteases that allow them to invade macerated or traumatized keratinized tissue. Infectious arthrospores persist in the environment for more than a year given optimal temperature and humidity, and are transmitted by close contact with other infected animals or contaminated fomites. The most common dermatophyte species that infect dogs and cats are *Microsporum canis*, *Microsporum gypseum*, and organisms that belong to the *Trichophyton mentagrophytes* species complex (especially *Arthroderma benhamiae*). *Microsporum canis* and organisms that belong to the *T. mentagrophytes* species complex are zoophilic dermatophytes (adapted to animal hosts), whereas *M. gypseum* is a geophilic dermatophyte (soil saprophyte).

Epidemiology and Signalment

Cats are more susceptible than dogs to dermatophytosis. The prevalence of infection is highest in regions with warm, humid climates. The risk of infection is higher in young animals and animals with concurrent immunosuppressive disorders, such as hyperadrenocorticism. Dogs that burrow in soil may also be at increased risk. Persian and Himalayan cats and Yorkshire and Jack Russell terriers appear to be predisposed.

History and Clinical Signs

Classically, dermatophytosis is characterized by one or more circular lesions of alopecia with an erythematous margin, superficial scale and crusts, and follicular papules and pustules. In dogs, lesions are most often on the face, distal limbs, and tail. When the claw is involved, there may be thickening of the ungual fold and deformity of the claw. Infection by *T. mentagrophytes* may result in widespread lesions with scar formation (Figure 109.1). Lesions in cats are extremely variable. In long-haired cats, dermatophytosis may simply be manifested as a poor hair coat with excessive shedding.



Figure 109.1 Fox terrier with dermatophytosis caused by *Trichophyton mentagrophytes* species complex organisms. *Source:* Image courtesy of the University of California, Davis Veterinary Dermatology Service.

Other forms of dermatophytosis include nodular inflammatory lesions known as kerions, and dermatophytic mycetomas, which are nodular lesions that coalesce and drain fluid. Persian and Himalayan cats appear to be prone to dermatophytic mycetomas.

Diagnosis

Diagnosis of dermatophytosis is based on clinical suspicion together with Wood's lamp examination, identification of hyphae and spores using skin and hair cytology, histopathology of skin biopsy specimens, and/or fungal culture. A positive Wood's lamp examination occurs when some strains of *M. canis* fluoresce within infected hair shafts. The sensitivity of Wood's lamp examination is low and false positives can occur when fluorescence of keratinized debris is misinterpreted as fungal fluorescence. The gold standard for diagnosis of dermatophytosis is fungal culture of hairs plucked from the edge of lesions, scrapings of crusts, or brushings of the haircoat (using a new toothbrush). Use of a microbiology laboratory is recommended whenever possible in order to properly distinguish dermatophyte growth from that of saprophytic molds and to prevent contamination of the practice environment.

Therapy

Dermatophytosis often resolves spontaneously within three months in otherwise healthy animals. Treatment is recommended for animals that are immunosuppressed, those that live in multipet households, and those that live with immunocompromised owners or children. Treatment should consist of systemic antifungal drugs (itraconazole is the drug of choice, but fluconazole, ketoconazole, griseofulvin or terbinafine also have activity against dermatophytes), with or without twice-weekly topical treatment (preferably a 1:16 dilution of lime sulfur) and environmental decontamination. Ideally, all in-contact animals should be examined and cultured using a toothbrush technique. Animals with positive cultures (and those with clinical signs) should be treated both systemically and topically. All unaffected, culture-positive animals should be treated topically along with any in-contact animals. Long-haired cats should be clipped in order to remove contaminated hair and facilitate penetration of topical treatments, although this is controversial because of the potential for contamination of the environment and for disruption of the skin. Clippers must be disinfected with 10% bleach afterwards.

Potential fomites (bedding, collars, grooming equipment) should be discarded if possible. Disinfection of hard surfaces should be performed with a 1:10 dilution of bleach, 0.2% enilconazole, or an enilconazole fogger (if available). Carpets and furniture should be thoroughly vacuumed and then steam cleaned, after which vacuum cleaners may need to be replaced.

Treatment is usually needed for at least 10–12 weeks. Animals should be examined and a culture performed monthly (and no earlier than weekly) during treatment. Treatment should be continued until lesions resolve and two successive cultures are negative. For group-housed animals, at least three successive negative cultures are recommended. If serial cultures are not possible because of financial limitations, treatment should be continued for 2–4 weeks after clinical signs resolve.

Prognosis

The prognosis for resolution of clinical signs is generally good, especially in households with one or only a few animals. Dermatophytic mycetomas may require long treatment durations; in some cats, surgery may be required for lesion resolution.

Public Health Implications

Dermatophyte species that cause disease in dogs and cats have the potential to cause disease in people. Young children and immunocompromised people are most susceptible. Protective gloves and clothing should be worn when handling infected animals. Young children and immunocompromised people should avoid any contact.

Malassezia Infections

Etiology/Pathophysiology

Malassezia spp. are lipophilic yeasts that normally colonize animal and human skin. *Malassezia pachydermatis* is the most commonly isolated yeast species from the skin and ears of healthy dogs and cats, and is most commonly found in the ear canals, lips, axillae, interdigital spaces, anal sacs, and occasionally the nose and vagina. Other species can also colonize the skin of healthy cats.

Malassezia proliferate opportunistically, and commonly contribute to chronic dermatitis and otitis externa in dogs, and to a lesser extent in cats. Underlying diseases that predispose to proliferation of *Malassezia* spp. include allergic dermatitis, endocrinopathies, intertrigo, primary keratinization/cornification disorders, a history of prolonged treatment with antibacterial drugs or glucocorticoids, and, in cats, underlying neoplasia or retrovirus infections. In some animals, hypersensitivity reactions to yeast antigens may contribute to the inflammatory response that results.

Epidemiology and Signalment

Predisposed dog breeds include American cocker spaniels, West Highland white terriers, basset hounds, poodles, and Australian silky terriers. Sphynx and Devon Rex cats have high rates of *Malassezia* spp. colonization when compared with domestic short-hair cats.

History and Clinical Signs

Clinical signs of *Malassezia* infection include erythema, pruritus, alopecia, scaling, and a greasy exudate. The most commonly affected sites are the ear canals, skinfolds (periocular and perioral skin, ventral neck, axillae, inguinal regions, and perineum) and interdigital skin. Chronic infections can result in hyperpigmentation, lichenification, and stenosis of the ear canal, and affected animals may emit a pungent odor.

Diagnosis

The diagnosis of *Malassezia* infection is usually based on cytologic examination of tape preparations. The yeasts stain darkly basophilic and exhibit wide-based budding, resembling "footprints." Mean counts of ≥1 yeast per oil immersion field (1000× magnification) for dermatitis and ≥5 organisms per oil immersion field for otitis are

considered abnormal in dogs. More than 12 yeasts/high dry field is considered abnormal in feline ear canals. The ear canals of healthy dogs and cats have mean counts of ≤ 2 yeasts/high dry field (400× magnification).

Therapy

Therapy of *Malassezia* spp. infections requires identification and treatment of the underlying cause, in addition to antifungal drug treatment. Topical therapy is adequate for many infections. Topical otic preparations for treatment of *Malassezia* otitis are used twice daily until there is cytologic resolution of infection, typically 2–4 weeks. These contain antifungals such as clotrimazole, miconazole or posaconazole, which are usually combined with a glucocorticoid and an antibacterial compound. Some antiseptic ear cleaners, such as Epi-Otic, also have activity against *Malassezia* and should be considered as an alternative to reduce unnecessary use of antibacterials.

Cleaning is performed on a 12- or 24-hour basis for 5–7 days, and then every second or third day until clinical signs resolve. Subsequently, weekly maintenance cleaning may reduce the risk of recurrence. *Malassezia* dermatitis can be successfully treated with twice-weekly shampooing with a 2% miconazole/2% chlorhexidine shampoo for three weeks, which also serves to prevent recurrence. Systemic antifungal drugs such as ketoconazole, itraconazole, fluconazole or terbinafine (30–40 mg/kg PO q24h) may be needed to treat more severe infections or infections of the claw bed.

Treatment should be monitored through serial dermatologic examinations and cytologic evaluation of tape preparations, and at least three weeks of treatment is usually required.

Prognosis

If the underlying cause can be resolved and there is good client compliance, the prognosis for resolution of *Malassezia* infections is generally good.

Public Health Implications

Malassezia pachydermatis can occasionally be carried on human skin. The risk of disease transmission appears low, although it may occur. Hand washing may theoretically reduce the risk.

Blastomycosis

Etiology/Pathophysiology

Blastomycosis is caused by the dimorphic fungus *Blastomyces dermatitidis*, which grows as a thick-walled budding yeast in tissues. Hyphae within soil produce conidia that are aerosolized and inhaled by the host, where they transform into yeasts, trigger a pyogranulomatous inflammatory response, and produce localized pulmonary or disseminated disease.

Epidemiology and Signalment

Blastomyces dermatitidis prefers warm, moist, sandy soil that is rich in organic debris such as decaying vegetation. The fungus is primarily found in North America around the Great Lakes, along the Ohio and Mississippi river valleys, and in the southeastern states. A smaller focus of endemicity exists in the northeast that extends into Ontario, Canada. Occasionally disease appears in nontraveled dogs that reside in nonendemic parts of the United States.

Young adult, large-breed (>15 kg) dogs are predisposed. Most affected dogs are apparently immunocompetent. Overrepresented breeds include coonhounds, pointers, Weimaraners, retrievers, and Doberman pinschers. Residence close to water sources and exposure to sites of soil disturbance also increase the risk of infection. Blastomycosis is rare in cats.

History and Clinical Signs

Infection with *Blastomyces* may result in disease that is localized to the lungs and associated lymph nodes, or signs that are severe and progressive with dissemination to extrapulmonary sites, which include the skin, eye, bone, prostate, and testes, and the CNS. Infection has also been reported in the mammary glands, nasal or oral cavities, cardiac tissues, and very rarely in the kidneys, liver, spleen, peritoneum, gastrointestinal tract, and urinary bladder. Neurologic involvement secondary to extension of intranasal *Blastomyces* granulomas through the calvarium has also been described.

In addition to nonspecific signs of illness, affected dogs may show signs that include cough, exercise intolerance and tachypnea, peripheral lymphadenopathy, ocular manifestations such as uveitis, chorioretinitis or panophthalmitis, nodular or ulcerated cutaneous or mucocutaneous lesions, and lameness due to fungal osteomyelitis or arthritis. Gastrointestinal signs, polyuria or polydipsia, nasal discharge, sneezing and/or epistaxis, mammary or testicular masses, facial distortion, cardiac arrhythmias, and neurologic signs due to meningoencephalitis or ependymitis are less common. Clinical signs of blastomycosis in cats resemble those in dogs.

Diagnosis

Thoracic radiographic findings in dogs with blastomycosis include unstructured, miliary or nodular interstitial patterns, a bronchointerstitial pattern, alveolar or mixed

alveolar-interstitial patterns, pulmonary mass lesions, tracheobronchial lymphadenopathy, and/or single or multiple pulmonary nodules that resemble pulmonary neoplasia. Radiographs of affected bone typically show osteolytic lesions, often accompanied by periosteal proliferation and soft tissue swelling.

A diagnosis of blastomycosis is often confirmed through cytologic examination of affected tissues, lung washes or body fluids. The yeasts are 8–15 µm in diameter, have a thick, refractile cell wall, and exhibit broad-based budding, although occasionally organisms are not visualized. The organisms are usually accompanied by pyogranulomatous inflammation (Figure 109.2).

Other methods of diagnosis include histopathology (e.g., of bone or tissue biopsies), fungal culture, antigen testing, and molecular diagnosis with PCR-based assays. Serologic tests for blastomycosis that detect antibody currently have poor sensitivity and specificity, and so the use of these tests is not recommended for routine diagnosis. When performed on urine, assays for *Blastomyces* cell wall galactomannan antigen (MiraVista Diagnostics, Indianapolis, IN) have high sensitivity (93.5%) and specificity (98%) for diagnosis of canine blastomycosis, but due to serologic cross-reactivity, results may also be positive in dogs with other fungal infections, especially histoplasmosis.

Therapy

The most widely used specific therapy for blastomycosis in dogs is itraconazole or fluconazole. The duration of treatment should be based on serial monitoring of clinical signs, radiographic lesions, and urine antigen titers (i.e., every 4–8 weeks). For dogs with pulmonary involvement, radiographic lesions and clinical signs may initially worsen with treatment. Initial worsening of radiographic lesions does not appear to affect survival. Urine antigen concentration declines with effective treatment. Although a positive residual urine antigen titer at the time treatment is discontinued does not necessarily predict that relapse will occur, a negative urine antigen test is recommended before treatment is discontinued. Most dogs require at least 4–6 months of treatment, and some dogs may require treatment for more than one year, especially those with osteoarticular infections or widespread dissemination. Treatment with amphotericin B could be considered for dogs with severe disease with widespread dissemination, followed by azole therapy after there has been a satisfactory clinical response to the amphotericin B.

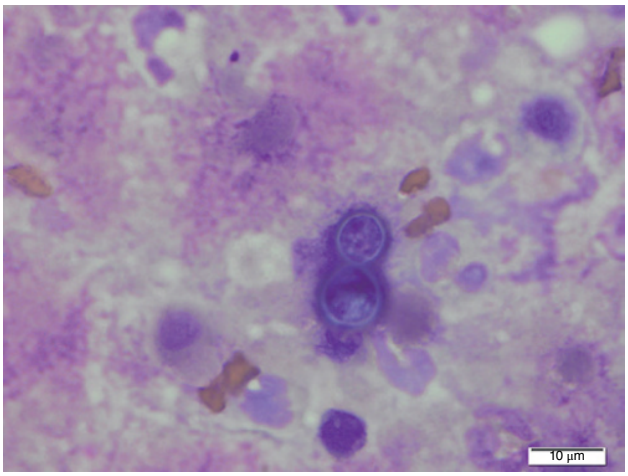


Figure 109.2 Cytology of a fine needle aspirate of a skin lesion from a dog showing a budding *Blastomyces* organism with associated pyogranulomatous inflammation. *Source:* Image courtesy of Dr Jed Overmann, University of Minnesota.

Prognosis

Cure rates of 50–75% have been reported in dogs with blastomycosis; an additional 20–25% of dogs experience disease recurrence after treatment is discontinued, which can occur as long as a year later. The most common radiographic sequelae to pulmonary blastomycosis are pulmonary bullae and persistent focal interstitial patterns, presumably as a result of pulmonary fibrosis. Involvement of the CNS, severe lung disease, and a high band neutrophil count are negative prognostic factors.

Public Health Implications

Blastomyces dermatitidis causes disease in people. Direct transmission between mammalian hosts does not occur, with the exception of inoculation of yeast via bite wound or needle sticks. Laboratory personnel are at risk if samples are cultured and should be warned that blastomycosis is suspected prior to submission. Bodies of deceased pets should be cremated rather than buried. Dogs are sentinels for human exposure.

Histoplasmosis

Etiology/Pathophysiology

Histoplasma capsulatum is a dimorphic, soil-borne fungus. Microconidia produced by the fungus are inhaled by mammalian hosts, and within the lungs transition to the yeast phase, which replicates by budding within alveolar macrophages. Some animals control the initial infection but remain latently infected with small numbers of yeasts. Subsequent immune suppression can lead to reactivation years later. Replication of *H. capsulatum* leads to a granulomatous inflammatory response, which

is sometimes accompanied by fibrosis. When a cell-mediated immune response is defective, yeast forms migrate to local lymph nodes (such as the tracheobronchial lymph nodes) and other tissues that contain mononuclear cells, such as the liver and spleen. Other common sites of dissemination include the bone marrow, small and/or large intestinal tract, pancreas, the skin, bones, central nervous system, and eyes.

Epidemiology and Signalment

Histoplasma capsulatum is found worldwide, but especially along the Mississippi, Missouri, Tennessee, and Ohio river valleys of the United States as well as in Latin America. *H. capsulatum* can be found in the intestinal tract and guano of bats, which constitute the primary reservoir of the organism and disseminate it geographically. *H. capsulatum* can also be found in high concentrations in decaying avian guano, but it is not shed in the feces of birds.

Cats are as susceptible, or slightly more susceptible, to histoplasmosis as dogs. Affected dogs and cats can be as young as several months of age, but most are middle aged, and geriatric animals can also be affected.

History and Clinical Signs

Approximately 40% of cats with histoplasmosis show respiratory signs such as dyspnea and tachypnea, and to a lesser extent cough and nasal discharge. Ocular signs such as chorioretinitis and/or uveitis occur in approximately one-quarter of cats, and around 20% of cats have evidence of osteomyelitis. Nodular or ulcerated and draining skin lesions, peripheral lymphadenopathy, vomiting, diarrhea, oral ulceration, and myelopathy have also been described.

Dogs appear to be particularly predisposed to gastrointestinal tract histoplasmosis. Involvement of the small and large intestines may result in malabsorption, diarrhea, dramatic weight loss, melena, dyschezia, tenesmus, and hematochezia. Profuse diarrhea may be chronic and persist for several months. Tracheobronchial lymphadenopathy is common and may contribute to cough through airway compression. Other signs include respiratory difficulty, icterus, vomiting, hepatomegaly, lymphadenomegaly, nasal discharge, ocular signs, polyuria and polydipsia, lameness due to osteomyelitis, cutaneous nodules, and neurologic signs such as seizures or paralysis/paresis.

Diagnosis

As with other deep mycoses, findings on routine laboratory testing are typically nonspecific and suggestive of inflammation. Dogs with acute progressive disseminated histoplasmosis may have increased band neutrophils, lymphopenia, monocytopenia, and thrombocytopenia. Increased liver enzyme activities, hyperbilirubinemia, and evidence of coagulopathies may be present in animals with hepatic involvement. In cats, plain thoracic radiographs can reveal diffuse, linear, nodular or miliary interstitial patterns. Alveolar, interstitial, and/or bronchial patterns, tracheobronchial lymphadenopathy, lung lobe consolidation, and/or rarely pleural effusion can be seen in dogs. Lesions in dogs can sometimes calcify. Abdominal imaging may show hepatomegaly, splenomegaly, abdominal lymphadenopathy or ascites. A thickened intestinal wall with architectural disruption of the bowel wall may be identified on ultrasound examination. Colonoscopic findings in dogs with colonic histoplasmosis include irregularity, ulceration, increased granularity, and friability of the colonic wall.

Cytologic examination of affected tissues or body fluids reveals pyogranulomatous or granulomatous inflammation. *H. capsulatum* yeasts are usually seen extracellularly and within mononuclear phagocytes, although they may not be identified within chronic, fibrosing lesions. The yeasts are 2–4 µm in diameter, oval, have a basophilic center and are surrounded by a clear halo due to shrinkage artifact (Figure 109.3).

Antibody assays for *H. capsulatum* have had poor clinical sensitivity and specificity, so are not recommended for routine diagnosis. An enzyme-linked immunosorbent assay (ELISA) for *H. capsulatum* antigen (MiraVista Diagnostics, Indianapolis, IN) is widely used in human patients for diagnosis of histoplasmosis, and as with blastomycosis, urine is the preferred specimen for testing

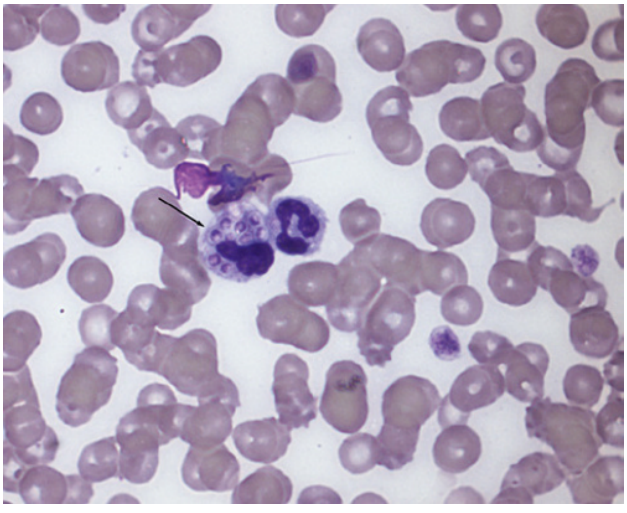


Figure 109.3 Cytology showing multiple intracellular *Histoplasma capsulatum* organisms within the cytoplasm of a circulating monocyte from a dog with disseminated histoplasmosis.

(sensitivity 95%). False positives occur as a result of serologic cross-reactivity in human patients with other disseminated mycoses, especially blastomycosis. Antigen levels become undetectable with successful treatment. This assay appears to have a similar performance in cats and dogs with histoplasmosis, although studies that evaluate large numbers of cats and dogs with confirmed histoplasmosis are required to fully establish the sensitivity and specificity of this assay.

Therapy

In human patients, itraconazole has consistently been more effective than fluconazole for treatment of histoplasmosis. Nevertheless, some animals can be cured with fluconazole monotherapy, so if funds or patient factors do not permit itraconazole treatment, fluconazole can be used. Amphotericin B should be used to treat dogs or cats with severe acute pulmonary, acute disseminated, or CNS disease, after which treatment should be continued with an azole. The decision to discontinue treatment should be based on lesion resolution and probably serial monitoring of urine antigen titers, although this requires further study.

Prognosis

The length of treatment and prognosis for histoplasmosis depend on the severity and chronicity of disease and the immune status of the host. At least six months of treatment is generally required. Many animals require treatment for 12 months or longer, and those with chronic disease may require treatment for more than two years.

Public Health Implications

Humans can be infected with *H. capsulatum* but direct transmission from cats and dogs has not been reported. Remains of infected animals should be cremated rather than buried.

Cryptococcosis

Etiology/Pathophysiology

Cryptococcosis is caused by dimorphic, basidiomycetous fungi that belong to the genus *Cryptococcus*. *Cryptococcus neoformans* and *C. gattii* cause the vast majority of infections. A filamentous form that produces basidiospores is thought to exist in the environment. Mammalian disease is believed to occur when basidiospores are inhaled, typically after an incubation period of several months, although in some cases, reactivation of subclinical infections may occur years after exposure. In animal tissues, the basidiospores are thought to convert to the yeast form, which is round to oval with a characteristic, variably sized polysaccharide capsule. Within tissues, *Cryptococcus* reproduces by narrow-based budding. After infection is established within the lung or nasal cavity, the organism can spread hematogenously to other sites, particularly the lymph nodes, eye, skin, and CNS. *Cryptococcus* has a predilection to invade the meninges, and typically causes meningitis or meningoencephalitis. In animals with nasal cavity involvement, extension of infection into the brain may also follow osteomyelitis of the cribriform plate.

Epidemiology and Signalment

Based on molecular methods such as multilocus sequence typing, cryptococcal strains worldwide have been divided into eight molecular types: VNI, VNII, VNIII, and VNIV (*C. neoformans*) and VGI, VGII, VGIII, and VGIV (*C. gattii*). Differences in epidemiology, pathogenicity, clinical features, and drug susceptibility have been associated with each molecular type. The environmental niche for *C. neoformans* is thought to be weathered bird (especially pigeon) guano, whereas *C. gattii* has been associated with *Eucalyptus* trees in Australia and a variety of other tree species on the west coast of North America.

The incidence of cryptococcosis in cats is eightfold higher than that in dogs. Siamese, Birman, and ragdoll cats have been predisposed in Australian studies but were not found to be at risk in the US. Similarly, German shepherd dogs, Doberman pinschers, and Great Danes appear to be predisposed in Australia, whereas American cocker spaniels are predisposed in the US.

History and Clinical Signs

Cryptococcosis is often a chronic infection in cats. Upper respiratory tract signs due to nasal cavity involvement are common, sometimes with associated mandibular lymphadenopathy. Single or multifocal ulcerated or nonulcerated cutaneous or mucocutaneous masses may also be present. Lower respiratory tract signs are uncommon, but can occur as a result of pleural effusion or severe mediastinal lymphadenomegaly. Neurologic signs vary depending on the location of lesions in the CNS. Optic neuritis and chorioretinitis develop in as many as one-third of affected cats, and almost always indicate CNS involvement. Other signs include peripheral lymphadenomegaly, lameness due to osteoarticular infection, and swollen digits. Rarely, involvement of the abdominal lymph nodes, kidneys, spleen, liver, and thyroid can occur in cats.

In contrast to cats, dogs often develop widespread dissemination with neurologic involvement. They may also present with signs relating to gastrointestinal or pancreatic involvement. Cryptococcal rhinosinusitis may be subclinical in dogs or may result in sneezing and mucopurulent nasal discharge. Cutaneous involvement is uncommon but, as in the cat, may be a marker for disseminated disease. Other clinical signs that are occasionally present in dogs include peripheral lymphadenomegaly or lameness (due to osteomyelitis or arthritis).

Diagnosis

Thoracic radiographs in dogs and cats with cryptococcosis are often normal, although interstitial to alveolar infiltrates or small nodular lesions may be present. Occasionally, pulmonary nodules, tracheobronchial lymphadenopathy, mediastinal masses, or pleural effusion are found.

Definitive diagnosis of cryptococcosis is based on evaluation of representative tissue specimens or body fluids (including cerebrospinal fluid) with cytology, culture, and occasionally histopathology (Figure 109.4), with or without serologic detection of cryptococcal antigen.

Latex agglutination assays for detection of cryptococcal polysaccharide capsular antigen are widely used in veterinary patients and are very (>85%) sensitive and specific, although false-negative and false-positive results can occur. ELISAs are also available. Serum antigen testing provides a rapid diagnosis when organisms cannot be visualized or cultured, and may prove advantageous when CSF collection is unacceptably risky. Even a titer as low as 1:2 can indicate cryptococcal infection.

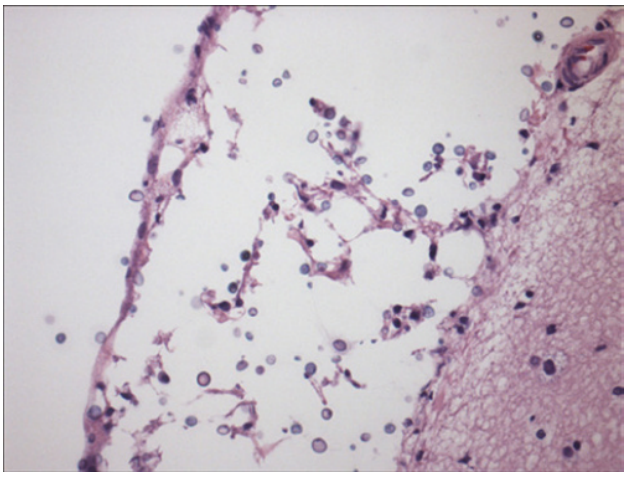


Figure 109.4 Histopathology showing large numbers of *Cryptococcus* organisms within the meninges of a 3-year-old domestic short-hair that died of disseminated cryptococcosis.

Because false-positive latex agglutination titers of up to 1:200 have been detected in cats, attempts to confirm infection using other diagnostic tests are recommended in animals that have titers <1:200. For dogs and cats suspected to have cryptococcal meningoencephalomyelitis that have negative serum antigen titers, CSF should be submitted for cytologic examination, antigen titers, and fungal culture.

Therapy

Some dogs and cats with cryptococcosis, especially those with lesions restricted to the skin, can be treated successfully with azole antifungal drug monotherapy. Fluconazole is a reasonable initial choice, because of its good penetration of the brain and eye. Generally, cats improve within 1–2 weeks of starting therapy. Treatment should be continued until there is complete lesion resolution and the cryptococcal antigen titer becomes negative. This typically takes 2–12 months, although longer periods of therapy may be required. For recovered animals that achieve an antigen titer of 0, the titer can be monitored every 3–6 months, so that relapse is diagnosed early. Some cats (especially those in California infected with molecular type VGIII) fail to respond completely to treatment, antigen titers persist at high levels, and relapse occurs after an initial treatment response. In some of these cats, prognosis is guarded and treatment with other azoles or combination therapy with amphotericin B may be necessary.

For cats with CNS cryptococcosis or those that fail to respond to azole antifungal drugs, a combination of amphotericin B and 5-flucytosine (250 mg PO q8h) or amphotericin B and fluconazole is recommended. Dogs with disseminated disease or CNS involvement should be treated initially with amphotericin B and fluconazole, because those treated with flucytosine often develop cutaneous necrosis 1–2 weeks after starting therapy. Treatment with 5-flucytosine and amphotericin B is continued for 2–4 weeks or until azotemia develops, after which treatment is continued with an azole. Anecdotally, administration of terbinafine to some dogs and cats that have failed azole or amphotericin B treatment has led to clinical improvement.

Prognosis

In studies from Australia, approximately 75% of cats with cryptococcosis were treated successfully. In one study, the median survival time of cats with CNS cryptococcosis was only 13 days (0–4050 days), but outcomes were more favorable if cats survived at least three days after diagnosis. The prognosis is guarded for dogs, with success rates that range from 30% to 55%. The median survival

time for dogs with CNS cryptococcosis in North America was seven days (0–3680 days).

Public Health Implications

Humans can develop cryptococcosis through environmental exposure. Notably, it is an important infection in people with AIDS. Direct transmission from animals to people has not been reported, but contaminated needlestick injuries may transmit the organism. *Cryptococcus* grows on routine fungal laboratory media as a yeast, so is less likely to represent a hazard to laboratory personnel than dimorphic fungi that grow as molds.

Coccidioidomycosis

Etiology/Pathophysiology

Coccidioides spp. (*Coccidioides immitis* and *C. posadasii*) are dimorphic fungi that exist in soil as chains of barrel-shaped arthrospores. The arthrospores are aerosolized and inhaled by animal hosts. This may be followed by localized pulmonary disease or dissemination to the tracheobronchial lymph nodes and then other anatomic sites in the face of an inadequate immune response. Infections often follow a pattern of moist conditions (required for growth of *Coccidioides* spp. in the soil), a dry period, then soil disruption, such as may occur with heavy rainfall, dust storms, or construction.

After inhalation, arthrospores are phagocytosed by alveolar macrophages. They then enlarge into a spherule (8–100 µm in diameter). Hundreds of endospores develop within the spherule, which are released when the spherule ruptures. This is associated with a pyogranulomatous inflammatory response.

Epidemiology and Signalment

In the environment, *Coccidioides* spp. are distributed in regions with arid soils, low elevations above sea level, and hot summers. Infections occur primarily in the southwestern United States, Mexico, and parts of Central and South America. In southwestern USA, highly endemic regions include the south-central valley of California ("Valley Fever") and Arizona. Latent infections occur in dogs and these can reactivate after treatment with immunosuppressive drugs. Coccidioidomycosis is rare in cats.

History and Clinical Signs

Development of clinical signs often follows a subacute to chronic course. Many dogs continue to otherwise appear healthy, with occasional periods of inappetence. Clinical signs of respiratory tract involvement include cough, tachypnea, and/or exercise intolerance. Rarely, diffuse pneumonia follows a more fulminant course, as reported in immunocompromised humans.

A small percentage of infected dogs develop disseminated infections. Sites of dissemination often include osteoarticular sites, the CNS, skin, peripheral lymph nodes, eye, testes, prostate, and pericardium. Rarely, other sites, such as abdominal organs, are affected. Dogs with skin involvement may have ulcerated skin lesions that drain serosanguinous fluid, or subcutaneous mass lesions. Neurologic signs result from fungal meningoencephalitis and include obtundation, blindness, nystagmus, ataxia, placing deficits, circling, cervical pain, tetraparesis, and seizures. Ocular manifestations include chorioretinitis, uveitis, optic neuritis, and endophthalmitis. Pericarditis may lead to signs of right-sided cardiac failure, with development of ascites and pleural effusion.

Diagnosis

Thoracic radiographs in dogs with disseminated coccidioidomycosis are often unremarkable. The most common radiographic finding in dogs with pulmonary coccidioidomycosis is tracheobronchial lymphadenomegaly. Although this may be the only finding, most dogs also have mild to moderate interstitial infiltrates. Nodular interstitial, interstitial-alveolar, bronchointerstitial infiltrates, and/or sternal lymphadenomegaly may also be present. Dogs with pericarditis may have cardiomegaly and pleural effusion, with hepatomegaly and decreased abdominal detail. Echocardiography in these dogs may reveal thickening and mass lesions of the pericardium, pericardial and pleural effusion, and cardiac tamponade.

A diagnosis of coccidioidomycosis is typically confirmed using serology for antibodies to *Coccidioides* spp., because of the low sensitivity of cytology and the fact that culture is hazardous to laboratory personnel and can have a long turnaround time. Cytologic examination of specimens from affected tissues or body fluids reveals granulomatous or pyogranulomatous inflammation. Occasionally, spherules can be identified as round, basophilic, double-walled, crinkled structures (8–70 µm in diameter) (Figure 109.5). Sometimes endospores (2–5 µm in diameter) can be seen in association with ruptured spherules.

Most diagnostic laboratories detect antibodies to *Coccidioides* using gel immunodiffusion. False-negative serologic test results are rare in dogs with coccidioidomycosis. Antibody titers typically range from 1:2 to 1:256. Dogs with active infection may have titers as low as 1:2, and healthy dogs in hyperendemic areas in Arizona have had titers as high as 1:16. As a result, positive titers of 1:16 or lower should always be interpreted in light of clinicopathologic abnormalities

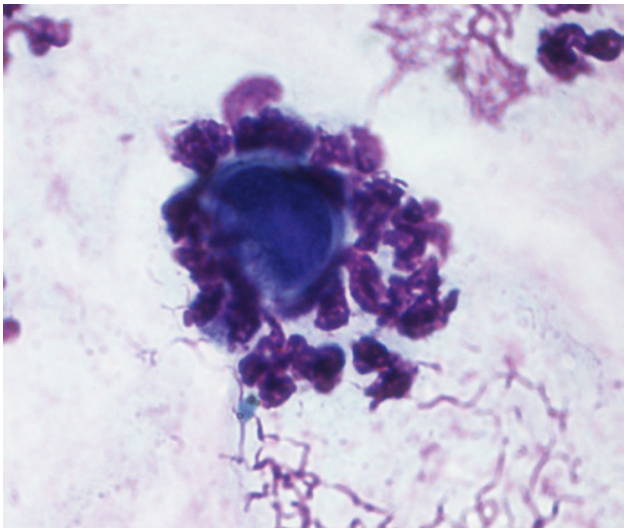


Figure 109.5 Cytology of a tracheal wash specimen showing a *Coccidioides* spherule surrounded by pyogranulomatous inflammation.

and, in hyperendemic areas, other diagnostic tests (such as cytology, histopathology or culture) should also be used to confirm the diagnosis.

Therapy

Dogs with pulmonary coccidioidomycosis often respond well to azole monotherapy with fluconazole or itraconazole. Treatment with amphotericin B is recommended either alone or in combination with an azole antifungal for dogs with refractory disease or those with severe clinical signs. Successful treatment of *Coccidioides* pericarditis has been reported after subtotal pericardiectomy and epicardial excision in conjunction with antifungal drug therapy. Referral to a specialist surgeon with experience in the technique is strongly recommended.

Prognosis

The prognosis for resolution for coccidioidomycosis depends on the severity of infection and the extent of dissemination. The duration of treatment ranges from six months (localized pulmonary coccidioidomycosis) to many years, and in some cases, life-long treatment is needed. IgG antibody titers decrease with successful treatment, which in general should be continued until lesions resolve and the titer is 1:2 or lower.

Public Health Implications

Coccidioidomycosis is an important and serious infection in people that is generally acquired from environmental exposure. Disease and death may occur from direct inoculation from needle-stick injuries and also from inhalation of the mycelial form, which can develop in tissues if they are stored for long periods after death of an infected animal. Physicians should be notified immediately in the case of inoculation or possible inhalation of a mycelial form. Necropsies should be performed with appropriate precautions and take place soon after death to prevent mycelial form growth. Bodies of infected animals should not be buried but should be cremated as soon as possible. Laboratories should be warned if coccidioidomycosis is suspected.

Aspergillosis

Etiology/Pathophysiology

Aspergillus are hyaline molds, the conidia of which are found commonly in soil, water, air, and decaying vegetation. *Aspergillus* spores are inhaled, and in the absence of adequate immune defenses, enlarge and germinate to form hyphae, subsequently leading to a variety of noninvasive to invasive disorders that include keratomycosis, fungal otitis externa, sinonasal aspergillosis (SNA), sinoorbital aspergillosis, bronchopulmonary and disseminated aspergillosis. Keratomycosis, otitis externa, feline sinoorbital aspergillosis, and bronchopulmonary aspergillosis in dogs are relatively rare conditions, and beyond the scope of this chapter. A variety of other molds less commonly cause infections in dogs and cats, including nonpigmented molds such as *Penicillium*, *Paecilomyces*, *Pseudallescheria*, and *Geotrichum* (hyalohyphomycoses); pigmented molds such as *Alternaria*, *Exophiala*, and *Cladophialophera* (phaeohyphomycoses); and zygomycetes such as *Basidiobolus*, *Conidiobolus*, and *Mucor*. The reader is referred elsewhere for detailed discussions of these pathogens.

Sinonasal aspergillosis is a subacute to chronic disease of the nasal cavity and sinuses that is most often caused by organisms that belong to the *A. fumigatus* complex. In most cases, affected dogs have no evidence of immune compromise, but sometimes SNA occurs as a result of implantation of a foreign body or other preexisting nasal disease, such as nasal neoplasia. SNA is a noninvasive disease, and the fungus does not extend beyond the mucosal epithelium. Production of toxins by the fungus and a profound host inflammatory response are thought to lead to extensive turbinate and bony destruction. Disseminated (invasive) aspergillosis in dogs is most often caused by *A. terreus* or *A. deflectus*, although other *Aspergillus* species have also been isolated.

Epidemiology and Signalment

Sinonasal aspergillosis in dogs is most common in large, nonbrachycephalic breeds. SNA uncommonly occurs in

cats, but diabetes mellitus has been identified in some affected cats.

Disseminated aspergillosis in dogs likely occurs as a result of an uncharacterized genetic immunodeficiency, because young adult female German shepherds are strongly predisposed, and immunosuppressive drug treatment is rarely present in the history of affected dogs. Disseminated aspergillosis is extremely rare in cats.

History and Clinical Signs

Clinical signs of SNA in dogs and cats consist of sneezing, serous to mucopurulent nasal discharge, depigmentation of the nasal planum (Figure 109.6), and, less commonly, epistaxis.

Nasal pain may be manifest in dogs as pawing at the face or withdrawal. Nasal airflow is usually normal or increased. Serous ocular discharge may occur as a result of destruction of the bones of the orbit. Rarely, palpation of the nasal bones or the hard palate reveals defects. Osteolysis of the cribriform plate occasionally leads to meningitis with neurologic signs such as obtundation or seizures.

Sites often involved in dogs with disseminated aspergillosis include the vertebral endplates and discs, renal pelvis, long bones, and lymph nodes. However, any organ may be affected, including the spleen, liver, heart, cardiac valves, pancreas, eyes, lungs, brain, meninges, small intestine, skin, spinal cord, thyroid, adrenal glands, prostate, and trachea. The most frequent clinical signs are lethargy, inappetence, pain, lameness, and ataxia and paresis secondary to discospondylitis.

Diagnosis

Imaging of the nasal cavity of dogs with SNA using plain radiography (open mouth view), computed tomography (CT) or magnetic resonance imaging (MRI) can reveal loss of turbinates, defects in the nasal septum, and/or increased soft tissue opacity within the nasal cavity. CT and MRI have increased sensitivity over plain radiography, and are the preferred imaging modalities. Osteolysis of the cribriform plate, orbit, and frontal bones may be identified using advanced imaging. In some animals, lesions are limited to the frontal sinus. Visualization of fungal plaques by rhinoscopy and sinuscopy confirms the diagnosis. Trephination or surgical exploration of the frontal sinuses may be necessary to visualize (and treat) this region. Cytologic examination of mucosal swabs, brush specimens of the nasal cavity, or nasal biopsies can reveal hyphae, which are septate and branch at 45° angles, and sometimes also conidia. Culture of *Aspergillus* from nasal biopsies supports the diagnosis, although negative culture results do not rule out SNA.



Figure 109.6 Nasal depigmentation and ulceration in a dog with sinonasal aspergillosis.

Disseminated aspergillosis may be suspected on the basis of signalment and clinical findings. In some cases, hyphae are visualized in tissue aspirates or urine sediment from affected dogs. Growth of a typical *Aspergillus* species (most commonly *A. terreus* or *A. deflectus*) from a normally sterile site confirms the diagnosis.

Both serum antibody and antigen assays have been evaluated for diagnosis of SNA and disseminated aspergillosis in dogs. Assays that detect serum antibodies to *Aspergillus* include ELISA and gel immunodiffusion (ID) assays. Different antibody assays vary in their sensitivity and specificity for diagnosis of SNA but in general, positive results suggest a diagnosis of SNA, but negative results do not rule out SNA. Dogs with disseminated aspergillosis frequently test negative, and so serum antibody testing is not recommended for diagnosis of this disease.

The sensitivity and specificity of serum *Aspergillus* galactomannan antigen ELISA (Platelia®) for diagnosis of SNA are low, and its use is not recommended for this condition. However, serum or urine antigen testing has high sensitivity for diagnosis of disseminated aspergillosis in dogs, and a high specificity when using a cut-off galactomannan index of 1.5. High-level false positives (>1.5) appear to occur only in dogs with other fungal infections, especially those caused by *Penicillium* or *Paecilomyces*, and dogs treated with Plasmalyte® fluid therapy.

In summary, a strong positive assay result in a dog with clinical abnormalities consistent with disseminated aspergillosis and no history of Plasmalyte administration supports a diagnosis of a mold infection, but fungal culture is required to confirm that *Aspergillus* is the causative agent. A negative result in a dog with disseminated disease suggests that *Aspergillus* is not the cause, but does not rule out the possibility of infection by another fungal species.

Therapy

Treatment of SNA requires thorough mechanical debridement of plaques with endoscopic biopsy forceps under anesthesia, followed by topical antifungal drug therapy. Frontal sinus trephination and curettage or open surgical debridement of the frontal sinus may be required. Provided the cribriform plate is intact, debridement is followed by lavage with 0.9% saline and suction, followed by topical therapy with clotrimazole or enilconazole. Several protocols for topical antifungal drug administration have been described. The reader is referred elsewhere for description of these protocols. Debridement and a second treatment are then performed one month later; sometimes, a third treatment may be necessary. Additional systemic treatment with antifungal drugs could also be considered, but it is not clear whether this improves outcome. Systemic azole antifungal drug therapy could be considered as an alternative to topical therapy in dogs with cribriform plate destruction, when topical treatment has the potential to lead to death or life-threatening neurologic signs.

Canine disseminated aspergillosis is treated with itraconazole, voriconazole, posaconazole, and/or amphotericin B. Terbinafine has been used in addition to azole therapy with limited success. At best, treatment leads to remission for months to more than a year, but usually antigen titers remain high and eventually relapse occurs, leading to euthanasia or death. Although expensive, voriconazole is a treatment of choice in humans with invasive aspergillosis, and has led to remissions of many months' duration in some dogs. *A. terreus* is resistant *in vitro* to amphotericin B, but clinical improvement still occurs after treatment of some dogs with lipid complexed amphotericin B. Caspofungin is also used to treat invasive aspergillosis in humans, but expense and the need for daily intravenous administration have limited its use in dogs.

Prognosis

Success rates for treatment of SNA have varied from less than 30% to 100%. Low success rates reflect extensive disease that is often present at diagnosis, together with irreversible turbinate loss. Dogs with turbinate loss are predisposed to recurrent bacterial infections of the nasal cavity, which lead to persistent nasal discharge and sneezing. Therefore, attempts should be made to reach a diagnosis as early as possible when SNA is on the differential diagnosis list. Treatment with antibacterial drugs without pursuing a diagnosis only leads to disease progression, and is inappropriate because primary bacterial infections of the nasal cavity are rare in adult dogs.

Many dogs with disseminated aspergillosis have advanced disease at diagnosis, sometimes with respiratory distress, pathologic fractures, vertebral subluxations, and cord compression. The prognosis for these dogs is poor.

Public Health Implications

Aspergillosis occurs in people who have significant immunosuppressive disorders, such as transplant recipients, and is usually due to *Aspergillus fumigatus* complex organisms. Infections are acquired from the environment, and transmission from dogs and cats has not been described.

Candidiasis

Etiology/Pathophysiology

Candida species are yeasts that belong to the normal gastrointestinal, urogenital, and cutaneous flora but can invade tissues and cause disease as a result of disruption of normal host defenses. *Candida* species can also be isolated from soil, inanimate objects, and hospital environments. The yeasts are small (3–6 µm), ovoid and reproduce by budding. Budding results in the formation of new yeast cells, pseudohyphae (chains of elongated yeast cells), and true septate hyphae.

Disease syndromes caused by *Candida* spp. that occur in dogs and cats include keratitis, cutaneous or mucocutaneous candidiasis, otitis, urinary tract infections (UTIs), gastrointestinal candidiasis, peritonitis, and disseminated infections. The most commonly isolated species is *Candida albicans*, and only *C. albicans* appears to cause disseminated disease in dogs and cats.

Epidemiology and Signalment

Predisposing factors in dogs or cats with local or disseminated candidiasis have included diabetes mellitus, treatment with immunosuppressive drugs or broad-spectrum antibacterial drugs, a history of gastrointestinal surgery, parvoviral infections, and/or underlying malignancy. Disseminated candidiasis has also been described in apparently immunocompetent animals, which may reflect an underlying genetic immunodeficiency. Urethrostomy or cystostomy tube placement may be in the history of some animals with *Candida* UTIs.

History and Clinical Signs

Lower urinary tract candidiasis may be subclinical or associated with signs of lower urinary tract disease. Cutaneous candidiasis may manifest as erythema, alopecia, erosions,

and crusting, often where disruption of cutaneous or mucocutaneous regions has occurred (such as a previous surgical site or around a feeding tube or cystotomy stoma). *Candida* peritonitis can follow intestinal surgery, treatment with broad-spectrum antibacterial drugs, and subsequent enterotomy site dehiscence. Mixed infections with *Candida* and intestinal flora may develop. Affected dogs are febrile, have abdominal pain, and may have other gastrointestinal signs such as vomiting and diarrhea.

Dogs with disseminated candidiasis frequently develop rapidly progressive clinical signs that include fever, inappetence, weight loss, and other clinical signs that reflect the specific organs involved. The latter can include the pancreas, liver, mesentery, spleen, kidneys, heart, lungs, lymph nodes, and less often the bone, intestinal tract, eyes, meninges, thyroid, and/or prostate gland. Ocular signs include keratitis, uveitis, chorioretinitis, and endophthalmitis. Thromboembolic disease may complicate disseminated infections.

Diagnosis

Definitive diagnosis of candidiasis requires visualization of *Candida* blastospores, pseudohyphae, and true hyphae within lesions by cytologic or histopathologic examination, as well as confirmation of its identity using fungal culture. Because *Candida* can be isolated from the skin and mucous membranes of healthy dogs and cats, infection must be confirmed with cytology or histopathology when *Candida* is isolated from these sites. A diagnosis of disseminated candidiasis should be considered whenever *Candida* is isolated from the eye, skin, or urinary tract of an animal that develops systemic illness, and aggressive treatment instituted without delay.

Isolation of *Candida* allows antifungal susceptibility testing. Some isolates (especially *C. glabrata* and *C. krusei*) are resistant to multiple antifungal drugs.

Therapy

Treatment of candidiasis should involve management of underlying immunosuppressive disorders and specific antifungal drug treatment. Systemic antibacterial drugs should be discontinued if not clearly indicated, or the spectrum of activity should be narrowed. Cutaneous and corneal infections are usually treated with a combination of topical antiseptics or antifungal medications and systemic antifungal drugs until lesions resolve. Dogs and cats with *Candida* UTIs should initially be treated with fluconazole, which concentrates in urine. Intravesicular treatment with 1% clotrimazole under anesthesia may be necessary in animals that fail to respond to treatment. Intravesicular treatment is continued weekly until *Candida* can no longer be isolated from the urine. Typically 1–4 treatments, spaced one week apart, are required.

Systemic candidiasis is treated aggressively with systemic antifungal drugs, especially fluconazole, and supportive care. One dog with *Candida* peritonitis was treated successfully with surgical lavage of the abdomen, abdominal drain placement, and intravenous fluconazole. Antifungal drugs other than fluconazole with activity against *Candida* include amphotericin B and caspofungin, both of which must be administered parenterally.

Prognosis

The prognosis for successful resolution of local *Candida* infections is good, but successful treatment of systemic candidiasis in dogs or cats is rarely described.

Public Health Implications

Human infections with *Candida* species result primarily from invasion by normal flora.

Sporotrichosis

Etiology/Pathophysiology

Sporothrix species are dimorphic, saprophytic fungi that cause disease that often results from cutaneous or subcutaneous inoculation of the organism through a puncture wound, but can also follow inhalation of the fungus. Direct contact with cats that have sporotrichosis, without an apparent break in the skin, can also result in transmission.

Sporothrix species prefer moist soil that is rich in decaying vegetation. The fungus is distributed worldwide in tropical and temperate zones, but is most prevalent in tropical or subtropical regions of the Americas. The *S. schenckii* species complex includes multiple *Sporothrix* species, the epidemiology of which is still incompletely understood.

Epidemiology and Signalment

Cats are more susceptible to sporotrichosis than dogs and are thought to facilitate spread of organisms in the environment. Contaminated claw or bite wounds are thought to be important modes of transmission. Male cats have been overrepresented. Sporotrichosis in dogs is uncommon, but tends to occur in hunting breeds. Introduction of the organism with plant foreign bodies may lead to infection in some dogs.

History and Clinical Signs

In dogs and cats, *Sporothrix* spp. most often cause focal or multifocal cutaneous lesions. These are crusted, thickened or nodular lesions that often ulcerate or drain serosanguinous fluid. Most cats have multiple cutaneous lesions. These lesions may develop as a result of autoinoculation during grooming or they may be a manifestation of a disseminated infection.

Transmission by inhalation is thought to occur in some cats that develop pulmonary and nasal cavity disease. Respiratory signs include sneezing, cough, tachypnea, increased respiratory effort, stertor, and/or nasal discharge. Cats also can develop generalized disease, with involvement of the lungs, liver, spleen, kidneys, lymph nodes, and/or testicles. Clinical signs of systemic involvement include fever, generalized lymphadenomegaly, anorexia, vomiting, and weight loss. Osteoarticular sporotrichosis has rarely been described in dogs.

Diagnosis

Cytologic examination or histopathology of affected tissues from cats reveals pyogranulomatous inflammation with large numbers of round to cigar-shaped yeasts, which can be found intracellularly within neutrophils or macrophages and extracellularly (Figure 109.7). The yeasts are 4–6 µm in diameter and typically exhibit a single bud with a narrow base.

Dogs tend to have very low numbers of organisms in skin lesions, which may not be readily detected. Definitive diagnosis of sporotrichosis can be made by fungal culture of aspirates or biopsies from lesions. Use of molecular assays to identify *Sporothrix* could also be considered.

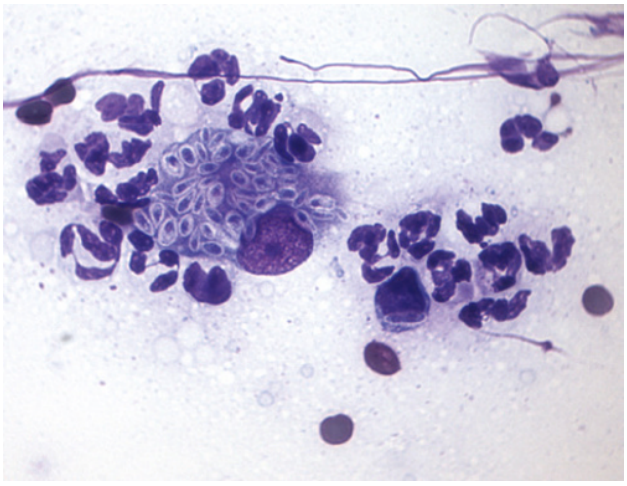


Figure 109.7 Cytology of an impression smear of a skin lesion from a cat with cutaneous sporotrichosis. Large numbers of intracellular pleomorphic yeasts are present.

Therapy

The treatment of choice for most dogs and cats with sporotrichosis is itraconazole. Alternative antifungal drugs for refractory disease include supersaturated potassium or sodium iodide, terbinafine, or amphotericin B. Unfortunately, potassium iodide formulations often lead to adverse gastrointestinal signs in cats. Localized hyperthermia has been used as adjunct therapy to treat fixed cutaneous lesions, because most strains of *Sporothrix* survive poorly at high temperatures. In this case, a thermal bag at a temperature of 40–42 °C is applied at least twice daily to lesions for 15 minutes.

Prognosis

In general, the prognosis for cure of sporotrichosis is good. Treatment durations of at least 4–6 months are generally required, but some cats require more than a year of treatment. Treatment should be continued for a month after complete resolution of lesions.

Public Health Implications

Inoculation from cat scratches, bites or direct contact with infected cats are important means by which people acquire sporotrichosis. Sporotrichosis should be considered as a differential diagnosis for any cat with a draining cutaneous lesion, and such cats should be handled with gloves and hands washed after contact. Owners of infected animals should minimize contact, and if contact is necessary, it should be recommended that they wear gloves and wash their hands immediately after handling the animal. Owners should also be warned of the risk of exposure to the organism in the environment. Needlestick injuries should be avoided and laboratory personnel warned of suspect cases.

Miscellaneous Fungus-Like Infections (Pythiosis and Rhinosporidiosis)

Etiology/Pathophysiology

A variety of fungus-like organisms that reside in aquatic environments and are thought to invade damaged host tissues can cause disease in dogs and cats. These include *Pythium insidiosum*, *Lagenidium* spp. and *Rhinosporidium seeberi*. *Pythium insidiosum* and *Lagenidium* are oomycetes (water molds), whereas *R. seeberi* is an aquatic protistan parasite (class Mesomycetozoea) that is taxonomically located between animals and fungi. *Pythium insidiosum* causes severe, progressive gastrointestinal or cutaneous disease in dogs

and rarely cats that is often fatal. In the US, pythiosis most often occurs in the Gulf Coast states but has also been recognized in other parts of the USA, including California and Arizona. *Lagenidium* is found primarily in the southern United States and causes ulcerative cutaneous lesions or systemic lymphadenopathy in dogs. *Rhinosporidium seeberi* is most often found in warm, wet environments such as the southeastern and south-central USA, where it causes polypoid masses in the rostral nasal cavity of dogs and rarely cats.

Epidemiology and Signalment

Pythiosis, lagenidiosis, and rhinosporidiosis most commonly occur in young, large-breed dogs that are apparently immunocompetent.

History and Clinical Signs

Gastrointestinal pythiosis in dogs is characterized by severe, focal intestinal wall thickening, often with mesenteric lymphadenopathy. Clinical signs include weight loss, anorexia, vomiting, diarrhea, and sometimes hematochezia. Cutaneous pythiosis in dogs occurs most often at the base of the tail, on the extremities, or the perineum, and is characterized by ulcerated mass lesions with draining tracts. Generally, gastrointestinal and cutaneous pythiosis do not occur concurrently.

Dogs with lagenidiosis are typically evaluated for cutaneous lesions that resemble those of cutaneous pythiosis. Local lymphadenopathy occurs in some dogs, and may occur in the absence of obvious cutaneous lesions. Dogs with lagenidiosis may also have intrathoracic or intraabdominal lesions, which may involve the great vessels, tracheobronchial, sublumbar and/or inguinal lymph nodes, lung or cranial mediastinum.

In dogs and cats, infection by *R. seeberi* leads to formation of pedunculate to sessile masses within the rostral third of the nasal cavity. The polyps range in size from a few millimeters to several centimeters. Clinical signs consist of subacute to chronic progressive sneezing with or without epistaxis, snuffling, and sometimes a serous, mucoid or serosanguinous unilateral nasal discharge.

Diagnosis

Diagnosis of pythiosis, lagenidiosis, and rhinosporidiosis is often initially based on the results of cytology or histopathology, which reveals broad, poorly septate hyphae that resemble zygomycete hyphae. Culture and/or PCR and sequencing can be used to distinguish between these organisms. Serologic assays that detect antibody are also available to assist diagnosis, but these do not discriminate between pythiosis and lagenidiosis.

Cytologic examination of smears, brushings or biopsies of *R. seeberi* polyps reveals pyogranulomatous inflammation with numerous *R. seeberi* endospores. Histopathology reveals abundant sporangia in various stages of development (Figure 109.8).

Therapy and Prognosis

Aggressive surgical resection is the treatment of choice for these infections. A combination of high-dose itraconazole (10 mg/kg PO q24h) and terbinafine (5–10 mg/kg PO q24h) should be used to treat dogs with nonresectable pythiosis or lagenidiosis, or when there is concern that not all margins have been cleared of disease. Dogs with nonresectable gastrointestinal pythiosis may also benefit from treatment with antiinflammatory doses of glucocorticoids. Prognosis is guarded to poor, but some dogs can be cured with aggressive therapy. To monitor for recurrence, ELISA serology can be performed at surgery and 2–3 months later. If serum antibody levels drop by more than 50% within three months, medical therapy can usually be discontinued.

Because *Rhinosporidium* polyps are often rostrally located, surgical excisions can often be extended caudally from the nares in order to remove the polyps. Many dogs have no recurrence of clinical signs thereafter, but some experience disease recurrence within months of surgery.

Public Health Implications

Human infections with *P. insidiosum* are rare and are acquired from the environment. However, routine precautions when handling infected tissues or exudate should be followed.

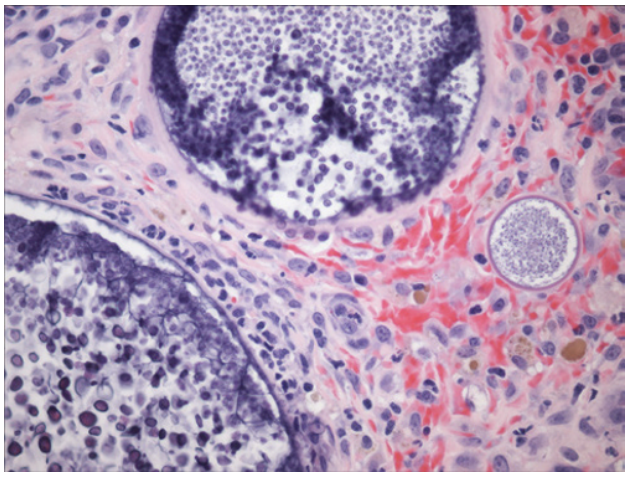


Figure 109.8 Histopathology of a polyp caused by *Rhinosporidium seeberi*. Sporangia that contain endospores are seen in various stages of development.

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110

Protozoal and Protozoa-Like Infections

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Parasites are responsible for some of the most important and widespread diseases of domestic dogs and cats. Some of these parasitic infections are also zoonotic and can infect humans. A thorough understanding of the pathogenesis and epidemiology of these parasitic diseases is required in order to treat infected pets and prevent the spread of disease efficiently. This chapter focuses on important protozoal diseases in dogs and cats with emphasis on etiology, pathophysiology, clinical manifestations, diagnosis, treatment, and prevention.

Toxoplasmosis

Etiology and Pathophysiology

Toxoplasma gondii is a tissue coccidian protozoon with a sexual life cycle in the intestine of felids, the definitive host, and an asexual phase in intermediate hosts. The intermediate hosts of *T. gondii* include all warm-blooded vertebrates including humans. Cats and intermediate hosts can be infected by bradyzoites in meat or by sporulated *T. gondii* oocysts from cat feces. Cats shed *T. gondii* oocysts in their feces within 3–10 days after infection by bradyzoites from tissue cysts and excretion continues for approximately 7–21 days (median eight days) with massive shedding which can reach hundreds of millions of oocysts per cat during the shedding period. After that initial period, risk of further oocyst shedding is limited. Oocysts in cat feces undergo sporulation in the environment and develop sporocysts containing infective sporozoites within 1–5 days in appropriate humidity, temperature, and oxygenation conditions [1].

After oral infection, *T. gondii* sporozoites release from the oocysts and can invade the gut, multiply as tachyzoites, disseminate systemically and localize in internal organs, the nervous system, and muscle tissues. In most cases, infection is subclinical and parasites are eventually encysted as tachyzoites in tissues, but severe and fatal disease can occur due to acute infection or reactivation of parasites in tissue cysts. In addition, in some host species and in humans, infection can cross the placenta and infect embryos intrauterinely.

Several *T. gondii* genotype strains have been described with variable virulence and host predilection. These include the more common genotypes I, II, and III described in North America and Europe as well as several atypical genotypes [2].

Epidemiology

Exposure to *T. gondii* in cat populations is widespread and positive serology may be detected in up to 74% of cats in domestic feline populations worldwide. Dogs have also been reported to have high exposure to *T. gondii* with seroprevalence rates ranging from 30% to 64% in different countries and populations. Most *T. gondii* infections are subclinical and hosts may remain chronically infected without developing clinical disease. Cats are often infected by preying on infected rodents and it has been shown that *T. gondii* infection can alter rodent behavior and make them less alarmed, consequently increasing their likelihood of falling prey to domestic cats. Toxoplasmosis is one of the most common zoonotic infections in humans and is responsible for human abortions, birth defects, encephalitis, and generalized disease [1,3].

Signalment

Cats and dogs of any age or gender can be affected. Young and immunosuppressed animals tend to develop more severe disease. Congenital infection is usually associated with more severe disease than infection of adult cats, often affecting the liver and respiratory tract.

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History and Clinical Signs

Clinical signs in cats are rarely related to the gastrointestinal stage of *T. gondii* development which is usually subclinical. Cats affected by systemic infection may show a variety of clinical signs including fever, anorexia, abdominal pain, respiratory distress, ocular inflammation, lethargy, and central nervous system disorders. These are associated with tachyzoite dissemination and their cytotoxicity with generation of local and systemic inflammation. Acute disease in dogs may be accompanied by neuromuscular, central nervous system (CNS), respiratory, gastrointestinal, hepatic, and more rarely ocular manifestations. Myositis and myocarditis are also prevalent in canine toxoplasmosis. Disease in both cats and dogs may result from new infection or from reactivation of latent infections by immune suppression such as cyclosporin treatment, distemper infection in dogs or feline immunodeficiency virus (FIV) in cats [4].

Diagnosis

Cats and dogs with acute systemic toxoplasmosis may develop nonregenerative anemia, leukopenia with lymphopenia, or neutrophilic leukocytosis, monocytosis, and eosinophilia. Serum biochemistry abnormalities during acute toxoplasmosis may include hypoproteinemia with hypoalbuminemia. Increased activities of alanine aminotransferase (ALT), creatinine kinase (CK), and aspartate aminotransferase (AST) are found in animals with hepatic or muscle necrosis.

Excretion of oocysts by cats during the limited shedding period can be detected by fecal examination or polymerase chain reaction (PCR). Oocysts are relatively small (10 µM) and can be concentrated by fecal flotation with centrifugation using sugar solutions such as Sheather's sugar solution. *Hammondia hammondi* and *Besnoitia* spp. produce oocysts which are morphologically indistinguishable from *T. gondii* occysts in cat feces.

Diagnosis of clinically ill cats and dogs is based on compatible clinical signs and laboratory abnormalities and by the detection of specific serum antibodies, demonstration of parasite DNA by PCR, or visualization of tachyzoites by cytology in clinical samples. *T. gondii* tachyzoites may be detected by cytology during acute toxoplasmosis in peritoneal and ascitic fluids, and more rarely in cerebrospinal fluid (CSF), blood and bronchoalveolar lavage washings or other tissues. PCR performed on CSF, aqueous humor, or any other body fluid or internal organ tissue is confirmative of infection with *T. gondii*.

Serology is carried out by the enzyme-linked immunoabsorbent assay (ELISA), immunofluorescence assay (IFA) (Figure 110.1), agglutination assays, and immunochromatographic kits.

Subclinically infected animals may display antibody levels, and therefore positive serologic results may only indicate previous infection, which is not necessarily acute. The demonstration of increased IgG levels by at least fourfold in paired sera taken at least two weeks apart or high IgM levels suggests active acute infection, although this is often not observed. Immunoblotting and ELISA assays have been developed for the measurement of specific *T. gondii* IgM, IgG, and IgA antibody classes in an effort to discern the kinetic pattern of antibody formation in feline infection.

About 80% of healthy cats experimentally infected with *T. gondii* develop detectable specific IgM antibodies within 2–4 weeks post infection and most become IgM seronegative by 16 weeks. However, some cats, particularly those with FIV or ocular toxoplasmosis, may have

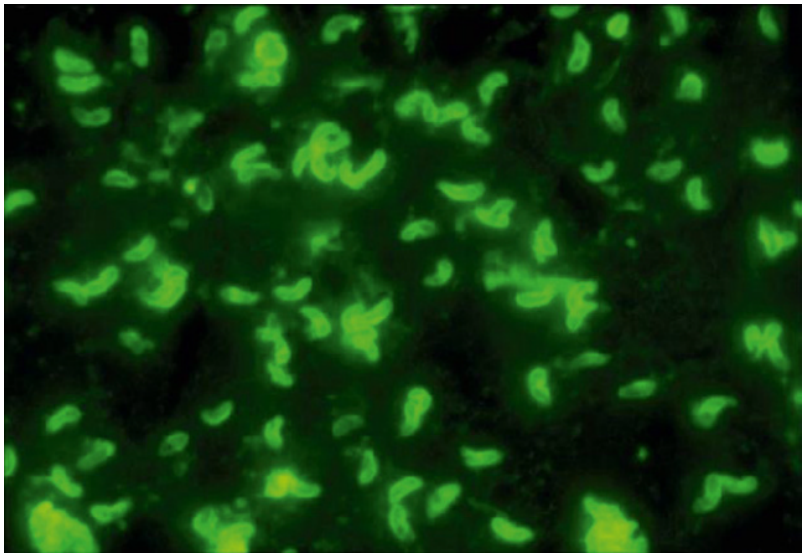


Figure 110.1 A positive indirect fluorescent antigen test serologic response to *Toxoplasma gondii* antigen. *Source*: Courtesy of Dr Monica Leszkowicz Mazuz, Kimron Veterinary Institute, Israel.

persistent IgM levels. Since some cats never develop a detectable IgM response and others have persistent IgM antibodies, it is not possible to accurately use IgM serology to predict recent infection, although a positive antibody titer can be suggestive of it. Furthermore, *T. gondii*-specific IgG can be detected by serum ELISA in healthy cats from 3–4 weeks after experimental infection. By this time, oocyst shedding has usually been completed and therefore IgG seropositive cats are usually considered of low risk to public health. However, *T. gondii*-IgG antibodies usually persist in the sera of infected cats for years or even for their lifetime due to the persistence of tissue infection.

In addition, anti-*T. gondii* antibodies can be measured in the CSF and aqueous humor to demonstrate local production of antibodies as an indication of organ infection. This local antibody production can be compared to the serum antibody concentration using an antibody coefficient to differentiate whether local production of antibodies is present or if antibodies have diffused from the circulation.

Therapy

Clindamycin is the current treatment of choice in dogs and cats with clinical toxoplasmosis. It is administered at 10–20 mg/kg PO q12h for at least two weeks to dogs and at 12.5 mg/kg PO q12h for 2–4 weeks to cats. Azithromycin at 10 mg/kg PO q24h for four weeks is an additional treatment choice for cats and trimethoprim-sulfonamide at 15 mg/kg PO q12h for 2–4 weeks is an alternative treatment for animals with intolerance to clindamycin. Uveitis due to toxoplasmosis is treated with 1% prednisolone acetate ophthalmic drops.

No vaccine is currently available commercially for the prevention of *T. gondii* infection in cats and dogs, or the prevention of oocyst shedding in cats. Avoiding exposure of cats and dogs to *T. gondii* infection includes prevention of hunting and feeding of raw or undercooked meat. Cat feces should be discarded properly every day to prevent exposure to sporulated oocysts.

Prognosis

Acute toxoplasmosis often starts improving 24–48 hours after initiation of clindamycin treatment. Ocular and CNS infections tend to respond more slowly and disease in immunocompromised patients usually has a poorer prognosis.

Neosporosis

Etiology and Pathophysiology

Neospora caninum is a coccidian parasite which is an important cause of abortion in livestock worldwide and can also cause neurologic disease in dogs. *Neospora caninum* can infect several domestic animal species including dogs, cattle, sheep, goats, horses, and chickens, and wild animal species including deer, rodents, rabbits, coyotes, wolves, foxes, and birds. Dogs, wolves, coyotes, and foxes are the definitive hosts of *N. caninum* [5].

The sexually reproductive stage of the parasite's life cycle occurs in the intestine of a canine definitive host which passes unsporulated oocysts in the feces. Infective oocysts are ingested by an intermediate host, such as cattle, following sporulation in the environment which happens within 24 hours. Tachyzoites of *N. caninum* develop in the infected intermediate host during acute infection followed by the development of bradyzoites walled off in tissue cysts as infection becomes chronic. Dogs acquire the infection mainly by ingesting parasite cysts from tissues of infected intermediate hosts, in particular cattle, and shed oocysts approximately five days after bradyzoite ingestion. In addition, transplacental transmission during pregnancy has been shown to occur in dogs, sheep, and cattle.

Epidemiology

The prevalence of *N. caninum* varies in different dog populations and has been reported to be associated with the dog's environment and lifestyle. Free-roaming dogs living in rural areas are more likely to be seropositive than urban dogs with less access to infected prey, bovine placentas, aborted fetuses or other potentially infected tissues. High seroprevalence rates of above 50% have been reported in beef farm dogs in South America, whereas populations of healthy dogs in Europe and the USA typically have seroprevalence rates below 15%.

Signalment

Dogs of any age or gender can be affected by *N. caninum* but disease is more common in dogs under the age of 1 year.

History and Clinical Signs

The clinical manifestations of canine neosporosis are due to inflammation and necrosis caused by cellular destruction induced by tachyzoites. As for *T. gondii*, disease by *N. caninum* can be caused by new infection, or by reactivation of parasites in cysts during host stress or immune compromise. Immune-suppressive treatment for other disease by cyclosporin, steroids or azathioprine may activate latent *N. caninum* infection. *Neospora caninum* may replicate in the lower respiratory system, skin, liver, and nervous system. Disease is mostly associated with the neuromuscular predilection of this parasite. Neurologic disease is especially severe in congenitally infected puppies and may be apparent shortly after birth or delayed and manifested months after birth, usually before the age



Figure 110.2 A young puppy with hindlimb paresis due to *Neospora caninum* infection. *Source*: Courtesy of Dr Monica Leszkowicz Mazuz, Kimron Veterinary Institute, Israel.

of six months. Typical signs in pups include ascending hindlimb paresis and ataxia which becomes progressively more severe (Figure 110.2), polymyositis, muscle atrophy, muscular back pain, head tilt, ocular abnormalities, urinary incontinence and dysphagia.

Infected adult dogs may suffer from encephalomyelitis, polymyositis, focal cutaneous nodules or ulcers, pneumonia, hepatitis, peritonitis, or myocarditis.

Diagnosis

The hematologic and serum biochemistry findings in clinical neosporosis are nonspecific. Increased serum activities of CK and AST may be evident in dogs with myositis due to neosporosis. CSF abnormalities include mild increase in protein and nucleated cells concentrations with predominantly mononuclear cells including monocytes and lymphocytes and occasionally neutrophils and eosinophils [6].

The diagnosis of canine neosporosis can be based on clinical signs and positive serology by ELISA or IFA. Pups usually seroconvert 2–3 weeks after infection and antibody levels are frequently high in clinically sick dogs. A fourfold increase in antibody levels is associated with recent infection and IFA titers of 1:800 or greater in conjunction with compatible clinical signs suggest clinical neosporosis. Serologic cross-reactivity between *N. caninum* and *T. gondii* antibodies is present in some assays but not expected in sera from dogs with medium to high titers. No correlation has been found between antibody level and clinical severity in dogs with neosporosis and subclinically infected dogs may also have high antibody levels to *N. caninum*. Suspicion of canine neosporosis can be confirmed by demonstrating the presence of the parasite's DNA by PCR of CSF or muscle biopsies [7]. *Neospora caninum* tachyzoites can occasionally be detected in the CSF by cytology.

Therapy

Clindamycin at 10–12 mg/kg PO q8h for at least one month is the main drug used for the treatment of canine neosporosis. Trimethoprim-sulfa at 15 mg/kg PO q12h alone or in combination with pyrimethamine at 1 mg/kg PO q24h for at least a month is another treatment option. Pyrimethamine may be combined also with clindamycin at the same doses. Ponazuril has been shown to be effective in cattle and mice but there are insufficient data on its efficacy against canine neosporosis. Treatment of neosporosis may only be partially effective or not effective at all and long-term treatment of two months or more is often required, until no further improvement is noted.

Prevention should be aimed at avoiding the ingestion of bovine placentas and raw bovine or prey meat by dogs, and also elimination of fecal contamination of ruminant feed by dog and wild canid feces.

It has been recommended to test all littermates of a puppy with neosporosis by serology for infection and treat all those who are positive, or further consider treatment of the whole litter for the sake of prevention, regardless of seropositivity. Bitches who have given birth to infected puppies should be tested for infection and not be bred. Immunosuppressive therapy should preferably not be administered to seropositive dogs due to potential reactivation of tissue cysts.

Prognosis

The prognosis for treated dogs with cutaneous neosporosis is more favorable than for those with CNS and neuromuscular disease. Young dogs with muscle contracture and rigid hyperextension of the back legs have a poor prognosis and often do not improve with treatment. Older juvenile dogs above 4 months of age and mature dogs with neurologic disease often respond to long-term treatment but may not return to complete function and cure. Untreated dogs with clinical neosporosis usually die.

Trypanosomiasis

Trypanosomiasis is a group of diseases caused by flagellated protozoans of the genus *Trypanosoma* which are mostly arthropod borne and transmitted by hematophageous insects. The life cycle of trypanosomes is shared by two hosts: a vertebrate animal and an arthropod vector. Trypanosomes are divided to two main groups. The Salivaria (including *T. brucei*, *T. conglonese*, and other species, develop in the anterior part of the vector's digestive tract and salivary glands, and are transmitted in saliva through biting. In contrast the Stercocaria

(*T. cruzi*), develop in the posterior gut of the vector and are transmitted in the fecal excretion of the vector. The Salivaria species cause African trypanosomiasis, mainly transmitted by tsetse flies (*Glossina* spp.), whereas the Stercocaria *T. cruzi* causes American trypanosomiasis and is transmitted by *Triatoma* bugs ("kissing bugs"). *Trypanosoma evansi*, which is closely related genetically to the tsetse-transmitted *T. brucei*, is transmitted mechanically by biting flies without development in the fly gut. The life cycle of African trypanosomes includes an epimastigote stage which develops in the tsetse fly and a trypomastigote stage found in the fly's saliva and in the blood and tissues of the animal. The life cycle of the American trypanosome *T. cruzi* includes an additional intracellular life stage in the animal host, the amastigote (also found in *Leishmania* spp.).

African trypanosomes infect a large variety of animals, with some species causing severe disease in humans, such as *T. brucei gambiense* which is responsible for the chronic debilitating disease sleeping sickness and *T. brucei rhodesiense* which causes a more acute severe form of human trypanosomiasis. Dogs and cats are not known to develop disease from these two important human pathogens. However, dogs do suffer from severe disease due to *T. congolense,* and both dogs and cats suffer from disease due to *T. evansi*. American trypanosomiasis is a zoonotic disease caused by *T. cruzi* which has both wildlife and domestic animal hosts. It induces acute or chronic disease associated with myocarditis and neuromuscular degeneration in dogs and humans.

Trypanosoma caninum is a newly discovered species that has been found in the skin and other tissues of dogs in Brazil. No apparent clinical signs have been attributed to this infection and the relatedness of this species to *T. cruzi* or African trypanosomes has not been determined [8].

American Trypanosomiasis

Etiology and Pathophysiology

Trypanosoma cruzi, the zoonotic agent of Chagas disease or American trypanosomiasis, can cause acute or chronic disease in dogs. Trypomastigotes of *T. cruzi* are shed in the triatomine vector feces onto the skin of a vertebrate host. The parasite crosses the skin in bruised areas or through rubbing or scratching and enters the bloodstream. Trypomastigotes that invade macrophages or myocytes transform into amastigotes which multiply intracellularly. Amastigotes transform back to trypomastigotes and are released from destroyed host cells into the blood and are ingested during a blood meal by the vector. Trypomastigotes are transformed to epimastigotes in the triatomine's gut and replicate until eventually transferring to the posterior gut where they transform back into infectious trypomastigotes before excretion in the insect's feces. The triatomine vectors defecate shortly after feeding on blood thereby infecting animals and humans. Dogs may also be infected orally by ingesting triatomine bugs, their excretions or infected animal tissues. This route of infection is also prevalent in humans. Furthermore, transplacental infection and transmission from contaminated blood transfusion products are additional modes of transmission which enable the parasite's spread.

Invasion of cells by *T. cruzi* trypomastigotes, replication as amastigotes and then transformation back to trypomastigotes result in cell rupture and tissue damage. Parasitemia with *T. cruzi* can be detected by examining canine blood smears three days post infection, reaching its peak 14 days later, and becomeing undetectable cytologically 30 days post infection. Acute cardiac disease may develop as early as 14 days after infection and resolve by one month. Chronic disease can develop after a long subclinical phase with progressive myocarditis and cardiomyopathy directly induced by the parasite or by an autoimmune reaction which is unrelated to the intracellular amastigote parasite load.

Epidemiology

Trypanosoma cruzi infects a large number of animal species in the American continent and Caribbean islands. These include wild animals such as armadillos, opposums and raccoons, and also dogs and humans. Cats may also be infected but less frequently than dogs and without apparent clinical disease. The disease is prevalent in humans in southern and central American countries from Argentina to Mexico. It has also been reported in the southern, United States, especially in Texas. Dogs are considered the main domestic reservoir for human infection in several areas, whereas wildlife hosts are the main reservoirs in others. Canine infection is more prevalent than its human counterpart in the United States where the seroprevalence in dogs in Texas and Louisiana ranges from 12% to 22% [3].

Signalment

Puppies and dogs younger than 1 year of age develop more severe, acute, and frequently fatal disease compared with older dogs.

History and Clinical Signs

Chagas disease myocarditis has three stages: acute, intermediate (latent), and chronic. The main findings of acute disease in puppies include lethargy, fever, lymphadenomegaly, pale mucous membranes, hepatosplenomegaly, and loss of appetite. This stage of the disease results from direct myocardial cell injury by trypomastigotes and the associated inflammatory response.

Meningoencephalitis due to parasite invasion of the CNS may also develop during the acute disease. Dogs older than 6 months of age develop less severe clinical signs of infection which may be inapparent. Survival of acute infection may be preceded by a long subclinical latent infection with no clinical signs and no apparent parasitemia. Some dogs develop the chronic form of the disease within 8–36 months after the acute phase. These dogs suffer from cardiac failure that often begins as right-sided and may progress to left-sided. Exercise intolerance, ascites, pleural effusion, pulse deficits and hepatomegaly can occur due to myocarditis, dilated cardiomyopathy and arrhythmias.

Diagnosis

Dogs with acute *T. cruzi* infection may have hematologic abnormalities that include anemia, thrombocytopenia, neutrophilia, monocytosis, eosinophilia, and lymphocytosis. Serum biochemical abnormalities during acute *T. cruzi* myocarditis may include increased muscle enzyme activity and prerenal or renal azotemia. Changes in cardiac electrical conductivity including arrhythmias and atrioventricular blocks will be evident on ECG during acute *T. cruzi* myocarditis.

Trypomastigotes may be evident in stained blood smears, and sensitivity can be improved by examining a Giemsa-stained thick buffy coat smear. Concentration of trypomastigotes by centrifugation of plasma is also more sensitive than examining blood smears. The parasite pellet from plasma may be examined microscopically following staining or used for DNA extraction and PCR. *Trypanosoma cruzi* trypomastigotes or rarely intracellular amastigotes may be demonstrated by examining lymph node cytology.

Serologic detection of antibodies to *T. cruzi* by IFA, ELISA, or immunochromatography is the most common diagnostic technique for the detection of latent and chronic infection. Antibodies are detectable three weeks after infection and persist for the lifetime of the dog irrespective of whether it remains in latent infection or develops chronic disease. Serologic cross-reactivity between *T. cruzi* and *Leishmania* is a considerable problem in settings where these infections overlap. PCR assays for the detection of *T. cruzi* are specific but are often not sensitive during the latent and chronic stages of the disease when parasitemia is rare.

Therapy

Benznidazole at 5–10 mg/kg PO q24h for 60 days or nifurtimox at 2–7 mg/kg PO q6h for 3–5 months often in association with prednisone are used at the acute disease stage. These drugs, particularly nifurtimox, have severe side-effects, are not FDA approved for dogs and are often difficult to obtain. Furthermore, infection may persist despite treatment.

Prognosis

Infected dogs should be monitored for cardiac dysfunction and are at risk for sudden death. Specific treatment for cardiac failure is often indicated.

Prevention

Prevention consists of limitation of exposure to triatomine vectors and access to potentially infected prey. Blood donors should be screened for *T. cruzi* infection in and around endemic regions.

African Trypanosomiasis and *T. evansi*

The African trypanosomes are a multitude of species for which some distinct strains have been reported. All the species that belong to the *T. brucei* complex and *T. evansi* are similar morphologically and indistinguishable by light microscopy, whereas *T. congolense* differs from the *T. brucei* complex by the length and shape of its flagella. All the African trypanosomes are strictly extracellular and develop in the form of trypomastigotes in the vertebrate host, which transform to epimastigotes in the tsetse vector. *T. brucei* is able to avoid elimination from the mammalian host by periodic change of antigenicity and evading the host's immune system.

Epidemiology

Tsetse flies, the vectors of *T. brucei* and *T. congolense*, are found only in sub-Saharan Africa and therefore the prevalence of diseases caused by these parasites is limited to this part of Africa. Because *T. evansi* is transmitted mechanically by tabanids and possibly by other insects present also outside Africa, it was able to spread away from Africa and be prevalent also in major parts of Asia and South America.

Signalment

European breeds of dogs and cats imported into Africa are considered more susceptible to clinical disease caused by species of African trypanosomes, compared with local domestic dogs and cats.

History and Clinical Signs

The clinical signs described in dogs with African trypanosomiasis include fever, anorexia, lethargy, lymphadenomegaly, hepatosplenomegaly, edema, ascites, petechial hemorrhages, uveitis, oculonasal discharge, corneal edema reminiscent of blue eye caused by canine adenovirus infection, and neurologic signs associated with meningoencephalitis.

Diagnosis

Dogs may have anemia, leukocytosis or leukopenia and thrombocytopenia. Serum biochemistry abnormalities

include increased activities of liver enzymes, azotemia, hypoalbuminemia, and hyperglobulinemia.

The diagnosis of African trypnosomiasis in dogs and cats involves detection of trypomastigotes by cytology of blood, body fluids or tissues using microscopy (Figure 110.3). PCR with sequencing is useful for detection of low parasitemias and for species determination. The flagella of *T. congolense* trypomastigotes does not extend separately beyond the body of the parasite whereas the flagella of *T. brucei* and *T. evansi* extends posteriorly after overlapping the parasite's body. ELISA, IFA, and the card agglutination trypanosomiasis test (CATT) are available for the detection of antibodies against *T. evansi*.

Therapy

Trypanosoma congolense infection in dogs can be treated with isometamidium chloride at 0.5 mg/kg injected deep intramuscularly. *Trypanosoma brucei* infection of dogs is apparently more resistant to drug therapy than *T. congolense* and its treatment consists of a higher dose of 1 mg/kg isometamidium chloride intramuscularly or diminazene aceturate at 3.5 mg/kg IM or SC [9]. *Trypanosoma evansi* in dogs and cats can be treated with diminazene aceturate at the same dose for dogs as for the treatment of *T. congolense* [10,11].

Prognosis

Dogs infected with *T. congolense* have been reported to be treated successfully, unless infection involved the CNS. Untreated disease is often fatal.

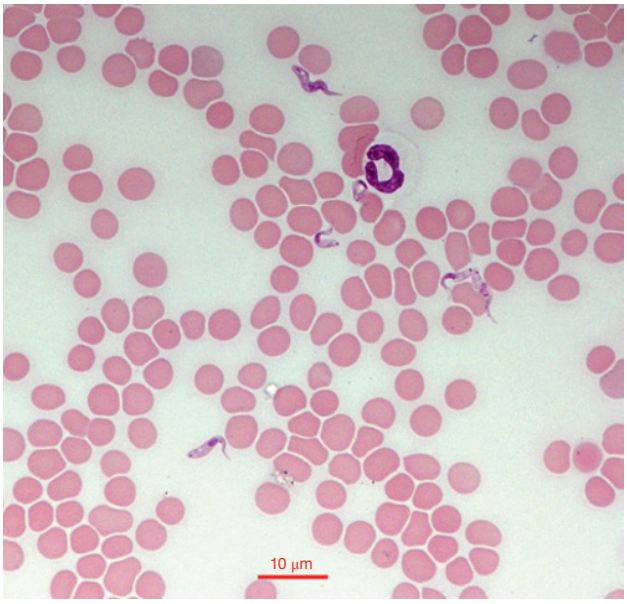


Figure 110.3 Trypomastigotes of *Trypanosoma congolense* in a blood smear from a naturallyinfected dog (May Grunwald–Giemsa stain).

Prevention of African trypanosomiasis can be achieved by eliminating dog contact with vectors by using deltamethrin-impregnated collars, or by injections of isometamidium chloride every 2–3 months.

Leishmaniosis

Etiology and Pathophysiology

The leishmanioses are a group of infectious diseases that affect humans and domestic and wild animals worldwide caused by diphasic protozoans of the genus *Leishmania* (Kinetoplasta, Trypanosomatidae). Most transmission cycles are zoonotic, involving reservoir hosts such as rodents, marsupials, edentates, monkeys, domestic dogs, and wild canids.

Canine leishmaniosis (CaNL) due to *Leishmania infantum* is a major zoonotic disease endemic in more than 70 countries. It is present in regions of southern Europe, Africa, Asia, South and Central America and has emerged in the United States mainly in foxhounds. In Europe, the domestic dog is a reservoir host of major veterinary and human importance [12].

Natural transmission of *L. infantum* infection between animals and from animals to humans occurs by the bite of a phlebotomine sand fly species (Diptera, Psychodidae, Phlebotominae) of the genera *Phlebotomus* (Old World) and *Lutzomyia* (New World). *Leishmania* completes its life cycle in the phlebotomine sand fly vector, which harbors the flagellated extracellular promastigote form, and in a mammal where the intracellular amastigote forms develop. A female sand fly ingests *Leishmania* while feeding on blood and then transmits the infective stages (metacyclic promastigotes) during a subsequent blood meal. The infective promastigotes inoculated by the sand fly into the skin of animals are phagocytosed in the mammalian host by macrophages and other phagocytic cells, in which they transform to amastigotes. In susceptible dogs or cats, amastigotes multiply and disseminate to internal organs.

The immune response elicited by susceptible animals is mainly an overwhelming humoral response that does not control infection. This robust humoral immune response coupled with a high parasite load leads to immune complex formation and deposition which causes a type III hypersensitivity reaction in several tissues and is associated with uveitis, polyarthritis or glomerulonephritis. In subclinical resistant animals, a protective T cell-mediated immune response predominates and controls the infection, preventing it from causing clinical disease.

Proven modes of non-sand fly transmission in dogs include infection through transfused blood products

from carriers and vertical transplacental transmission, as documented in foxhounds in North America, and venereal transmission.

Epidemiology

At least 2.5 million dogs are estimated to be infected in southwestern Europe alone, and the disease is spreading north into the foothills of the Alps and the Pyrenees. The number of infected dogs in South America also is estimated in millions, and there are high infection rates in some areas of Venezuela and Brazil, where a high prevalence of canine infection is associated with high risk of human disease.

The seroprevalence reported in dogs in the Mediterranean basin ranges from 5% to 30%, depending on the region. Surveys employing other detection methods to estimate the prevalence of *Leishmania* infection by amplification of *Leishmania* DNA from different tissues or by detection of specific anti-*Leishmania* cellular immunity have revealed even higher infection rates, approaching 70% in some foci. Most dogs in these areas appear to have chronic infection that may be lifelong, but only a low proportion of dogs develop severe disease.

In cats, serologic and PCR surveys in southern Europe indicate that *Leishmania* infection is more widespread than clinical disease. Epidemiologic studies have described rates ranging from 0.4% to 30% based on serologic and molecular techniques. However, it is important to highlight that clinical illness in cats is less frequently reported than in their canine equivalents.

Signalment

Dogs and cats of either gender can suffer from clinical leishmaniosis. Some dog breeds such as the boxer, Rottweiler, cocker spaniel and German shepherds appear to be more susceptible to the disease and other breeds (Ibizan hound) are more resistant. Disease is most common in young adult (>6 months of age), adult, and older dogs. Cats of any breed can be affected by this infection. Disease is most common in adult or older cats [13].

History and Clinical Signs

The clinical manifestations of this infection are very broad and variable, mainly due to the various types of immune responses which may be elicited in the dog in response to the parasite, the different organs affected and the different types of pathogenic mechanisms of disease that can be activated. Infection with *L. infantum* causes chronic infection, which can sometimes occur in a subclinical or mild self-limiting illness, or as a moderate or severe illness in dogs which can be fatal. Four clinical stages of the disease have been described based on the severity of the disease (clinical and laboratory abnormalities) and serology results, establishing different therapeutic regimens and forecast for each stage of the disease.

The main clinical findings found on physical examination in classic CaNL include skin lesions, local or generalized lymphadenomegaly, loss of body weight, exercise intolerance, decreased appetite, lethargy, splenomegaly, polyuria and polydypsia, ocular lesions, epistaxis, onychogryposis, lameness, vomiting, and diarrhea [12,13].

Skin lesions are the most frequent manifestation of CaNL in dogs brought for treatment due to suspicion of the disease. Several dermatologic lesion patterns have been described: exfoliative dermatitis with alopecia which can be generalized or localized over the face, ears and limbs; ulcerative dermatitis; nodular dermatitis; mucocutaneous proliferative dermatitis; and papular dermatitis.

The most common ocular manifestations of CaNL are anterior uveitis, blepharitis (exfoliative, ulcerative, or nodular), and keratoconjunctivitis, either common or sicca. About 25% of dogs with clinical leishmaniosis have ocular and periocular lesions including keratoconjunctivitis and uveitis. Ocular consequences of systemic hypertension such as retinal detachment and/or hemorrhages, retinal arterial tortuosity, and hyphema are present in the disease but not diagnosed frequently.

Some degree of renal pathology is present in most dogs with CaNL and subsequent renal disease due to immune-complex glomerulonephritis eventually develops and is believed to be the main cause of death in dogs with CaNL.

The most common clinical signs and clinical-pathologic abnormalities compatible with feline leishmaniosis (FeL) include lymph node enlargement and skin lesions such as ulcerative, crusty or nodular dermatitis mainly on the head or distal limbs, ocular lesions mainly with uveitis, feline chronic gingivostomatitis (FCGS) and mucocutaneous ulcerative or nodular lesions. Clinical illness is frequently associated with impaired immune competence, such as retroviral infections or immunosuppressive therapy.

Diagnosis

The most common laboratory findings in CaNL are hyperglobulinemia mainly with polyclonal gammaglobulinemia, hypoalbuminemia, decreased albumin:globulin ratio, mild to severe proteinuria, mild to moderate nonregenerative anemia, renal azotemia, elevated liver enzyme activities, thrombocytopenia, and thrombocytopathy. Hypergammaglobulinemia and mild normocytic normochromic anemia are commonly reported in FeL.

The pathologic findings observed by cytology or histology in CaNL and FeL are macrophagic, neutrophilic-macrophagic and lymphoplasmacytic inflammation in affected tissues and reactive hyperplasia of lymphoid organs.

The clinical diagnosis of leishmaniosis could be complex because of the broad spectrum of clinical and clinicopathologic abnormalities which are often not specific. For this reason, it is important to separate the diagnosis of *Leishmania* infection from clinical disease and to apply different diagnostic techniques for each situation [14]. Accurate diagnosis of CaNL and FeL often requires an integrated approach consisting of a clinicopathologic assessment and specific laboratory tests. The detection of *L. infantum* infection in dogs and cats includes parasitologic (cytology, histology, immunochemistry, and culture), molecular (conventional, nested, and real-time PCR) and serologic methods (qualitative and quantitative antibody tests). Detection of specific serum antibodies to *L. infantum* should preferably be based on quantitative serologic techniques, such as the IFA and ELISA.

The challenges of serology include cross-reactivity with other pathogens such as other *Leishmania* and *Trypanosoma* species, and with antibodies elicited by vaccination against CaNL. High antibody levels are associated with severe parasitism and moderate to severe disease. However, the presence of low antibody levels is not necessarily indicative of disease and further work-up is necessary to confirm CaNL and FeL by other diagnostic methods such as cytology, histopathology, and PCR. Information provided by PCR should not be separated from the data obtained from clinicopathologic and serologic evaluations. These should all be combined for a comprehensive assessment. It is essential to know the terms and limitations of each diagnostic test and make an adequate clinical interpretation [12–14].

Therapy

Treatment for CaNL depends on the severity of disease. Different therapeutic regimens have been established for each stage of CaNL. The drugs most frequently used in moderate to severe CaNL (stage 2 and 3) are a combination of meglumine antimoniate at 75–100 mg/kg q24h or 40–75 mg/kg BID for four weeks SC and allopurinol at 10 mg/kg/BID/PO for at least one year. Alternatively, a combination of miltefosine at 2 mg/kg/ PO q24h for four weeks and allopurinol at the same dose described above is also employed. Other drugs have been proposed for the treatment of CaNL but their efficacy or safety are limited.

Clinical cure in CaNL is often obtained and is associated with reduction in the parasite load and infectiousness to sand flies, but infection may persist and clinical relapse might occur and therefore life-long follow-up post therapy should be maintained.

The most common drug used for FeL is allopurinol administered alone at a dose of 10 mg/kg/BID/PO for at least six months. Treatment with meglumine antimoniate alone has been reported in rare cases of FeL. Most cats recover clinically following prolonged treatment and as for dogs, follow-up with routine laboratory tests, serology, and PCR is essential for the prevention of clinical relapses [12–14].

Prognosis

The prognosis of dogs and cats with leishmaniosis depends mainly on the severity of disease. Different prognosis is expected for each stage of CaNL with generally poor prognosis observed in dogs with renal insufficiency or severe renal disease associated with profuse proteinuria. The prognosis in cats is generally fair and a poorer prognosis is associated mainly with the presence of concomitant diseases and immune suppression.

Prevention

Several preventive measures are available for CaNL. The use of individual topical pyrethroid insecticides in collars or spot-on formulation has been shown to be effective in reducing *L. infantum* infection and, therefore, they are commonly applied to dogs in endemic areas to prevent infection.

Vaccination is also considered a promising tool for controlling CaNL. Second-generation vaccines for CaNL are commercially available in Europe and Brazil, with different efficacy rates in reducing the incidence of the clinical illness in field. Domperidone, a hyperprolactinemic immunomodulatory drug, has recently been licensed in some European countries for preventive use against CanL. However, limited studies exist regarding its efficacy in preventing the disease.

Dog culling practiced in Brazil as a control measure has been reported to have little impact on the incidence of human and canine leishmaniosis [15].

To date, preventive measures for this infection in cats are not commercially available.

Hepatozoonosis

Etiology and Pathophysiology

Hepatozoonosis is an arthropod-borne infection caused by apicomplexan protozoa of the family Hepatozoidae which are phylogenetically related to the piroplasms (*Babesia*, *Theileria*, and *Cytauxzoon*). Two different species of *Hepatozoon* infect dogs: *Hepatozoon canis* globally and *Hepatozoon americanum* in some parts of

the United States, mainly the southeastern states. *Hepatozoon canis* infects the hemolymphatic tissues and causes anemia and lethargy whereas *H. americanum* primarily infects muscular tissues and induces severe myositis and lameness [16,17]. Feline hepatozoonosis is caused by *H. felis*, which is prevalent in the Mediterranean basin, Asia, Africa, South, Central and North America. It infects muscle tissues including the myocardium and has not been associated with severe clinical disease [18]. Recently, *H. canis* and *H. silvestris* infections have been described in cats in Europe.

In contrast to most tick-borne pathogens which are transmitted via the tick salivary glands, *Hepatozoon* spp. infect vertebrates when they ingest arthropod hosts containing infective sporozoites. The main vectors of *H. canis* are the ticks *Rhipicephalus sanguineus* and *R. turanicus* worldwide and *Amblyomma ovale* in South America, whereas the Gulf Coast tick *Amblyomma maculatum* is the vector of *H. americanum* in North America. The vector of *H. felis* has not been identified to date but transplacental transmission in the feline host has been shown. Transplacental transmission from dam to pups has also been demonstrated for *H. canis* infection but not for *H. americanum*. Transmission by carnivorism and predation of the canine host on intermediate or wildlife transport hosts with ingestion of parasite cyst forms from their tissues has been shown for *H. americanum* and is considered as a main route of dog infection with this parasite [19].

The life cycle of *H. canis* revolves between the canine and tick hosts. When dogs ingest the vector tick or tick parts, *H. canis* sporozoites are released from sporocysts in the intestine and penetrate the gut wall. The sporozoites invade mononuclear cells and disseminate hematogenously or via the lymph to hemolymphatic target organs that include the bone marrow, spleen, and lymph nodes and to other internal organs such as the liver, kidney, and lungs. Meronts in which asexually dividing merozoites develop are formed in the dog's tissues in the process of merogony and may cause cellular necrosis in tissues. Merozoites release from mature meronts, invade neutrophils and monocytes, and develop into gamonts. Alternatively, merozoites can produce secondary meronts in the target tissues. The tick, which serves as the definitive host, is infected by ingesting leukocytes containing gamonts when feeding on a parasitemic dog. Morphologically indistinguishable male and female *H. canis* gamonts are released from the dog leukocytes within the tick gut, associate in syzygy, and differentiate in the process of gametogenesis to distinct gametes. After fertilization, the zygote divides and sporogony takes place with the formation of oocysts that release into the tick's hemocoel. The oocysts are large, spherical forms consisting of a membrane that envelops multiple sporocysts in which the infective sporozoites are found.

The life cycle of *H. americanum* differs from that of *H. canis* particularly with regard to the parasite's target tissues in the dog, the formation of distinct large cysts and the inflammatory reaction formed in response to infection. Sporocysts of *H. americanum* sporozoites from the hemocoel of an infected vector tick ingested by dogs release infectious sporozoites following contact with bile in the gut. Sporozoites are thought to cross the gut wall, and then taken up by host macrophages and transmitted via the lymph system or hematogenously to the target organs consisting of skeletal and cardiac muscles. *Hepatozoon americanum*-infected macrophages lodge between striated muscle fibers in these tissues and form muscle cysts. Concentric layers of mucopolysaccharide material are deposited by the infected cell forming a cystic structure referred to as "onion skin cyst." The encysted zoite undergoes merogony and multiple merozoites are formed. Eventually, the cyst ruptures, releasing mature individual merozoites into the surrounding tissue and eliciting a strong local inflammatory response. The pyogranulomatous inflammatory response is associated with severe musculoskeletal pain. The merozoites are taken up by leukocytes and are thought to undergo additional merogonic cycles or enter the blood vasculature, develop into gamonts and circulate in monocytes.

Epidemiology

Hepatozoon canis infection is reported mainly from tropical, subtropical, and temperate climate regions where vector tick species are abundant. Infection with *H. canis* has also been reported in dogs in the southeastern United States, mainly in some regions where *H. americanum* is also prevalent, and co-infections of both species have been reported. In Europe, autochthonous dog infection is found mostly close to the Mediterranean basin. It has also been described in dogs imported into nonendemic countries such as Germany, in foxes in European countries where autochthonous canine infection is rare or has not been reported, and in Slovakia and Poland where *R. sanguineus*, its tick vector, is not present. The prevalence of *H. canis* infection differs between regions. The rates of infection based on blood smear examination or PCR range from 1% to 64%.

The presence of *H. americanum* infection in the United States has expanded north and east from Texas, where it was first detected in 1978. It is found in several southeastern states, and occasionally cases are reported in other locations including Nebraska, Vermont, Washington, and California. *Hepatozoon americanum* infects wild coyotes (*Canis latrans*) and in experimentally infected young coyotes, it causes similar disease to that seen in dogs. Surveys of free-ranging coyotes in Oklahoma showed that 40–50% were infected naturally with *H. americanum*.

Signalment

Infection with *Hepatozoon* species is more common in dogs and cats with frequent outdoor access and those with contact to tick vectors. *Hepatozoon americanum* is often detected in hunting and guard dogs in contact with prey and potentially infected wild mammals. No age or breed predilections have been reported.

The pathogenesis of *H. canis* infection is influenced by immunodeficient conditions including immunosuppressive treatment, an immature immune system in young pups, concurrent infectious diseases or debilitating concomitant diseases. Co-infections with *Toxoplasma*, *Leishmania*, *Babesia*, *Ehrlichia canis*, or viral infections might predispose to clinical illness.

History and Clinical Signs

Hepatozoon canis infection varies from being subclinical to a severe disease in which dogs present with lethargy, fever, cachexia, and pale mucous membranes due to anemia. In contrast to the generally mild disease usually found in *H. canis* infection, dogs diagnosed with *H. americanum* infection are presented with fever, gait abnormalities, muscular pain induced by myositis, generalized muscular atrophy and mucopurulent ocular discharge with decreased tear production associated with inflammation of the extraocular muscles. Clinical signs may start 4–6 weeks after infection due to the pyogranulomatous inflammatory response that occurs when the encysted parasite cyst ruptures in muscle tissue. American canine hepatozoonosis can have an acute presentation or a waxing and waning chronic pattern. Pain associated with disease may be generalized or localized in the lumbar and cervical spine, long bones, or joints. Gait abnormalities range from limb stiffness to complete recumbency and inability to rise. Chronic infections can be associated with polydipsia and polyuria due to renal amyloidosis or glomerulonephritis and an ophthalmic examination may reveal uveitis. *Hepatozoon felis* infection has not been associated directly with overt clinical manifestations but *H. silvestris* has been reported to cause severe disease in domestic cats.

Diagnosis

Subclinical infection or mild disease is the most common presentation of *H. canis* infection and it is usually found in dogs with a low level of parasitemia (1–5%) (Figure 110.4). Severe illness can be found in dogs and may be associated with white blood cell concentrations as high as 150×10^9 leukocytes/L. High parasitemia rates of up to 100% can accompany extreme neutrophilia. A case–control study of dogs with *H. canis* parasitemia

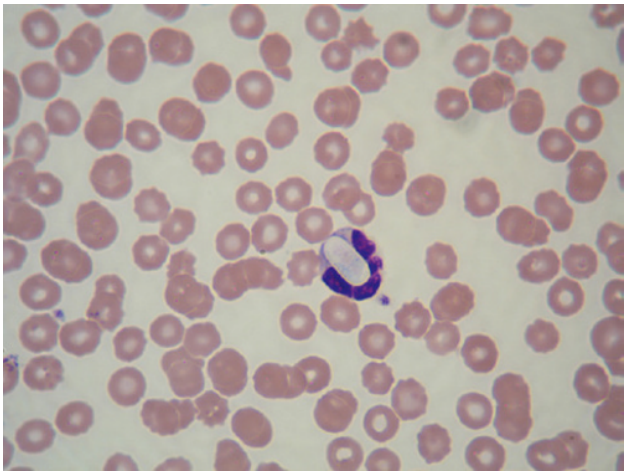


Figure 110.4 *Hepatozoon canis* gamont in a neutrophil from the blood smear of a naturally infected dog (May Grunwald–Giemsa stain 1000× magnification).

indicated that 15% had a high number of circulating parasites (>800 gamonts/μL) accompanied by elevated body temperature, lethargy, weight loss, anemia, and hyperglobulinemia. An association between the severity of clinical signs and the level of parasitemia was also found in a study of canine hepatozoonosis from Turkey. The most frequent hematologic abnormality reported in *H. canis* infection is mild to moderate normocytic normochromic nonregenerative anemia and, more rarely, regenerative anemia. Abnormalities in serum chemistry include hyperproteinemia with hyperglobulinemia due to polyclonal gammopathy, hypoalbuminemia and increased creatine kinase and alkaline phosphatase activities. Meronts of *H. canis* are commonly found in the spleen, bone marrow, and lymph nodes by cytology and histopathology. Although lesions of the periosteum are more frequently associated with *H. americanum* infection, periostitis has also been described as a rare finding in *H. canis* infection.

A marked neutrophilia is also one of the consistent hematologic findings in *H. americanum* infection with leukocyte counts of $30–200 \times 10^9$/L blood, although the level of parasitaemia is typically very low. A mild to moderate normocytic normochromic nonregenerative anemia is frequent. Serum biochemical abnormalities include increased alkaline phosphatase activity and hypoalbuminemia. Histopathology of skeletal muscles from dogs with *H. americanum* infections reveals pyogranulomatous myositis and large round to oval "onion skin" cysts (250–500 micrometer diameter). Radiography of the long bones or pelvis demonstrating periosteal proliferation can be used for screening suspected animals.

Hepatozoon canis infection is usually diagnosed by microscopic detection of intracellular *H. canis* gamonts in stained blood smears. Gamonts can be detected in the

blood at 28 days post infection. The gamonts are found in the cytoplasm of neutrophils and monocytes, have an ellipsoidal shape and are about 11 ×4 micrometers. In contrast, *H. americanum* parasitaemia usually does not exceed 0.1% of the leukocytes and rare gamonts may be detected in the blood from 32 days post infection. The confirmation *of H. americanum* infection can be achieved by muscle biopsy and demonstration of typical parasite cysts and granulomas or by PCR. PCR of blood for *H. canis* or *H. americanum* is a sensitive and specific diagnostic option. Diagnostic real-time PCR assays that can also quantify the parasitic load are able to detect both *H. americanum* and *H. canis* and distinguish between the two species. *Hepatozoon felis* infection is usually associated with a low parasitaemia and is best detected by blood PCR.

Serologic testing for *H. canis* or *H. americanum* by an IFA test or ELISA is used in epidemiologic studies but not commonly employed for clinical diagnosis in practice.

Therapy

The current treatment for *H. canis* is the administration of imidocarb dipropionate at 5–6 mg/kg IM or SC every 14 days until gamonts are no longer present in blood smears. The decrease of parasitemia is slow and usually requires several imidocarb treatments. Studies with follow-up by evaluation of buffy coat smears and sensitive PCR indicated that complete elimination of the parasite may frequently not be achieved with imidocarb dipropionate alone and also with combinations of imidocarb dipropionate and toltrazuril/emodepside, or imidocarb dipripionate with clindamycin [20].

Hepatozoon americanum is treated with a combination oral therapy of trimethoprim-sulfadiazine (15 mg/kg q12h), pyrimethamine (0.25 mg/kg q24h), and clindamycin (10 mg/kg q8h) for 14 days. Ponazuril (10 mg/kg PO q12h for 14–28 days) has been suggested as an alternative to the combination antiprotozoal treatment. After initial improvement of clinical disease signs is obtained, remission can be prolonged with the oral administration of the coccidiostat decoquinate at 15 mg/kg mixed in food q12h for two years. Relapse of clinical disease is frequent following discontinuation of treatment. Supportive therapy with nonsteroidal antiinflammatory drugs is effective in relieving pain and fever in dogs with *H. americanum* infection and administered initially with the combination antiprotozoal therapy.

No controlled trials have been published on the treatment of feline hepatozoonosis. Single cases have been treated with doxycycline, a single dose of 2 mg/kg primaquine PO or imidocarb at 2.5 m/kg IM with undetermined efficacy in eliminating the infection.

Prognosis

The prognosis of treated dogs with a low *H. canis* parasitemia is generally good even if decrease of parasitemia is slow and requires several imidocarb treatments. The prognosis for dogs with high parasitemia is good to guarded and sometimes associated with the outcome of a concurrent illness.

Hepatozoon americanum infection may be fatal without treatment within several months. Prognosis with antiprotozoal treatment followed up by long-term decoquinate therapy is guarded.

Prevention

Prevention of both *H. canis* and *H. americanum* infections consists of the use of topical acaricides and environmental parasiticides. Furthermore, avoidance of tick ingestion while scavenging or grooming, and of eating raw prey meat potentially harboring infectious tissue stages of the parasite is recommended [16].

To date, hepatozoonosis has not been shown to be established in recipient dogs following transfusion. Transfusion of the blood gamont stage is not likely to result in establishment of infection in the recipient dog as the gamont stage found in blood has to continue to the sexual parts of the parasite's life cycle in the tick before the parasite replicates.

Feline Cytauxzoonosis

Etiology and Pathophysiology

Feline cytauxzoonosis is an emerging tick-borne disease with an expanding geographic distribution caused by parasites from the genus *Cytauxzoon* (phylum Apicomplexa, class Piroplasmea, order Piroplasmida). Parasites of the genus *Cytauxzoon* are closely related to those of the genera *Babesia* and *Theileria*.

Cytauxzoon felis is a species infecting domestic cats and wild felids in the United States and South America and detailed clinical, parasitologic, and epidemiologic information is available on this infection. Other *Cytauxzoon* parasites which are genetically different and of decreased pathogenicity have been described in Europe in domestic cats and wild felids but limited information is available on these species.

Cytauxzoon felis is transmitted by the tick *Amblyomma americanum* in the United States. *Amblyomma cajennense* and other ixodid ticks have been presumed as vectors in South America. Other routes of transmission have not been well studied for this infection. The tick vector for *Cytauxzoon* spp. infection in felids in Europe remains unknown as well as other possible modes of transmission.

The wildlife animal reservoir for *C. felis* infection in the United States is the bobcat (*Lynx rufus*) where infection is mostly subclinical and a persistent erythroparasitemia is commonly found. Conversely, clinical illness is frequently found in infected domestic cats. *Cytauxzoon felis* infection in the cat varies in its clinical manifestation from a severe acute fatal disease to subclinical chronic infection.

Cytauxzoon species are detectable in two main forms in the mammalian host: schizonts in histiocytic cells and merozoites in erythrocytes. A phase of asexual schizogenous reproduction, within the host's mononuclear phagocytic cells, is responsible for the pathologic processes resulting in clinical illness. Large schizonts can occlude small blood vessels and cause thrombosis in the visceral organs and the brain. The onset of clinical disease occurs usually 1–3 weeks after tick-transmitted infection and the entire disease course is rapid, with cats frequently succumbing to infection within days.

Epidemiology

The geographic distribution and seasonality of cytauxzoonosis due to *C. felis* is largely correlated with relevant tick vector activity and presence of bobcats. This infection is present in the south-central, southeastern, and mid-Atlantic regions of the United States. Infected domestic cats are commonly from rural or suburban wooded areas. The prevalence of *C. felis* infection in domestic cats is variable in different published studies. In healthy cats, prevalence of *C. felis* infection ranged from 0.3% to 28%. Cytauxzoonosis accounted for 1.5% of all feline admissions to the veterinary teaching hospital at Oklahoma State University between 1998 and 2006 [21–23].

Signalment

Disease due to *C. felis* can occur in cats of any age and either gender with no identified breed predilections. Likewise, no signalment predispositions have been found in feline infections due to other species of *Cytauxzoon*.

History and Clinical Signs

Outdoor cats are more likely to be infected during spring and summer due to the presence of tick vector. Immune suppression has not been found to be a risk factor for infection with *C. felis*. *Cytauxzoon* spp. infection has been associated with living in a cat colony and outdoor lifestyle in domestic cats from Europe.

The clinical signs of *C. felis* infection are nonspecific and include an acute onset of anorexia, lethargy, and fever. Other clinical signs include increased vocalization, weakness, dehydration, icteric or pale mucous membranes, pigmenturia, mild to moderate lymphadenomegaly, splenomegaly and hepatomegaly, generalized pain, tachypnea and tachycardia with or without respiratory distress, dull mentation, and seizures.

Cytauxzoon spp. appear to mainly cause a subclinical infection with evidence of erythroparasitemia in domestic and wild felids in Europe. So far, evidence of clinical manifestations of a tissue schizogonic phase, as found for *C. felis*, has not been observed in *Cytauxzoon* spp. infection in Europe.

Diagnosis

Laboratory abnormalities due to *C. felis* infection include pancytopenia, hyperbilirubinemia, mild to moderate normocytic normochromic nonregenerative anemia, thrombocytopenia, lymphopenia, neutropenia, mild to moderate elevation of liver enzyme activities (ALT and ALP), prerenal azotemia, electrolyte disturbances (hypocalcemia, hypokalemia, and hyponatremia), hyperglycemia, mild hypoproteinemia with hypoalbuminemia and hypocholesterolemia.

Detection of *Cytauxzoon* in stained blood smears is useful in the diagnosis of erythroparasitemia. Infection may also be visualized by microscopic identification of schizont-laden macrophages in cytology of fine needle aspirates of lymph nodes, spleen or liver. PCR is a valuable tool to detect low parasitemia with higher sensitivity than blood smear. Furthermore, PCR and genetic characterization can distinguish between infection with *Cytauxzoon* and small *Babesia* spp. Serology is not used in the clinical setting.

Therapy

The combination of the antimalarial atovaquone (15 mg/kg PO q8h) and the macrolide azithromycin (10 mg/kg PO q24h) for 10 days is currently considered the best treatment option for acute cytauxzoonosis due to *C. felis*, with an approximately 60% survival rate in sick cats, while other treatments such as imidocarb dipropionate (3.5–5 mg/kg IM repeated at 14-day intervals if needed) have been reported to result in lower survival rates [23].

Medical management of this disease requires supportive treatments.

Prognosis

The prognosis for acute cytauxzoonosis in domestic cats due to *C. felis* is guarded to poor.

Prevention

So far, there is no vaccine commercially available for the prevention of *Cytauxzoon* infection. Prevention is focused

on avoidance of tick bites. A combination of tick control that targets the specific tick vectors and indoor lifestyle is the best strategy to reduce tick exposure.

Babesiosis

Etiology and Pathophysiology

Babesia are tick-borne protozoan parasites of erythrocytes that infect domestic and wild animals, and humans. *Babesia* belongs to the phylum Apicomplexa, class Piroplasmea, and order Piroplasmida [24].

Canine infections caused by different *Babesia* species are protozoal tick-borne diseases with worldwide distribution and global significance. Large-form *Babesia* spp. include *Babesia rossi*, *B. canis*, and *B. vogeli*. These species were previously considered subspecies of *B. canis*. They are identical morphologically but differ in the severity of clinical manifestations which they cause, their tick vectors, genetic characteristics, and geographic distribution. Therefore, they are currently considered separate species. Another yet unnamed large *Babesia* species most closely related to *B. bigemina* was found to infect immunocompromised dogs in the United States. The small *Babesia* spp. include *B. gibsoni*, *B. conradae*, and *B. vulpes* (formerly referred to as *B. microti*-like piroplasm and *Theileria annae*).

Babesiosis of domestic cats has mostly been reported in South Africa where infection is mainly due to *B. felis*, a small *Babesia* species that causes anemia and icterus. In addition, *B. cati* was reported from a cat in India and sporadic cases of infection in domestic cats by unnamed *Babesia* parasites have been reported in France, Germany, Thailand, and Zimbabwe. *B. canis* infection was reported from three cats in a study from Spain and Portugal in domestic cats with molecular evidence for infection. Additionally, infection of domestic cats with a genetically distinct species related to *B. canis* and named *B. canis* subsp. *presentii* was described in Israel [25].

Dogs and cats are infected when *Babesia* sporozoites are injected with saliva into the host's skin during a blood meal. The parasites invade the erythrocytes and form ring-shaped trophozoites which replicate within the erythrocyte and form merozoites observed as pairs of attached pear-shaped parasites in some *Babesia* species. Merozoites may further divide, forming eight or more parasites in the same erythrocyte and eventually lysing the cell, discharging into the blood to invade additional erythrocytes. Ticks feeding on infected blood take up merozoites and sexual parasite development in the tick gut is followed by sporogony in its salivary gland or ovaries. The parasite can be transmitted from the tick salivary glands during a tick bite or transovarially through its oocytes, as found in some *Babesia* species.

Babesia gibsoni infection has also been shown to be transmitted via blood transfusion and transplacentally. Furthermore, several studies have provided evidence that *B. gibsoni* is likely transmitted directly from dog to dog via bite wounds, saliva, or ingested blood [25,26].

Epidemiology

The geographic distribution of the causative agents and thus the occurrence of babesiosis is largely dependent on the habitat of tick vector species, with the exception of *B. gibsoni* where evidence for dog-to-dog transmission indicates that infection can be transmitted among fighting dog breeds independently of the limitations of vector tick infestation. *Babesia vogeli* and *B. gibsoni* have worldwide distribution, whereas *B. rossi* and *B. canis* have been mostly restricted to Africa and Europe, respectively. The unnamed large *Babesia* sp. most closely related to *B. bigemina* and *B. conradae* has been reported only from North America whereas *B. vulpes* was reported in Europe and North America.

Signalment

Puppies and dogs of any age with concomitant disease or immune suppression suffer clinical babesiosis due to *B. vogeli* more frequently compared to healthy adult dogs. Breed and gender do not appear to be predisposing factors.

Babesia canis, B. rossi, and *B. vulpes* have been reported to more frequently affect young to adult outdoor hunting and shepherd dogs. Breed and gender do not appear to be predisposing factors.

Disease due to *B. gibsoni* is found mostly in fighting dogs and breeds such as the pit bull terrier and tosa. Gender and age do not appear to be predisposing factors. Gender, breed, and age have also not been reported to be predisposing factors for *B. conradae* infection.

Splenectomized and immune-compromised dogs are more susceptible to infection with any *Babesia* species.

History and Clinical Signs

The main clinical findings reported in dogs suffering from *B. canis* infection include dehydration, lethargy, anorexia and fever, *Babesia vogeli* usually causes a subclinical infection or mild to moderate clinical disease which often accompanies other concomitant diseases or immunosuppressive conditions or affects splenectomized dogs. Severe fatal hemolytic anemia has been reported in puppies.

The most virulent large-form *Babesia* is *B. rossi*. Babesiosis due to *B. rossi* can manifest with uncomplicated common clinical signs as described for other babesial species or with complicated clinical disorders

including acute renal failure with anuria, icterus, hypotension, acute respiratory distress syndrome (ARDS), vomiting, diarrhea, pancreatitis, myalgia, rhabdomyolysis, ascites, pulmonary edema, encephalomyelitis, and peracute shock. The clinical findings associated with *B. gibsoni* infection include fever, splenomegaly, lymphadenomegaly, hepatomegaly, and lethargy. *Babesia conradae* infection has been described as more virulent than *B. gibsoni* infection, resulting in higher rates of mortality. The most common clinical findings reported in dogs infected with *B. vulpes* from the northwest of Spain include fever, lethargy, weakness, and pigmenturia.

Diagnosis

The main clinicopathologic findings reported in dogs suffering from *B. canis* infection include mild to severe thrombocytopenia, hyperfibrinogenemia, mild to moderate normocytic-normochromic nonregenerative anemia, hemolysis and neutropenia. Hemoglobinuria has also been described in naturally infected dogs. Common laboratory abnormalities in dogs infected with *B. vogeli, B. gibsoni* and *B. conradae* are regenerative anemia and thrombocytopenia. Although they are both small *Babesia* species, more pronounced anemia occurs in *B. conradae* infection than with *B. gibsoni* infection. Dogs with *B. vulpes* infections in northern Spain have demonstrated moderate to severe regenerative anemia, thrombocytopenia and azotemia. Hyperglobulinemia and proteinuria can also occur in *Babesia* infected dogs. The hemolytic anemia and thrombocytopenia associated with *Babesia* infections appear to occur by multiple mechanisms including immune-mediated destruction. Positive Coombs' testing, spherocytosis, positive saline agglutination tests and anti-platelet antibodies can occur. Therefore, it is important to rule-out babesiosis in patients with suspected idiopathic immune-mediated hemolytic anemia and thrombocytopenia. Detection of large or small species of *Babesia* in stained blood smears has been the standard for diagnosis for many years. This method is reliable when a moderate to high parasitemia is present, but there is not always a correlation between the level of parasitemia and the severity of clinical signs. A fresh smear is recommended for the accurate diagnosis of infection. Serology can indicate past infection or a present persistent one. Some serologic cross-reactivity exists between *Babesia* species. False-negative results are likely in peracute or acute infection and therefore convalescent antibody titers are needed to prove acute infection. Some evidence suggests that seroconversion may not occur in immunocompromised or young animals. The PCR is particularly useful in the diagnosis of babesiosis in dogs with a low parasitemia level including suspected carrier dogs or chronically infected animals and for speciation of parasites. However, a negative PCR does not rule out infection. Several molecular methods including seminested PCR, reverse line blotting (RLB), and restriction fragment length polymorphism (RFLP) PCR permit discrimination between species.

Therapy

Large *Babesia* spp. infections of dogs and cats are commonly treated with one dose of imidocarb dipropionate at 5–6 mg/kg (dog) and 2.5 mg/kg (cat) IM or SC with good clinical response. *Babesia gibsoni* and *B. conradae* infections are often resistant to imidocarb dipropionate and diminazene aceturate. The treatment of choice for these small *Babesia* species is a combination of the antimalarial atovaquone and the macrolide azithromycin. This combination is also likely to be a good treatment option for *B. vulpes* infection. The most commonly used dose of atovaquone is 13.5 mg/kg, administered PO q8h with fatty food to maximize drug absorption, in combination with azithromycin at 10 mg/kg PO for 10 days. Clindamycin in combination with metronidazole and doxycycline for a minimum of three months has also been used for treatment of *B. gibsoni*, although its overall efficacy is uncertain. The use of clindamycin alone is not recommended by some authors given the potential for selection of resistance and may subsequently interfere with alternative treatments.

The treatment of choice for *B. felis* in cats is primaquine phosphate. Published dosages range from 0.5 to 1.0 mg/kg PO, IV, or IM once, or administered daily on three consecutive days. Clinical and parasitologic cure are commonly not achieved in small babesial spp. infections in dogs and cats and clinical relapses may occur frequently. Medical management of infection may require supportive treatments including blood transfusions, intravenous fluids, and the use of antiinflammatory drugs [24–27].

Prognosis

The prognosis of dogs and cats infected with large forms of *Babesia* is generally good with appropriate therapy. Canine infection with small *Babesia* spp. may be more resistant to treatment and have a poorer prognosis.

Prevention

The prevention of babesiosis relies mostly on topical and environmental acaricidal treatments aimed at reducing exposure to vector ticks and transmission of the pathogen to dogs and cats. As *Babesia* species are transmitted by blood product transfusions, it is recommended to screen canine blood donors for *Babesia* infection on a regular basis and consider screening cat blood in relevant areas. Nonvectorial dog-to-dog transmission of

babesiae by fighting is preventable and can be responsible for the spread of babesiosis into previously nonendemic areas. A vaccine against *Babesia* is commercially available in some countries in Europe.

Giardiasis

Etiology and Pathophysiology

The genus *Giardia* includes intestinal flagellated protozoan parasites that infect a large number of host species, ranging from mammals to amphibians and birds. The most important *Giardia* species, *G. duodenalis*, infects cats, dogs, livestock, and humans with a broad host range and considerable public health significance. *Giardia duodenalis* is currently considered a multispecies complex. Multigeneic sequence analyses have identified different genetic assemblages of *G. duodenalis* including assemblages A and B in man and animal species, assemblages C and D in dogs, assemblage E from ruminants and pigs, assemblage F from cats, and assemblage G from rodents. To date, no association has been made regarding specific assemblages and the induction of certain characteristic clinical signs or the degree of their severity [2,3].

The life cycle of *Giardia* is direct and has two stages: the trophozoite and a cyst. The infective stage of the parasite, the cyst, is encysted when released into the feces and is immediately infectious. Cysts remain infectious for months in cool, damp conditions and accumulate in the environment. When ingested by the host, cysts excyst in the duodenum, releasing motile trophozoites. The latter undergo repeated mitotic division and form environmentally resistant cysts. Cysts pass through the intestine in feces and are spread by contaminated water, food, and fomites, and by direct contact. *Giardia* is transmitted mostly by ingestion of cysts in contaminated food or water. Following the ingestion of cysts and their exposure to the gut environment, each cyst releases two trophozoites which attach to the villi of the small intestinal epithelium. Trophozoites multiply by binary fission and eventually form cysts which are shed in the feces. The parasite presence in the intestine induces diarrhea by hypersecretion and malabsorption with increased intestinal permeability. *Giardia* infection in most dogs and cats is subclinical, but some animals suffer from severe diarrhea and weight loss which can become chronic.

Epidemiology

Infection rates with *Giardi*a in dogs and cats vary in the 5–30% range. The infection rates found in a large multicountry study in Europe were 24.8% in dogs and 20.3% in cats. Shedding *Giardia* is often subclinical and has frequently not been associated with clinical signs in population surveys. However, diarrhea and illness due to *Giardia* infection have been associated with puppies and kittens of young age as well as immune-suppressed animals and pets living in crowded conditions.

The relationship between human and animal *Giardia* infection is not clear. Humans certainly infect each other frequently and although they share the same *G. duodenalis* assemblages with animals with whom they have close contact, such as household dogs, it is not known how frequently infection is actually acquired from household animal contact or whether both human and pets acquire it from a common source, such as contaminated water [2].

Signalment

There is no breed or gender predilection. Young, immune-suppressed animals or those living in crowded conditions are more predisposed to the disease.

History and Clinical Signs

Most feline and canine *Giardia* shedders are infected subclinically. Those affected clinically suffer primarily from diarrhea and weight loss if disease becomes chronic. Diarrhea can be acute, intermittent or chronic and is mucoid, soft to watery and rarely bloody. Diarrhea can worsen and become bloody in animals co-infected with other intestinal parasites such as *Ancylostoma* spp., *Coccidia* or *Tritrichomonas foetus*. Vomiting and fever are rare. Reinfection with *Giardia* after successful treatment may occur.

Diagnosis

Giardia infection can be diagnosed by stool examination to identify cyst and trophozoite stages in direct fresh stool smears or by flotation for cysts. Sheather's sugar centrifugation and zinc sulfate centrifugation can be used for concentrating cysts. Rapid detection of *Giardia* antigen can be made using immunochromatographic kits, or by immunofluorescence, ELISA, and PCR in the parasitology laboratory [28].

Therapy

Dogs and cats can be treated with febendazole at 50 mg/kg PO q24h for 3–5 days, or with combined febantel, pyrantel, and praziquantel according to the febantel component at 37.8 mg/kg PO q24h for 3–5 days, or with metronidazole at 15–25 mg/kg PO q12–24h for 5–7 days. Since *Giardia* strains may have different antiprotozoal

susceptibilities, treatment with one of these drug options should be replaced by another if it is not successful in effectively relieving clinical signs. Furthermore, co-infections should be diagnosed and treated and sanitary management with quaternary ammonium disinfectants should be instituted to prevent reinfection.

Prognosis

The prognosis of treated dogs and cats is usually good and clinical signs are ameliorated, although some animals could suffer from persistent or recurrent infection.

Prevention

Disinfection of kennels, cages, and the animal's direct environment, boiling or filtering drinking water and removal of feces are important for controlling the spread of infection among animals that live in close proximity. Bathing of dogs and cats in infected kennels may decrease transmission of giardiasis between individual animals.

Miscellaneous Infections

Amebiasis

Amoebas are unicellular protozoal organisms with motile cytoplasm and a flexible cell wall. Molecular phylogenetic studies have shown that amoebas do not form a single taxonomic group and are found in many lineages of eukaryotic organisms. In older nomenclature classifications, most amoebas were placed in the class or subphylum Sarcodina, a group of single-celled motile organisms that possess pseudopods or move by protoplasmic flow. However, the amoeboid organisms are not classified together in one group any longer. Amoebas can be classified as enteric and residing in the gastrointestinal tract or nonenteric and associated with visceral and CNS invasion. Amoebas of different species are a rare cause of disease in dogs and cats. Different species of *Acanthamoeba*, *Balamuthia*, *Hartmannella*, and other amoebic genera and species may infect dogs and cats and colonize various organs, causing pneumonia, meningoencephalitis, renal disease, gastrointestinal disease of the small or large bowel, dermatitis, nasal disease, and keratitis [29,30].

Affected cats and dogs may be febrile and show a variety of clinical signs including neurologic abnormalities. Diagnosis is based on finding amoebae in excretions as cysts or trophozoites, or in tissues by cytology or histopathology and genetic characterization by specific PCR assays. Treatment consists of metronidazole for enteric infection and other antiprotozoal and antifungal drugs such as amphotericin B, ketoconazole, and miltefosine for deep organ infection.

Trichomoniasis

Trichomonas spp. are flagellated protozoa that belong to the order Trichomonadida, reproduce by binary fission, and do not produce cysts. Cats and more rarely dogs can be infected with *Tritrichomonas foetus* which is transmitted by the direct fecal–oral route and causes diarrhea [31,32]. *Tritrichomonas foetus* survives in feces and humid environment outside the animal's body for up to a few days. The parasite has been reported in numerous countries and has a worldwide distribution, with infection rates of up to 32% in cat populations from different countries in Europe [32]. Subclinical infection with *T. foetus* is common and there is not a direct relationship between infection and clinical signs. Infection is more common in cats from multicat settings and breeding catteries and clinical signs are more common in young cats under 12 months of age.

Tritrichomonas foetus attaches to the intestinal epithelium and induces a lymphoplamsmacytic and neutrophilic inflammatory response with large bowel diarrhea and frequent passage of soft liquid feces which may contain mucus and fresh blood [33]. Irritation of the anus may be present with swelling and edema. Diagnosis is made by identification of the organism in fresh feces by direct microscopic examination in which typical forward movement directed by the parasite's flagella and undulating membrane can be detected. Stained thin fecal smears may aid in the detection of the parasite with its typical form which is different from the *Giardia* trophozoites (Figure 110.5), when its presence is suspected

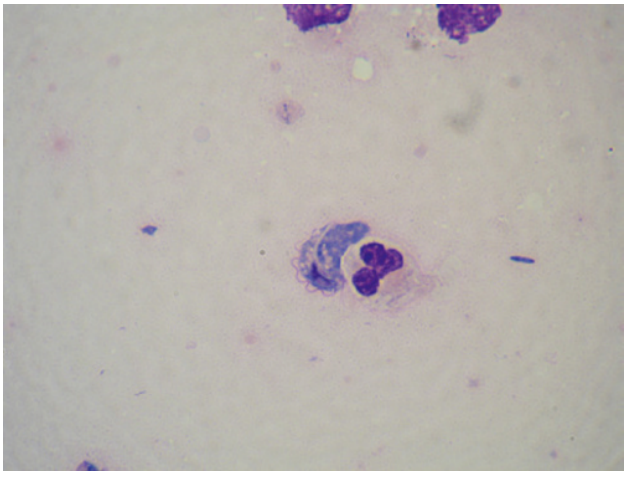


Figure 110.5 *Tritrichomonas foetus* in a stained fecal smear from a naturally infected cat (May Grunwald–Giemsa stain 1000× magnification).

based on wet smear microscopy. PCR is able to diagnose infection with high sensitivity and specificity, and culture in an "in pouch" medium is also used for diagnostic purposes. The drug of choice for treatment of *T. foetus* in cats is ronidazole at 30 mg/kg PO q24h for 14 days. Ronidazole is neurotoxic to cats at higher doses and is also teratogenic and should not be used to treat pregnant or lactating queens or young kittens.

Pneumocystosis

Pneumocystis is a genus of pathogens most closely related to Ascomycetes fungi. Current research has indicated that *Pneumocystis* species appear to be host specific. Five species have been described, including *Pneumocystis jirovecii* which infects humans and *P. carinii* which is a pathogen of rats, although much of the previous scientific literature has related to *P. carinii* as a human pathogen. Dogs may be infected with a different *Pneumocystis* species or strain provisionally termed *P. canis*.

Pneumocystis causes pneumonia in dogs and its transmission is thought to be air-borne in inhaled respiratory aerosol from infected hosts. Young dogs less than 1 year of age of either gender may be infected and Cavalier King Charles spaniels, Shetland sheepdogs and miniature dachshunds are predisposed to disease. Immunoglobulin deficiency and other congenital or acquired states of immune suppression have been reported in infected dogs [34]. Trophozoites and cysts of *Pneumocystis* are found in the lung alveolar spaces where the pathogen and its associated inflammatory response damage the alveolar septa. Dogs with pneumocystosis suffer from respiratory distress, tachypnea, weight loss, tachycardia, and exercise intolerance which progress and worsen over weeks to months. Thoracic radiographs show diffuse interstitial to alveolar patterns of lung disease and fluid collected on bronchoalveolar lavage or lung aspirates may show *Pneumocystis* trophozoites and cysts by cytology. Lung histopathology and PCR are also helpful in confirming infection. *Pneumocystis* does not grow in fungal culture and serologic tests have not provided a reliable diagnosis for canine infection.

The antimicrobial treatment of choice for canine pneumocystosis is trimethoprim-sulfonamide at 15 mg/kg PO q8h for three weeks. Pentamidine isethionate at 4 mg/kg IM q24h for two weeks is also used for pneumocytosis treatment, as well as atovaquone at 15 mg/kg PO q24h for three weeks, and a combination of clindamycin and primaquine (3–13 mg/kg PO q8h for three weeks). Supportive therapy to ease the respiratory distress is necessary in acute pneumocystosis.

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111

Coccidia

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Cystoisospora spp.

Etiology/Pathophysiology

Within the last few years, canine and feline enteric coccidia belonging to the genus *Isospora* were reorganized and are now recognized by the genus *Cystoisospora*. This designation is now well accepted but not well integrated. The reader should recognize that both terms refer to the same genus.

Coccidia are obligate intracellular parasites classified in the phylum Apicomplexa, and are commonly identified infecting the gastrointestinal tract of dogs and cats. Dogs are the definitive host to four species of *Cystoisospora*: *C. canis*, *C. ohioensis*, *C. burrowsi*, *and C. neorivolta*. The latter three species are generally grouped together as *C. ohioensis* complex. Cats are the definitive host for two species of *Cystoisospora*: *C. felis* and *C. rivolta*. *Cystoisospora* spp. are very species specific; dogs are not infected with cat *Cystoisospora* spp. and cats are not infected with dog *Cystoisospora* spp.

To truly understand the pathophysiology of these organisms, one must first understand the life cycle. The typical Apicomplexa life cycle consists of sexual and asexual reproductive events that occur inside and outside the host. A sporozoite is the infective stage and is the end-product of sporogony, a form of asexual reproduction. For *Cystoisospora* spp., this occurs in the environment outside the host. Sporozoites are contained within a sporulated oocysts. If this environmental sporulated oocyst is ingested by the target host, the sporozoites emerge from the oocyst, or excyst, in the small intestine. It should be noted that *Cystoisospora* spp. have the ability to utilize paratenic hosts as a means of completing the life cycle. If a paratenic host ingests the sporulated oocysts, the sporozoite will invade the extraintestinal soft tissues and encyst. This stage is infective to the final host if the paratenic host is ingested. In the small intestine, the sporozoite excysts from the sporocyst and invades small intestinal cells. The site, location, and number of asexual generation vary with each species of *Cystoisospora*. Once the sporozoite invades the cell wall, it essentially hijacks the host cell and can evade the host immune response. After another round of asexual reproduction by endogeny to produce first-generation schizonts (aka meronts) containing merozoites, the host intestinal cell is ruptured, releasing the merozoites to invade other cells. This process continues for a programmed number of cycles until the last cycle which is the sexual phase known as gametogony. Here, the merozoites differentiate into either a microgametocyte (male) or a macrogametocyte (female). The microgametocyte leaves the cell in search of a macrogametocyte to fertilize. The end-product of the sexual stage is a gametozoite known as an oocyst.

Pathologic changes to the host occur when developing stages (merozoites and gametozoites) emerge and rupture the epithelial cells. This leads to gastrointestinal bacteria colonizing the ruptured enterocyte.

Epidemiology

Transmission of *Cystoisospora* spp. is fecal–oral. Oocysts that are shed are not immediately infective to the next host. The oocyst needs time to sporulate in the environment (eight hours) to be infectious. *Cystoisospora* spp. also infect the definitive host via predation of a paratenic host. When this route is utilized, a paratenic host consumes sporulated oocysts, but asexual and sexual development do not occur. Sporozoites then enter extraintestinal tissue and form monozoic cysts, commonly found in mesenteric lymph nodes. Once a definitive host consumes the paratenic host, the life cycle continues as described previously. Infections are generally self-limiting.

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The distribution of *Cystoisospora* is worldwide. Due to the fecal–oral route of transmission, cases are associated with crowded and unhygienic environments. In the United States, prevalence of canine *Cystoisospora* spp. has been estimated to be between 3.1% and 4.4% while feline *Cystoisospora* spp. prevalence has been estimated to be between 3.9% and 6.3%.

Signalment

In most surveys, *Cystoisospora* spp. are detected in puppies and kittens less than 6 months of age. There does not appear to be a breed predilection. Patients that are most susceptible to clinical disease include nursing, recently weaned, and immunocompromised dogs and cats.

History and Clinical Signs

Clinical symptoms are more common in puppies and kittens acquired from unsanitary or overcrowded environments. *Cystoisospora* spp. can cause large or small bowel diarrhea, although patients may be asymptomatic despite shedding oocysts. Other clinical symptoms reported include anemia, dehydration, vomiting, anorexia, and weight loss. Physical exam findings of patients with *Cystoisospora* spp. are nonspecific and can include abdominal pain, increased gas or fluid in the gastrointestinal tract, and thickened loops of bowel.

Diagnosis

History, clinical symptoms, and detection of the organism are needed for a definitive diagnosis of coccidiosis. Fecal flotation, centrifugal or passive, can be performed and examined for the presence of characteristic oocysts (Figure 111.1).

It is important to differentiate oocysts of *Cystoisospora* spp. from those of *Eimeria* spp., which are not pathologic to canine and feline patients. Coprophagy of the feces of animals such as cattle, sheep, and chickens may lead to spurious detection of *Eimeria* spp. in canine and feline fecal samples. Both *Eimeria* and *Cystoisospora* are species specific and therefore pathogenic only to their target species.

Therapy

Asymptomatic adult patients demonstrating fecal oocysts may be monitored for development of clinical signs. Patients that meet criteria of history, clinical signs, and detection of the organism are treated symptomatically for diarrhea, and concurrently with antiprotozoal medications such as ponazuril, sulfonamides, or amprolium (Tables 111.1 and 111.2).

Table 111.1 Enteric coccidia of the dog and cat

Organism	Diagnostic stage	Size (μM)
Cystoisospora spp.		
Canine		
C. canis	Oocyst	30 × 38
C. ohioensis	Oocyst	19 × 23
C. neorivolta	Oocyst	11 × 13
C. burrowsi	Oocyst	17 × 20
Feline		
C. felis	Oocyst	30 × 40
C. rivolta	Oocyst	20 × 25

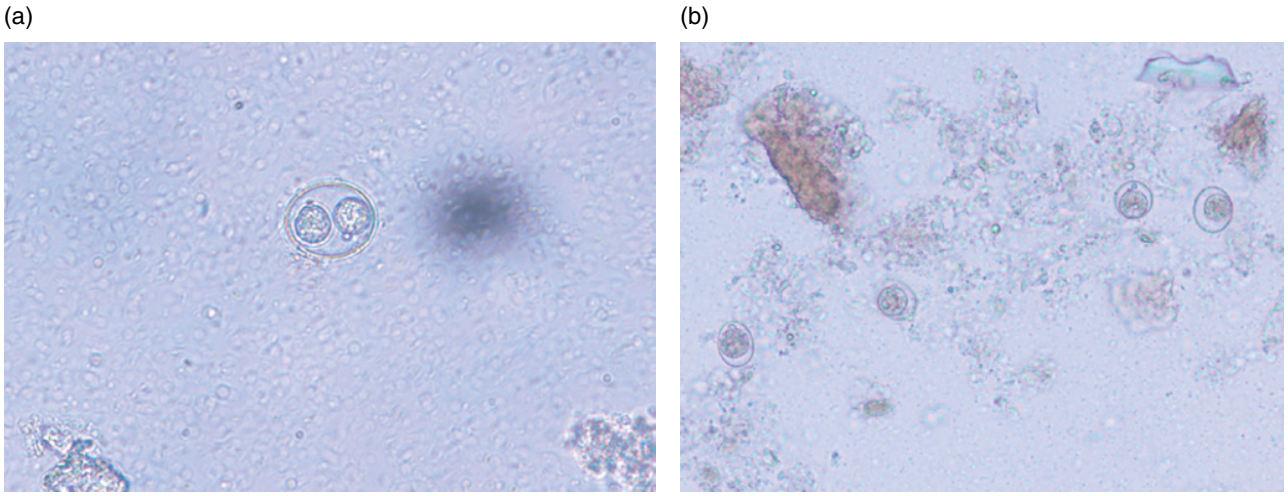


Figure 111.1 (a) Sporulated and (b) unsporulated *Cystoisospora ohioensis*. *Source:* Courtesy of the National Center for Veterinary Parasitology, Oklahoma State University.

Table 111.2 Treatment of enteric coccidiosis in dogs and cats

Antiprotozoal agent	Treatment regimen
Ponazuril[a]	20 mg/kg PO twice 1–7 days apart OR 50 mg/kg PO once
Sulfadimethoxine[b]	50–60 mg/kg PO daily for 5–20 days
Trimethoprim-sulfonamide[c]	15–30 mg/kg PO every 12–24 hours for 5 days
Amprolium[d]	300–400 mg PO daily for 5 days (canine)
	60–100 mg PO daily for 7 days (feline)
Furazolidone	8–20 mg/kg PO every 12–24 hours for 5 days

[a] Ponazuril is coccidiocidal and may be superior to other drugs.
[b] Sulfadimethoxine is the only approved drug for treatment of coccidiosis in the United States.
[c] Trimethoprim-sulfonamide combinations may cause acute hepatic necrosis, keratoconjunctvitis sicca, macrocytic anemia, and type III hypersensitivity reactions.
[d] Amprolium can cause anorexia, depression, diarrhea, and CNS disease due to induction of thiamine deficiency.
PO, by mouth (*per os*).

Symptomatic therapy begins by withholding food initially, followed by small, frequent meals with a bland diet once symptoms diminish. A class of medications commonly utilized to treat coccidiosis are the sulfonamides, which may be potentiated for better efficacy. Sulfadimethoxine is labeled in the US for dogs with bacterial enteritis associated with coccidiosis. Sulfonamides block folic acid synthesis and are effective against the schizont, an asexual stage. Sulfonamides are coccidiostatic, therefore fecal analysis may remain positive for oocysts during the course of therapy. Toxicity with use of sulfonamides has been reported and includes crystalluria, renal toxicity, keratoconjunctivitis sicca, type 3 hypersensitivity disorders, acute hepatic necrosis, and hematopoietic disorders. Dobermans are at increased risk for immune-mediated complications.

Ponazuril, a medication used to treat equine protozoal myeloencephalitis, has recently gained popularity as an off-label treatment for canine and feline coccidiosis. The mechanism of action is incompletely understood. A key improvement over previous treatments is that ponazuril is coccidiocidal rather than coccidiostatic, and fecal flotation can be negative 1–2 days post treatment. Amprolium, another coccidiostat, has also been used for canine and feline coccidiosis. It is a competitive inhibitor of thiamine and is most effective against the first-generation schizont.

Prognosis

Prognosis following proper diagnosis and treatment of canine and feline coccidiosis is good. Patients who recover from *Cystoisospora* spp. infections have species-specific immunity, but remain susceptible to infection with other *Cystoisospora* spp. infections. For example, a puppy that acquires a *C. canis* infection and recovers remains susceptible to infection with *C. ohioensis*. While patients with coccidiosis respond to appropriate therapy, untreated infections can lead to death from dehydration.

Public Health Implications

Due to the species specificity, *Cystoisospora* spp. of dogs and cats are not zoonotic to humans.

Cryptosporidium spp.

Epidemiology/Pathophysiology

There are many species of *Cryptosporidium* that infect a wide range of hosts, including dogs and cats. This genus is considered by some parasitologists to be more closely related to a group of the Apicomplexa known as the gregarines, which infect mostly invertebrates. Recently, gregarine-like stages have been described in multiple *Cryptosporidium* spp. This may lead to a reclassification of this genus in the future, and could possibly explain why most of the medications effective against coccidia are ineffective against *Cryptosporidium* spp.

The major host of *C. canis* is the dog; for *C. felis*, the major host is the cat. Unlike *Cystoisospora* spp., *Cryptosporidium* spp. are not host specific, although dog and cat *Cryptosporidium* spp. tend to favor the major host. This is an important distinction as other species, such as *C. parvum*, can be zoonotic. The life cycle is similar to that of *Cystoisospora*. The oocyst that is infective to the host contains four sporozoites that are not contained within sporocysts. The sporozoite will penetrate the host epithelial cell where trophozoites undergo schizogony to form merozoites. These merozoites will, in turn, invade other epithelial cells and undergo another round of schizogony. This is followed by the sexual phase, or gametogony, where microgametocytes are produced, fuse, and form zygotes. Zygotes can ultimately form either a thick-walled oocyst that is infective (sporulated) when it leaves the host, or a thin-walled oocyst that remains within the host and leads to autoinfection.

Pathologic changes occur when epithelial cells are damaged by emerging stages. Malabsorption ensues, and diarrhea is the primary clinical presentation. The severity of the infection is limited by developing immunity. Infection can be self-limiting if a host has a competent immune system. However, clinical disease may be prolonged in dogs and cats with a compromised immune system.

Epidemiology

Transmission of *Cryptosporidium* spp. is fecal–oral. Oocysts that are shed are immediately infective to the next host. Oocysts are stable in the environment, and high population densities as well as unsanitary conditions favor transmission. Young and immunocompromised animals are considered to be at greater risk. The infective dose is low; very few oocysts are required to produce an infection leading to clinical disease.

The distribution of *Cryptosporidium* spp. in dogs and cats is worldwide. Prevalence of *Cryptosporidium* spp. in dogs and cats varies, but has been estimated at 5%.

Signalment

Most cases of cryptosporidiosis have been reported in dogs and cats with a compromised immune system, those co-infected with other pathogens, or with preexisting conditions of the gastrointestinal tract (inflammatory bowel disease [IBD], lymphoma, feline leukemia virus [FeLV], canine distemper). Gastrointestinal symptoms may be more common in cats than in dogs.

History and Clinical Signs

The majority of canine and feline patients with detectable *Cryptosporidium* spp. oocysts are asymptomatic. When clinical disease is present, small bowel diarrhea, anorexia, and weight loss are common. Water loss secondary to malabsorption can lead to severe fluid imbalance.

Diagnosis

A combination of a direct saline smear and fecal flotation is preferred as the initial step, as oocyst excretion coincides with the onset of clinical signs. However, these techniques have poor sensitivity due to the small size of the oocyst. Fecal smears may be stained to enhance detection. Direct fluorescent antibody, enzyme-linked immunosorbent assay (ELISA), and polymerase chain reaction (PCR) are also available. These detection methods provide greater sensitivity than that observed with other detection methods.

Therapy

Direct treatment of the organism is difficult and the main goal of therapy is supportive. Initiation of highly digestible diets, fiber, and probiotics may be of benefit. Intravenous fluid administration may be needed to treat severe dehydration.

Published data regarding the treatment of cryptosporidiosis are lacking. Treatment protocols at this point are anecdotal and treatment needs to be calibrated to the needs and response of the individual patient. Azithromycin (10 mg/kg PO, SID until resolution), nitazoxanide (25 mg/kg PO, BID for seven days), paromomycin (150 mg/kg PO, SID for at least five days), and tylosin (10–15 mg/kg PO, BID-TID for 14–21 days) have been used. Paromomycin has the potential for nephrotoxicity and should not be used in dehydrated patients.

Prognosis

In an immunocompetent animal, infection with *Cryptosporidium* spp. usually resolves. Conversely, treatment of immunocompromised animals can be very difficult, and extended supportive measures may be necessary.

Public Health Implications

Health professionals should be aware that there have been cases of *Cryptosporidium* spp. transmission from animals to people. In a majority of cases, the pathogen was *C. parvum* and the source of infection was farm animals. However, *C. felis* and *C. canis* have been reported in the feces of some people. With no established treatment protocol for these cases, it is recommended that immunocompromised people avoid contact with animal feces, in particular the feces of strays and young pets (<6 months old) and utilize proper handwashing techniques.

Microspora

Microsporidia typically parasitize invertebrates, but *Encephalitozoon caniculi* can occasionally cause disease in dogs and cats following exposure. The life cycle is direct as environmentally resistant spores are passed in the urine or feces of an infected host and are consumed by a susceptible host. After ingestion and host cell penetration, organisms can be found in many cell types, with kidney and brain being the major organs affected. Transplacental transmission can occur, resulting in weakness, stunted growth, and later development of CNS disease and renal failure. Diagnosis is by detection of stained urine sediment. Serologic testing is also available.

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112

Surgical, Traumatic, and Bite Wound Infections

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Surgical and Traumatic Wound Infections

Etiology/Pathophysiology

In its most basic form, a wound is a break in the protective barrier organ that is the skin. Wounds can be created by almost anything, but are usefully described or defined in ways that reflect their degree of bacterial contamination, cause (i.e., bite wound, surgical site infection), and the depth or degree of tissue damage that accompanies them (i.e., superficial vs deep).

All wounds, regardless of cause or conditions present at their creation, can become infected. The likelihood of wound infection is directly related to the number and pathogenicity of bacterial contamination of the wound and inversely related to the overall health of the patient and the wound environment. This relationship can be defined as:

$$\text{Infection risk} = \frac{\#\text{ of bacteria} \times \text{virulence}}{\text{Host resistance}}$$

A threshold number of 10^5 bacteria per gram of tissue has often been quoted for the establishment of infection in a wound. The relationship of contamination to infection is borne out by the significant relationship between wound classification as clean, clean-contaminated, contaminated, and dirty (a proxy for the level of bacterial contamination in wounds) and infection risk in small animals. This number, however, is not absolute, as a wound may become infected after contamination with fewer organisms if the host cannot respond appropriately to bacterial contamination (discussed later) or if the bacteria in the wound possess specific virulence factors. For example, *Staphylococcus aureus* bacteria that do not express compounds anchored to their cell walls that adhere to matrix molecules in the host tissue do not cause invasive infection.

The health of the host and local wound environment are also very important in determining resistance to infection. Although a number of systemic conditions are associated with risk of surgical infection in humans, few of these risks have been investigated in veterinary patients. However, it is likely that patients with significant co-morbidities or extremes of age may be more susceptible. The use of perioperative antibiotics can be viewed as a means of increasing host resistance to infection. Finally, intraoperative management of the patient, including surgical time, surgical technique, use of surgical implants, anesthesia time, and maintenance of normothermia, plays a role in host resistance to infection.

Epidemiology

The bacterial flora of a wound is initially determined by its location (i.e., perineal) and cause (i.e., bite wound), but as time passes, opportunistic nosocomial pathogens such as *Pseudomonas aeruginosa* and *Enterococcus* species become more prevalent. These bacteria often have inherent (*Enterococcus*) and acquired resistance to multiple classes of commonly used antibiotics.

In acute, nonbite wounds, bacterial culture and sensitivity are unlikely to be helpful, as bacteria isolated will reflect wound contamination that may or may not lead to infection. In this circumstance, empiric, broad-spectrum antibiotic treatment based on common flora of the skin is an appropriate first-line therapy. This should take into account the potential for bacterial resistance associated with previous antimicrobial therapy, in which case culture may be warranted.

The presence of biofilms is increasingly recognized as a factor in the pathogenesis of chronic wounds and surgical site infections associated with foreign materials or implants.

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Biofilms are multispecies aggregates of microbes that manufacture a protective carbohydrate matrix. Within this matrix, they are shielded from their environment, including the immune system and antibiotic therapy. Moreover, bacteria within biofilms assume a sessile rather than planktonic state, which diminishes the likelihood that they will be detected using conventional culture techniques.

Antimicrobial resistance is a growing problem in veterinary and human medicine and is seen in both nosocomial and community-acquired infections. Mechanisms of antimicrobial drug resistance have been well reviewed, and prevention and management of resistant bacterial infections are discussed in Chapter 114.

Signalment

Any animal can develop a surgical site infection or sustain a traumatic wound that becomes infected.

History and Clinical Signs

Surgical site infection is more likely to occur after contaminated surgeries or surgery on contaminated areas (e.g., perineal region), surgeries that involve the implantation of foreign material (orthopedic implants, mesh, bone allografts), and those that involve prolonged anesthesia time. However, any patient undergoing surgery is at risk of surgical site infection. Traumatic wounds that involve significant tissue trauma, that do not receive appropriate early treatment, that are penetrating in nature, or that leave embedded foreign material behind (e.g., pieces of bark) are more likely than superficial lacerations to become infected.

Wound infection is suspected based on the presence of redness, pain, exudate, or swelling of the wound area. In some cases, wound infection is characterized by an apparent delay or interruption of normal healing. Wound infections from surgical or traumatic causes can also be systemically apparent, causing fever, pain, tachycardia, and other signs associated with bacteremia or systemic inflammatory response. Sometimes systemic signs are more prominent than the superficial appearance of the inciting wound, highlighting the need for exploration and debridement of wounds.

Although it seems that wound infection should occur shortly following creation of the wound, it may take days or weeks (even months, in the case of wounds in which implants are placed) before signs of infection become evident. In addition, wound and surgical site infections can occur at various tissue levels, ranging from superficial or incisional infection to deeper or cavitary infection. The depth of infection can play a role in determining the most appropriate course of treatment.

Diagnosis

Box 112.1 defines criteria used in the diagnosis of surgical site infections. Though this scheme was designed to

Box 112.1 Criteria for surgical site infection (SSI) definition

Superficial incisional SSI

Infection occurs within 30 days after operation
and
infection involves only skin or subcutaneous tissue of the incision
and at least one of the following.

1) Purulent drainage, with or without laboratory confirmation, from the superficial incision
2) Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision
3) At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat *and* superficial incision is deliberately opened by surgeon, *unless* incision is culture negative
4) Diagnosis of superficial incisional SSI by the surgeon or attending clinician

Suture abscess (minimal inflammation and discharge confined to points of suture penetration) is *not* considered a SSI.

Deep incisional SSI

Infection occurs within 30 days after operation if no implant is left in place or within one year if implant is left in place and infection appears to be related to the operation
and
infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision
and at least one of the following.

1) Purulent drainage from the deep incision but not from the organ/space component of the surgical site
2) A deep incision spontaneously dehisces or is deliberately left open by a surgeon when the patient has at least one of the following signs or symptoms: fever, localized pain, or tenderness, unless site is culture negative
3) An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiographic examination
4) Diagnosis of a deep incisional SSI by a surgeon or attending clinician

Infections that involve both superficial and deep incision sites *and* organ/space SSI that drain through the incision are reported as deep incisional SSI.

Organ/space SSI

Infection occurs within 30 days after the operation if no implant is left in place or within one year if implant is left in place and the infection appears to be related to the operation

and

infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation

and at least one of the following.

1) Purulent drainage from a drain that is placed through a stab wound into the organ/space
2) Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space
3) An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination
4) Diagnosis of an organ/space SSI by a surgeon or attending clinician

Source: Modified from Horan *et al.* (1992).

assist the diagnosis of surgical site infection, it is applicable to the diagnosis of any wound infection.

When an infection is present, clinical signs, particularly pain, lethargy, local swelling, drainage (ranging from serous to purulent to sanguineous in gross appearance), are generally present. Draining tracts can occur in cases of deep traumatic or surgical site infection, particularly if devitalized tissue (e.g., bone sequestrum) or foreign material (e.g., plant material, retained gauze sponge, surgical implant) are present. Draining tracts may occur relatively distant to the inciting foreign material, depending on tissue planes.

A patient suspected of having an infected wound should be thoroughly evaluated with a physical examination and by imaging appropriate to the area of interest if the wound is believed to involve tissue deeper than the skin and subcutis. Patients with traumatic wounds to the trunk should be evaluated with thoracic and abdominal radiographs to evaluate for pneumothorax or pneumoperitoneum, and abdominal or thoracic effusion.

Though many patients with chronic or superficial infections are relatively unaffected, those with significant or deep injuries, uncontrolled infections, continued bacterial contamination, devitalized tissue, and/or abscess formation can show significant systemic illness. Evaluation of these patients should include, in addition to those diagnostics listed earlier, evaluation of a complete blood count, biochemical profile, and urinalysis. Blood and urine cultures may be submitted. Exploration and debridement of infected areas should be performed shortly after initial treatment for sepsis and shock (described elsewhere in this text).

Therapy

Superficial infections that involve only cellulitis without evidence of deeper extension or abscess formation may be managed with oral antibiotic therapy alone. However, antibiotic therapy is not a replacement for exploration and debridement.

Wound management commences after managing more life-threatening concerns, critical diagnostics, and instituting necessary fluid replacement, analgesia, and supportive care. To prevent cross-contamination of the wound and hospital environment, the wound should be covered with a clean dressing and personnel handling the patient and/or wound should wear examination gloves at all times.

Wound Preparation

Under appropriate general anesthesia or heavy sedation, the wounds are packed with damp gauze or clean water-soluble lubricant to prevent further contamination. Hair is clipped widely around the wound area. The most obvious wound openings may represent the "tip of the iceberg," particularly when dealing with deep surgical site infections or bite wounds, so skin must be prepared to allow for extensive exploration and, if indicated, drain placement. Following hair removal, the wound and surrounding tissues are cleaned with an appropriate antiseptic detergent, such as chlorhexidine gluconate.

Exploration and Initial Debridement

The wound should be opened to its full extent to allow for complete exploration. Probing a smaller wound is not sufficient to determine its extent or level of contamination. The wound should be thoroughly assessed for involvement of deeper tissues or cavities (i.e., extension into the abdomen or thorax), necrotic or devitalized tissue, and foreign material. Necrotic, extensively contaminated, or devitalized tissue is judiciously removed using sharp dissection. Because many infected wounds are left open during initial treatment, serial debridement over several days is appropriate for important tissues of uncertain viability, which in some cases can partially or completely recover.

Lavage

Normal saline, a buffered isotonic fluid (i.e., lactated Ringer's solution [LRS]), or, in the case of significantly contaminated or large wounds, clean tap water can be used to copiously lavage the area. Though the hypotonicity of tap water is theoretically cytotoxic to cells in the wound, the clinical effect of this is not significant and may be outweighed by the practical utility of using a large sprayer or shower head to remove gross debris from a large wound area. The use of tap water lavage has not been shown to increase wound infection rates compared to saline in several human studies. Some authors promote intermediate pressure irrigation of 5–8 pounds per square inch, which can be generated by lavaging wounds using a 35 mL syringe and 18 gauge needle or catheter. Commercially available wound lavage units or a sink sprayer (tap water) may also be used. Warmed fluids should be considered to limit hypothermia, particularly in smaller patients, more extensive wounds, or wounds on the trunk.

Bandaging

Infected wounds are best managed as open wounds until healthy, at which time closure or reconstruction may be considered. When wounds communicate with a body cavity, the cavity should be evaluated, lavaged with warm, sterile isotonic solution, and drainage established through the use of a thoracostomy tube or closed-suction abdominal drain. A basic bandage includes the following components.

- *Contact layer*: directly interacts with the wound surface. A number of wound dressings are available and have been extensively reviewed elsewhere. This layer should ideally provide a protected, moist wound environment without macerating the tissue surrounding the wound. Some contact layers have antimicrobial properties or can be used with topical ointments that may provide a useful complement to systemic antibiotic therapy.
- *Secondary layer*: provides protection of wound and absorption of wound drainage.
- *Protective layer*: protects the bandage from dislodgment and environmental contamination.

Bandages should be changed as needed. During the first 1–2 days of wound evaluation (when further sharp debridement may be needed) or with more traditional dressings such as wet-to-dry, the bandage should be changed every 12–24 hours. Bandages should be changed when wound fluid reaches the protective layer of the bandage (also referred to as strikethrough). Some contact dressings such as alginates are intended to be left in place for 3–5 days.

Negative pressure wound therapy (NPWT) has been recently described as an alternative to conventional wound management. A number of NPWT devices are on the market, with increasing expansion into the veterinary field. NPWT can facilitate the development of a healthy granulation tissue bed following initial wound debridement without the need for frequent dressing changes.

Wound Closure

Wound closure is often possible in small animals due to the elasticity and quantity of truncal skin and availability of versatile axial pattern and other skin flaps. Wound closure or reconstruction of an infected wound should not be attempted until the wound is free of debris and necrotic tissue, a healthy wound bed is established, appropriate antimicrobial therapy has been started, the periwound tissues are healthy (not erythematous, macerated, or edematous), and the patient in good health. Many wounds, particularly those on extremities, are difficult to reconstruct or close and may be managed until contraction and epithelialization complete the healing process (second intention healing). Wounds in the perineal region are often best left to heal by second intention because of the difficulty of maintaining bandages in the area. In these cases, owners can be instructed to lavage the wound once or twice daily with tap water with a conventional shower head and apply an antimicrobial cream such as silver sulfadiazine to the area. An e-collar is provided to prevent self-trauma.

Prognosis

The prognosis for wound infections is variable depending on the source, location, and extent of infection (local vs systemic, deep vs superficial). Wound infections are often not amenable to a "quick fix." Owners should be counseled that management of an infected surgical or traumatic wound will likely require serial anesthesia and surgery to debride and potentially to later close the wound. Owners will need to accept that plans to reconstruct or close the wound may be delayed based on the appearance of the wound, and that multiple bandage changes or home wound management may be necessary. In some cases, the consequences of wound infection can negate the benefit associated with a surgery, such as for a total joint replacement. Fortunately, most appropriately managed wound infections can be satisfactorily managed, with patients returning to excellent health and quality of life.

Public Health Implications

Surgical wound infections with antibiotic-resistant bacteria are of significant human and animal health concern.

Bite Wounds

Etiology/Pathophysiology

Although dog and cat bite wounds are managed similarly to other infected or traumatic wounds (see earlier), the frequency and potential severity of bite wounds seen in small animal practice merit particular discussion.

Dogs can bite with significant force, and the orientation of their teeth results in puncture wounds from the canine and crushing or lacerating wounds from the incisor and molar/premolar teeth. Dogs also pull and shake victims following bites, resulting in avulsion of cutaneous vasculature and subcutaneous tissue. Dog bite wounds can be relatively minor lacerations and puncture wounds, or can be associated with extensive, life-threatening injury. Particularly severe are "big dog/little dog" injuries to small dogs or cats in which the victim is lifted and shaken by the aggressor. Although the limbs, head, and neck are common sites, injuries to the thorax and abdomen are relatively common in small-breed dogs. Dog bite wounds can be superficially dramatic, but often the skin wounds are the "tip of the iceberg," with extensive damage and contamination of underlying tissues lying deep to several small puncture wounds.

Due to the presence of contamination and the potential for serious tissue injury, dog bite wounds can lead to the systemic inflammatory response syndrome (SIRS) and septicemia. Without appropriate therapy, patients that survive the initial attack can die of these sequelae. It is important to recognize that a patient that seems relatively stable on initial presentation following a dog attack can rapidly progress to SIRS and septicemia.

Epidemiology

All bite wounds are considered to be contaminated due to the inoculation of the wound with the oral flora of the biter, the skin flora of the victim, and the bacteria or fungi in the environment. The common flora of the canine and feline oral cavity has been reviewed elsewhere, with *Pasteurella multocida* commonly cultured from both species.

Cat bite wounds are more likely to become infected due to the inoculation of oropharyngeal bacteria into deeper tissues. Cat–cat bite wounds are often not diagnosed until an abscess and associated clinical signs develop.

It is important to consider that organisms that cause hematologic disease such as hemotropic mycoplasmas and *Babesia gibsoni* are likely transmitted by bite wounds and follow-up testing may be warranted in some patients.

Signalment

Though any dog or cat can sustain a bite wound, smaller (≤10 kg) male dogs are overrepresented. Studies have identified higher percentages of certain breeds within this number, including Jack Russell terriers, dachshunds, pinschers, Yorkshire terriers, and Maltese dogs.

History and Clinical Signs

Dogs suspected or known to have been in a dog fight, particularly if multiple dogs were involved or if a size disparity was present, should be encouraged to undergo prompt evaluation by a veterinarian.

Diagnosis

The patient should be thoroughly examined, with prompt initial attention paid to cardiovascular and respiratory systems. The clinician should be ready to establish intravenous access and provide respiratory support if necessary through supplemental oxygen, intubation, tracheostomy, or thoracocentesis if indicated. A complete neurologic examination should be performed, particularly if wounds affect the head, neck, back, or extremity. Following initial assessment and stabilization, radiographs of the thorax and abdomen with or without focused assessment with sonography for trauma (FAST) scan for pleural and peritoneal fluid are warranted for wounds over the trunk. However, the absence of apparent free air or other abnormalities on radiographs does not guarantee that damage to the thoracic or abdominal body wall is not present.

Acute bite wounds are not infected, so wound cultures are often not helpful. More chronic wounds should be sampled for aerobic and anaerobic bacterial cultures.

Therapy

Initial stabilization will depend on the condition of the patient and will not be discussed in detail here, but should include the prompt administration of antibiotics. Intravenous administration of a broad-spectrum antibiotic or combination of antibiotics with good activity against skin and oropharygeal flora is warranted. As with infected surgical or traumatic wounds, it is wise to cover the open wound with a clean dressing and to wear gloves during initial assessment to prevent cross-contamination of the wound and hospital environment during assessment and stabilization.

As for infected surgical and traumatic wounds, surgical debridement and the establishment of drainage are important tenets in the successful management of dog bite wounds. The patient is carefully evaluated and the hair liberally clipped in wounded areas. In patients with

thick hair coats, it may not be possible to evaluate for smaller puncture wounds without removing hair along the majority of the neck and trunk. The presence of multiple bites is common and, as mentioned earlier, small puncture wounds can be the only external indication of significant damage to deeper tissues.

After stabilization and anesthesia, the skin is prepared as noted in the general section discussing management of infected wounds. After skin preparation and draping, the wounds should be opened and aseptically explored to determine the extent of tissue damage. Simply probing the cutaneous defects is insufficient for bite wounds. Once each wound area is explored, and debris and devitalized tissue removed, the wound is lavaged with isotonic fluid such as normal saline or LRS. Once opened, wounds can be left open and bandaged or, if minimally extensive, closed with appropriate placement of a drain. The reader is referred to surgical texts for a more detailed description of drain placement.

If there is any doubt about the state of the wound, if the wound is already infected, or if it is particularly severe, the author's preference is to leave wounds open and bandage them for several days. Delayed primary closure or tertiary closure may be pursued when the patient is stable, the wound bed is healthy, and the clinician is sure that no further tissue necrosis will occur.

Prognosis

As for infected traumatic and surgical wounds, the prognosis associated with bite wounds varies with the severity and location of the wound and the general health status of the patient.

Public Health Implications

In a dog or cat that has been or may have been bitten by a wild animal, potential rabies exposure protocols consistent with state regulations should be followed. All draining wounds in cats in particular should be handled with appropriate precautions due to the potential for sporotrichosis and other zoonotic diseases such as tularemia.

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113

Canine Infectious Respiratory Disease Complex

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Canine infectious respiratory disease complex is a multifaceted disease of immunologically naive, immunocompromised, and otherwise healthy dogs. Formerly known as kennel cough or infectious tracheobronchitis, studies show that the syndrome is far more complex than previously imagined, with a multitude of contributory pathogens and risk factors as well as variable outcomes.

Etiology/Pathophysiology

Canine infectious respiratory disease (CIRD) is a complex rather than a single disease in which various pathogens, including viruses, bacteria and mycoplasma, co-infect naive, immunocompromised or previously vaccinated dogs. CIRD usually presents in an acute, self-resolving (uncomplicated) form characterized by a dry, hacking cough with retching and gagging; the syndrome is generally initiated by viral pathogens. Occasionally, in immunocompromised or immunologically naive animals, the pathologic changes induced by viral disease predispose dogs to subsequent infection with opportunistic bacteria and *Mycoplasma*, thereby resulting in more severe (complicated) upper respiratory signs, bronchopneumonia, and death. Susceptibility to the complex is multifactorial and stems from both host and environmental factors. Many pathogens implicated in this complex are ubiquitous, being particularly prevalent in overcrowded housing facilities such as animal shelters, training and boarding facilities. The individual's stress induced by the new environment and exposures to novel pathogens both likely play a role in the development of clinical signs and disease.

Generally, respiratory signs are present for days to weeks and most animals show mild to moderate clinical signs. In most cases, viruses cause initial infection and result in clinical signs within 3–5 days of infection. Viruses that have been identified include canine influenza virus (CIV), canine respiratory coronavirus (CRCoV), canine parainfluenza virus (CPiV), canine adenovirus-2 (CAV-2), canine herpes virus (CHV), and rarely canine distemper virus (CDV). Research suggests that novel viral pathogens (canine reovirus, canine bocavirus, canine pneumovirus, and canine hepacivrus) may also contribute to the disease, but reports remain preliminary.

The tropism of viral agents associated with CIRD varies but mostly includes lymphoid and epithelial tissues throughout the upper and lower respiratory tracts, though notable exceptions are CHV and CDV with pronounced tropism towards monocytic cells. In more severe cases, viral infections cause either a bronchopneumonia or bronchointerstitial pneumonia due to their propensity to infect and damage type I pneumocytes. As the condition progresses, desquamation of the respiratory epithelium and aggregation of inflammatory cells further reduce the lungs' natural defenses, increasing the potential for secondary bacterial colonization and infection. Notably, CRCoV leads to loss of cilia from respiratory epithelium, thereby increasing the severity and duration of clinical signs associated with secondary infections.

While many animals develop only mild, self-limiting disease induced by viral infection, some animals go on to develop progressive clinical signs subsequent to secondary bacterial colonization. Bacteria and *Mycoplasma* which have been implicated in the development of CIRD include *Bordetella bronchiseptica*, *Streptococcus canis*, *Streptococcus equi* subsp. *zooepidemicus*, and *Mycoplasma cynos*.

Bordetella bronchiseptica, once presumed to be the sole player in the development of canine infectious upper airway disease, remains one of the most common pathogens detected and possesses unique mechanisms to evade host immune responses and allow for primary bacterial infection of the airways. Primarily, *B. bronchiseptica* expresses

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adhesins along the cell membrane, which facilitate colonization of the ciliated respiratory epithelium. Following adherence, the bacteria release exotoxins that reduce the body's ability to clear the disease and increase its susceptibility to other organisms. *S. equi* subsp. *zooepidemicus* infections, in particular, have been associated with a rapidly progressive and often fatal hemorrhagic pneumonia. Mycoplasmas have long been suspected to be part of the commensal flora of both upper and lower respiratory tracts, though *M. cynos* has been found to be present in significantly greater numbers of affected animals with moderate disease.

Epidemiology

Most of the organisms involved with CIRD are primary pathogens of the respiratory epithelium and thus require aerosol exposure or contact with fomites to facilitate infection. Following exposure, clinical signs generally develop within 3–5 days and the animal may shed virus for up to 8–10 days, though influenza virus can be shed for up to several weeks following infection. The course of disease associated with *S. equi* subsp. *zooepidemicus* seems to be much more rapid, with several case series reporting death within two days of exposure, sometimes without clinical evidence of respiratory disease. Animals in intensive housing with close exposure to other animals are at increased risk for development of clinical signs. Furthermore, prolonged housing in shelters or kennels increases the risk of developing disease and seroconverting.

Signalment

Canine infectious respiratory disease has a propensity for young, immunologically naive animals and immunocompromised patients. No sex or breed predilections have been identified. The greatest known risk factors stem from immune status and environmental history (see later).

History and Clinical Signs

Canine infectious respiratory disease usually presents as a dry, hacking cough often followed by a terminal retch. In particular, paroxysms of cough may be elicited by gentle tracheal palpation. In most cases, the infection is isolated to the upper respiratory tract so most affected dogs lack systemic signs, though mild lethargy and exercise intolerance are sometimes reported.

A history of recent exposure to other animals or housing facilities increases the suspicion of this disease. Animal shelters and rehoming kennels may provide the first exposure to immunologically naive animals, causing outbreak of clinical disease. Intuitively, greater length of exposure increases the risk of developing clinical signs. Additionally, the environmental stresses (i.e., crowded housing and poor nutrition) placed upon the animals may contribute to increased morbidity in these populations.

Most organisms associated with CIRD are found throughout the United States, though CIV seems to have a particularly higher seroprevalence in racing greyhounds and dogs from Florida (H3N8) and the Midwest (H3N2). Certain organisms like CHV are more prone to develop into clinical respiratory disease in patients undergoing immunosuppressive therapy.

Diagnosis

In an ideal world, diagnosis of the diseases associated with CIRD would precede therapy and help guide the use of (or withholding of) antimicrobials. However, even with the best intentions, identification of many of these organisms can be difficult. Furthermore, as many cases of CIRD are mild and self-resolving, diagnosis is often made based on clinical suspicion, taking into consideration the dog's age, environmental history, health, and vaccine status.

In most cases of uncomplicated disease, the physical exam is unremarkable with the exception of an inducible cough. Thoracic auscultation and radiography are generally unrewarding in milder cases. With progressive disease, nonspecific signs of systemic health and respiratory disease may be noted, including oculonasal discharge, pyrexia, adventitious lung sounds, and other indicators of malaise. Ideally, in more severe cases, fluid from a bronchoalveolar lavage (BAL) should be collected using sterile technique and submitted for cytologic analysis, bacterial culture (aerobic and *Mycoplasma* +/- anaerobic) and saved for potential molecular techniques (real-time polymerase chain reaction [PCR]) to detect viral organisms. Recently, the development of PCR panels run on nasal or oropharyngeal swabs has introduced a novel approach to the diagnosis of these diseases. Unfortunately, no published reports validate the sensitivity and specificity of these panels and false positives (due to contamination and/or vaccination) can occur along with false negatives (due to low virus shedding).

Therapy and Prevention

Most cases of CIRD in the otherwise healthy individual are self-limiting and respond well to basic supportive care. Strict environmental containment should be employed to prevent horizontal transmission. Affected

animals should be quarantined beyond complete resolution of clinical signs. Within the veterinary hospital, personal protective equipment (gowns, gloves, shoe covers, and masks) should be used, with care taken to disinfect potential fomites (scales, medical equipment, bowls, and cages). Bactericidal and virucidal disinfectant solutions with rapid action should be used consistently to limit the spread of disease since the pathogens involved with this complex can remain in the environment for weeks to months.

Antimicrobial therapy, when indicated, should be directed by culture of BAL or tracheal wash fluid. In the absence of microbiology results, empiric therapy may be directed to those bacterial pathogens suspected. Tetracycline antibiotics (such as doxycycline 5 mg/kg PO BID for 14–28 days) achieve excellent tissue penetration and are a good choice for *B. bronchiseptica* and *Mycoplasma* infections, but some strains of *S. equi* subsp. *zooepidemicus* have proven antimicrobial resistance to this class of drugs. Alternatives include macrolide antibiotics (azithromycin), potentiated penicillins (amoxicillin/clavulanic acid) or fluoroquinolones (enrofloxacin). Given the potential for disease in young animals, the clinician should consider potential adverse effects of the use of these drugs, including enamel discoloration with tetracyline (less severe with doxycyline) and cartilage development abnormalities with fluoroquinolones. When bronchopneumonia is suspected, routine supportive care including intravenous fluid administration, saline nebulization, and coupage is useful to help expectorate airway secretions.

In refractory cases involving paroxysms of cough and retching, antitussive medications like hydrocodone/homatropine (Hycodan®) or butorphanol (Torbugesic®) can help to relieve clinical signs, though these drugs should not be used in cases of suspected bronchopneumonia as they prevent expectoration of respiratory secretions. The use of antiinflammatory doses of corticosteroids remains controversial.

The most effective strategy for prevention employs strategic immunization and environmental controls to prevent exposure and limit passage of disease. Most owned dogs are immunized (parenterally) against CDV and CAV-2 as part of their core vaccines. Parenteral CAV-2 vaccination is considered a core vaccine due to its ability to cross-protect against CAV-1, but the intranasal vaccine does not provide this protection and is considered noncore but recommended for dogs likely to encounter the virus. Though considered to be noncore, routine vaccination for CPiV and *B. bronchiseptica* is recommended for animals likely to enter facilities where the diseases may be encountered (boarding and grooming facilities, training kennels). A vaccine for CIV (Nobivac® bivalent canine flu H3N8/H3N2) has been licensed in the US and shown to reduce clinical signs and virus shedding, though is still considered noncore. There are no licensed vaccines for CHV, CRCoV, and *S. equi* subsp. *zooepidemicus* at the present time. The reader is advised to consult the most recent AAHA Canine Vaccination Guidelines (2017 at time of publication) for more information regarding vaccine recommendations.

Prognosis

Overall prognosis for otherwise healthy dogs with uncomplicated CIRD is generally good, with most dogs recovering within 7–10 days after receiving only basic supportive care. Dogs with complicated infections (such as with *S. equi* subsp. *zooepidemicus* and *M. cynos*) have a more guarded prognosis. *S. equi* subsp. *zooepidemicus* progresses rapidly following the development of clinical signs and can lead to death due to sepsis, acute respiratory distress syndrome, and multiple organ dysfunction. Disease of the lower respiratory tract in conjunction with *M. cynos* infections seems to yield moderate clinical signs early following exposure, though these seem to lessen within 2–3 weeks.

Public Health Implications

Most pathogens involved in CIRD do not appear to present zoonotic risk, though there remains a possibility of human infection with these diseases. Several reports suggest that both healthy and immunocompromised individuals may be susceptible to *B. bronchiseptica* following administration of modified-live vaccines to companion animals. Given this potential, care should be used when administering all aerosol (intranasal) vaccines; only trained healthcare providers should administer and restrain the animal during this procedure. There have been no confirmed cases of zoonotic transmission of *B. bronchiseptica* from canine to human.

Likewise, though canine respiratory coronavirus has yet to be implicated in the development of respiratory disease in humans, these viruses as a family are known to jump species lines and may have the potential for zoonotic transmission. A notable example is the severe acute respiratory syndrome (SARS), beginning in Asia in 2002 (caused by the SARS-CoV), which is thought to have spread to human patients through wild captive mammals. Further coronavirus outbreaks in the Middle East and Western Europe (2012) continue to demonstrate the infectious and adaptive nature of these viruses that likely originated from animal reservoirs.

Finally, there appears to be some zoonotic risk of transmission of *S. equi* subsp. *zooepidemicus* from canine patients to both healthy and immunocompromised human handlers. Most reported cases of infection in humans develop subsequent to ingestion of contaminated milk and dairy products or contact with infected equine patients. Concurrently, contact with respiratory secretions – either aerosolized or in contact with mucous membranes – appears to be capable of infection causing acute nephritis, meningitis, pneumonia, and death.

Conclusion

Canine infectious respiratory disease is an evolving and multifaceted condition with many implicated pathogens and varied outcomes. Simple cases often respond to nonspecific supportive care while more severe cases may prove lethal even with the most advanced therapy. Prevention, through appropriate sanitation, husbandry and vaccination, remains the most effective way to limit disease transmission and morbidity. The zoonotic implications of many of the organisms associated with the complex deserve further study.

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Part 3

Therapeutic Considerations

114

Antimicrobial Therapy in Dogs and Cats

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To optimize antimicrobial therapy, clinicians should have a working knowledge of available antimicrobials and their spectrum of activity. Of equal importance is an understanding of clinically important side-effects, drug–drug interactions, and knowledge of circumstances in which certain antimicrobials should be avoided, or dosage adjustments should be considered to minimize potential adverse effects. This chapter will summarize these important considerations for commonly used antimicrobials in small animal medicine. The common classes of antimicrobials used and the clinically important antimicrobial side-effects/drug–drug interactions in dogs and cats are summarized in Tables 114.1 and 114.2, respectively.

Common Classes of Antimicrobials

Aminoglycosides (AG)

The AG spectrum of activity is primarily limited to gram-negative aerobes, including *Pseudomonas aeruginosa*. *In vivo*, AGs are considered synergistic with beta-lactams. AGs penetrate the bacterial cell envelope in part through an oxygen-dependent active transport mechanism as well as passive diffusion. By co-administering AGs with penicillins, the penicillins interfere with bacterial cell wall synthesis, enhancing the penetration of AGs into the bacterial cell envelope.

The dose-dependent nephrotoxicity of the AGs limits their clinical use. AGs bind the brush border of the proximal renal tubular cells and accumulate in lysosomes through active reabsorption. Through the inhibition of lysosomal phospholipase, phospholipid metabolism is inhibited, resulting in renal tubular cell death. Risk factors for nephrotoxicity include high dosages, multi-dose protocols, long duration of treatment, pre-existing renal dysfunction, dehydration, concurrent use with other nephrotoxic drugs or diuretics, and young or old age.

The active tubular reabsorption of AGs is a saturable process with an increase in nephrotoxicity when lower, more frequent dosing protocols are used. Despite AGs having a short elimination half-life, they demonstrate a post-antibiotic effect and concentration-dependent bacterial killing. Nephrotoxicity correlates with drug trough concentrations and is not observed following a high single dose; but is cumulative and occurs in association with multidose protocols, within 5–7 days after initiating therapy. Once-daily dosing is recommended to minimize nephrotoxicity while maintaining efficacy.

Aminoglycoside nephrotoxicity is reversible if recognized early so close monitoring is recommended. AGs should be avoided in patients with underlying kidney disease. If an alternative antimicrobial with an appropriate spectrum of activity is not available, dose reduction is recommended in azotemic patients. To help prevent nephrotoxicity, all patients should be well hydrated before and during the course of therapy. As mentioned above, once-daily dosing is recommended, and when possible the duration of therapy should be limited to 5–7 days. To detect proximal renal tubular damage, urine should be examined prior to and daily during therapy for the presence of granular casts, proteinuria, and glucosuria. Serum BUN and creatinine levels should also be monitored. Therapy should be discontinued if markers of nephrotoxicity develop.

Aminoglycosides also accumulate in the inner ear, leading to dose-dependent ototoxicity. Auditory toxicity is more common with amikacin, while vestibular toxicity is more common with gentamicin, especially in cats. Also, the use of AG is contraindicated in patients with disease of the neuromuscular junction (e.g., myasthenia gravis) due to inhibition of acetylcholine release and decreased receptor sensitivity leading to neuromuscular blockade.

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Table 114.1 Classes of antimicrobials used in small animal veterinary medicine including mechanism of action, spectrum of activity, and common drugs of each class

Drug class	Mechanism of action	Spectrum of activity	Examples*
Aminoglycosides (AG)	Alter protein synthesis – irreversibly bind the 30S ribosome Synergistic with beta-lactams	Gram-negative aerobes (including *Pseudomonas*)	Gentamicin Amikacin Neomycin
Amphenicols	Inhibit protein synthesis – reversibly bind the 50S ribosome subunit	Gram-positive aerobes Gram-negative aerobes Anaerobes *Rickettsia rickettsii* *Mycoplasma* spp. *Chlamydia* spp.	Chloramphenicol
Beta-lactams • Penicillins	Cell wall synthesis inhibitor via binding to penicillin binding protein (PBP) Synergistic with AG	Gram-positive aerobes (including *Enterococcus)* Anaerobes Spirochetes • *Leptospira* spp. • *Borrelia* spp.	Penicillin G Ampicillin/amoxicillin Amoxicillin/clavulanate Ampicillin/sulbactam Ticarcillin Methacillin/oxacillin
Beta-lactams • Cephalosporins	Cell wall synthesis inhibitor via binding to PBP	First generation • Gram-positive aerobes • Gram-negative aerobes (some) • Anaerobes (some) Second generation • Gram-negative aerobes • Gram-positive aerobes • Anaerobes (*Bacteroides*) Third generation • Gram-negative aerobes • *Pseudomonas* spp. (ceftazidime) • Gram-positive aerobes Borrelia Fourth generation • Gram-negative aerobes • Gram-positive aerobes Extended spectrum • Gram-positive aerobes • Gram-negative aerobes (some) • Anaerobes	First generation • Cephalothin • Cefazolin • Cephalexin • Cephadroxil Second generation • Cefoxitin • Cefotetan Third generation • Ceftiofur • Ceftazidime • Cefotaxime • Ceftriaxone • Cefpodoxime proxetil Fourth generation • Cefepime Extended spectrum • Cefovecin
Beta-lactams • Carbapenems	Cell wall synthesis inhibitor via binding the PBP	Gram-positive aerobes Gram-negative aerobes (including *Pseudomonas* spp.) Anaerobes	Imipenem Meropenem
Fluoroquinolones	Inhibit DNA gyrase (topoisomerase II) – target in gram-negative bacteria Inhibit topoisomerase IV – target in gram-positive bacteria	Gram-negative aerobes • Many including *Brucella* Gram-positive aerobes (limited) • *Mycoplasma* • *Chlamydia* • *Mycobacteria* • *Rickettsia rickettsii*	Enrofloxacin Ciprofloxacin Marbofloxacin Pradofloxacin

Table 114.1 (Continued)

Drug class	Mechanism of action	Spectrum of activity	Examples*
Lincosamides	Inhibit protein synthesis – reversibly bind the 50S ribosome subunit	Gram-positive aerobes Anaerobes • *Clostridium perfringens* • *C. tetani* • *Bacteroides* • *Fusobacterium* • *Actinomyces* • *Mycoplasma* spp. Protozoans • *Toxoplasma* • *Neospora*	Clindamycin
Macrolides	Inhibit protein synthesis – reversibly bind the 50S ribosome subunit	Gram-positive aerobes • *Campylobacter jejuni* (erythromycin) • *Mycoplasma* spp. • *Chlamydia* • *Mycobacterium* spp. (azithromycin, clarithromycin)	Erythromycin Azithromycin Clarithromycin Tylosin
Nitroimidazoles	Disrupt bacterial DNA synthesis – under anaerobic conditions converted to a unstable intermediate (nitroso free radical)	Anaerobes • *Bacteroides fragilis* • *Clostridium perfringens* • *Fusobacterium* Protozoans • *Giardia* spp.	Metronidazole
Potentiated sulfonamides	Target bacterial folic acid synthesis at two different steps: 1 Inhibitors of dihydrofolate reductase (trimethoprim, ormetoprim) 2 PABA analog (sulfonamides)	Gram-positive aerobes Gram-negative aerobes • *Nocardia* Protozoans • *Toxoplasma* • *Neospora* Atypical *Mycobacteria*	Trimethoprim/ sulfadiazine Ormetoprin/ sulfadimethoxine Trimethoprim/ sulfamethoxazole
Tetracyclines	Alter protein synthesis via reversibly binding the 30S and 50S ribosome	Gram-positive aerobes • *Staphylococcus* spp. • *Streptococcus* spp. • *Clostridium tetani* • *Nocardia* Gram-negative aerobes (some) • *Bordetella* spp. • *Brucella* Spirochetes • *Leptospira* spp. • *Borrelia* spp. Rickettsial • *E. canis* • *R. rickettsii* • *Anaplasma* spp. • *Wolbachia* *Mycoplasma* spp. *Chlamydia* spp.	Doxycycline Minocycline

* Note that not all organisms listed under "Spectrum of activity" are susceptible to each specific example of antibiotic listed. Please see text and other resources for more comprehensive sensitivity information.

Table 114.2 Clinically important side-effects and drug–drug interactions associated with antimicrobials commonly used in small animal medicine

Antimicrobial	Side-effect	Drug–drug interaction
Aminoglycosides	Nephrotoxicity (dose-dep.) Ototoxicity (dose-dep.) Neuromuscular blockade (inhibition of ACh release)	Synergistic with penicillins
Chloramphenicol	Bone marrow suppression (dose-dep.) Irreversible aplastic anemia (people, idiosyncratic)	Phenobarbital/propofol (dog, CYP 2B inhibition)
Carbapenems	CNS toxicity (imipenem > meropenem) Nephrotoxicity (imipenem)	
Fluoroquinolones	Articular cartilage erosions/blisters (growing animals) Retinal toxicity (cats, dose-dep.)	Antacids/sucralfate (decreased oral absorption) Theophylline (CYP1A inhibition)
Macrolides		Theophylline (CYP3A inhibition, erythromycin, clarithromycin)
Lincosamides	Esophageal structures (cats, clindamycin)	
Metronidazole	Neurotoxicity/cerebellovestibular ataxia	
Potentiated sulfonamides	Idiosyncratic (dogs) • Blood dyscrasias • Hepatoxicity • Polyarthritis • Cutaneous skin eruptions • KCS Dose dependent (dogs) • Nonregenerative anemia • Inhibition of thyroid hormone synthesis	
Tetracyclines	Tooth enamel discoloration (young, tetracyclines, oxytetracycline) Esophageal strictures (cats, doxycycline)	Antacids/sucralfate (decreased oral absorption)

ACh, acetylcholine; CNS, central nervous sysem; KCS, keratoconjunctivitis sicca.

The clinical situation where the risk of the systemic side-effects of nephrotoxicity and ototoxicity may be avoided is the use of orally administered neomycin in the treatment of hepatic encephalopathy. The AGs have poor oral bioavailability. In patients with hepatic encephalopathy, the goal of therapy is to target the ammonia-producing bacteria within the gut. However, if the integrity of the gastrointestinal tract is compromised, systemic absorption and the associated side-effects may theoretically occur.

Amphenicols (e.g., Chloramphenicol)

Chloramphenicol has a wide spectrum of activity against gram-positive and gram-negative organisms. Many anaerobic bacteria are also sensitive to chloramphenicol, including *Clostridium*, *Bacteroides* (*B. fragilis*), and *Fusobacterium* species. Other susceptible bacteria include *Chlamydia* spp., *Mycoplasma* spp., and *Rickettsia rickettsii*.

In dogs and cats, chloramphenicol can result in bone marrow suppression. This side-effect is considered dose-dependent and more likely if patients, especially cats, are treated for an extended duration. In people, the major route of chloramphenicol metabolism and elimination is glucuronidation. This suggests that decreased glucuronidation may contribute to the increased risk of toxicity in cats. In addition, 25% of the dose is reported to be excreted unchanged in the urine of cats compared to most other species, in which elimination is primarily via hepatic metabolism. Therefore, dose reduction should be considered in cats with kidney disease.

In dogs, chloramphenicol is a potent inhibitor of the hepatic microsomal cytochrome P450 enzyme system, specifically the subfamily CYP2B11. Through this CYP inhibition, the metabolism of barbiturates, like phenobarbital, and propofol may be impacted. Dogs concurrently prescribed chloramphenicol and phenobarbital have an increased risk of phenobarbital toxicity and dogs anesthetized with propofol may have prolonged recoveries if they are also being treated with chloramphenicol.

Chloramphenicol is associated with an irreversible aplastic anemia in people that is an idiosyncratic toxicity. Due to this unpredictable toxicity in people,

the use of chloramphenicol in veterinary medicine is limited primarily to patients with cultured bacterial isolates that have maintained their sensitivity to chloramphenicol but are multidrug-resistant organisms (e.g., methicillin-resistant *Staphylococcus pseudintermedius*). When prescribing chloramphenicol, owners need to be educated about the associated risk of exposure and toxicity to themselves and the need to wear gloves whenever the drug is being handled to avoid accidental ingestion or exposure.

Beta-Lactams

Penicillins

The broader spectrum (e.g., amoxicillin, ampicillin) or potentiated penicillins (e.g., amoxicillin/clavulanate and ampicillin/sulbactam) have an increased spectrum of activity against gram-negative organisms, including some of the beta-lactamase-producing bacteria and anaerobes. Ticarcillin has a strong gram-negative spectrum with activity against *Pseudomonas* spp. Methicillin/oxacillin has activity against the beta-lactamase-producing bacteria (e.g., *Staphylococcus* spp.) and is used primarily for susceptibility testing.

Beta-lactams have relatively limited side-effects and are clinically well tolerated. The most common side-effect is gastrointestinal upset, which is most commonly associated with amoxicillin/clavulanate, especially in cats. Hypersensitivity or allergic reactions to the penicillins are not very common in small animal medicine, in comparison to people. The beta-lactams are largely excreted in the urine and in patients with kidney disease, dose reduction may be necessary. However, due to the wide margin of safety of these drugs, dose reduction is often not routinely pursued in patients with mild to moderate azotemia.

Cephalosporins

The cephalosporins have a broad spectrum of activity against gram-positive organisms, with the exception of the *Enterococcus* spp. which are not susceptible. The cephalosporins as a group have some anaerobic activity but relative to the penicillins and potentiated penicillins (e.g., amoxicillin/clavulanate), their anaerobic spectrum is limited. Generally, the gram-negative spectrum of activity increases from the first- to third-generation cephalosporins. However, some of the less frequently dosed third-generation (e.g., cefpodoxime) and extended-generation cephalosporins (e.g., cefovecin) have a bacterial spectrum more consistent with the first-generation cephalosporins, including activity against many gram-positive and some gram-negative organisms but no activity against *Enterococcus* or *Pseudomonas* species.

Cefpodoxime is an oral formulation dosed once a day, and cefovecin an injectable slow-release formulation that delivers antibacterial activity for 14 days. Cefovecin's extended persistence may provide convenient dosing but in the event of an adverse effect, the drug cannot be withdrawn and in the case of treatment failure, continued drug exposure may contribute to antimicrobial resistance. The clinical use of cefovecin should be limited to fractious or noncompliant patients that cannot be medicated daily.

The fourth-generation cephalosporins have both gram-positive and gram-negative activity and their use should be limited to patients with a cultured susceptible gram-negative or gram-positive isolate, patients with susceptible mixed infections, or a serious to life-threatening susceptible multidrug-resistant and/or nosocomial infection(s). The later generation cephalosporins are expensive, require frequent dosing, and in some cases, a constant rate infusion is necessary for effective therapy.

Carbapenems

Carbapenems are considered powerful antibiotics with a very broad spectrum of activity. Therefore, their use should be dictated by the results of bacterial culture and antimicrobial susceptibility testing. The carbapenems are expensive and must be administered parenterally. Side-effects, more common with imipenem than meropenem, include central nervous system (CNS) toxicity and nephrotoxicity. Imipenem is available co-formulated with cilastatin (an inhibitor of imipenem metabolism) which minimizes nephrotoxicity. In the absence of cilastatin, imipenem is converted to a nephrotoxic metabolite in the proximal renal tubule, resulting in necrosis. In many patients, the use of meropenem may be better tolerated as it is more soluble and can delivered in smaller volumes relative to imipenem.

Fluoroquinolones

The spectrum of activity of fluoroquinolones classically targets aerobic gram-negative organisms. Pradofloxacin is a third-generation fluoroquinolone that has recently been approved in the US for the treatment of skin infections in cats. Pradofloxacin has an extended spectrum against many gram-positive organisms and anaerobes in addition to having a good gram-negative spectrum.

Fluoroquinolones are associated with significant side-effects and clinically important drug interactions. Articular cartilage erosions or blister lesions occur in growing animals, especially dogs treated with high doses. Clinical signs of lameness and joint swelling have been reported as early as two days following therapy in

experimental dogs given four times the recommended dose of ofloxacin. The use of fluoroquinolones is generally avoided in young puppies (<8 months), but in an experimental study in young beagles (13–16 weeks old), an oral dose of ciprofloxacin 10 mg/kg/day for 14 days did not induce joint lesions.

A species-specific side-effect of the fluoroquinolones is dose-dependent retinal toxicity in cats. Cats are functionally deficient in the ATP-binding cassette subfamily G member 2 (ABCG2) protein, encoded by the ABCG2 gene. This membrane-associated protein functions at the blood–retinal barrier to limit xenobiotics (e.g., fluoroquinolone) from entering the retina. When fluoroquinolones are administered to cats, the photosensitive fluoroquinolones have access to the retina, leading to retinal degeneration and blindness. All fluoroquinolones have the potential to cause retinal lesions with a modest overdose in cats, although there are differences between the fluoroquinolones. Retinal toxicity has been reported for enrofloxacin at 4-times the label dose and orbifloxacin at 18-times the label dose. In contrast, marbofloxacin and pradofloxacin did not cause retinal lesions when administered at 20-times and 10-times the label dose, respectively. To minimize retinal toxicity in cats, the recommended label dose should not be exceeded, rapid IV infusions and prolonged treatment durations should be avoided, and dose adjustment in patients with underlying kidney disease should be considered.

Two important drug–drug interactions are associated with clinical use of fluoroquinolones. Orally administered fluoroquinolones chelate with di- or tri-valent cations (e.g., calcium, aluminum, or magnesium), resulting in decreased absorption. The co-administration of fluoroquinolones with antacids containing aluminum or magnesium, or sucralfate should be avoided. If co-administration is necessary, separate the administration times by at least two hours (e.g., give the fluoroquinolone at least two hours before any products that contain di- or tri-valent cations). Fluoroquinolones inhibit the hepatic microsomal cytochrome P450 enzyme system, specifically CYP1A2 in people. CYP1A inhibition will decrease the elimination of substrate drugs, like theophylline, resulting in clinical signs of theophylline toxicity (tachycardia, excitability, tremors, or seizures). In clinical practice, it would be best to avoid the concurrent therapy of a fluoroquinolone (e.g., ciprofloxacin) with theophylline. Alternatively, a significant reduction in the theophylline dose can be considered to avoid toxicity.

Lincosamides and Macrolides

The lincosamides and macrolides have a similar spectrum of activity to include most gram-positive organisms. The most common side-effects are gastrointestinal signs, including vomiting and diarrhea after oral administration. Clindamycin capsules have been associated with esophageal strictures in cats. Stricture formation is thought to occur secondary to prolonged esophageal mucosal contact of the capsule if administration is not preceded or followed by food or liquid.

Potential drug interactions associated with some macrolides are their ability to inhibit the metabolism of other drugs which are substrates of the CYP3A subfamily of the microsomal cytochrome P450 enzyme system. Erythromycin and clarithromycin are inhibitors of CYP3A (i.e., CYP3A4 in people) which will inhibit the metabolism of CYP3A substrate drugs (e.g., theophylline), leading to toxicity when prescribed concurrently. Azithromycin is not a cytochrome P450 inhibitor.

Nitroimidazoles (e.g., Metronidazole)

Metronidazole has activity against anaerobes to include *Bacteroides* (*B. fragilis*), *Fusobacterium*, and *Clostridium* species. Other organisms susceptible to metronidazole include *Giardia* and *Trichomonas*. An overdose of metronidazole is associated with neurotoxicity leading to cerebellovestibular ataxia in dog and cats. The mechanism of toxicity is thought to be inhibition of the gamma-aminobutyric acid (GABA) neurotransmitter. At toxic doses, clinical signs include ataxia, nystagmus, and proprioceptive deficits which are reversible once the drug is discontinued. To avoid toxicity in patients with impaired liver function, dose reduction is recommended (e.g., an empirical dose reduction to 7.5 mg/kg twice a day for metronidazole in patients with underlying liver failure or cirrhosis).

Potentiated Sulfonamides

The potentiated sulfonamides provide broad-spectrum activity against gram-positive and gram-negative organisms and some activity against *Coccidia* and *Toxoplasma*. *Pseudomonas aeruginosa* is not susceptible to the potentiated sulfonamides. Many *Staphylococcus* spp., including methicillin-resistant *Staphylococcus pseudintermedius* (MRSP), remain susceptible to the potentiated sulfonamides. The major limitation of the use of potentiated sulfonamides in veterinary medicine, and specifically in dogs, is the risk of an idiosyncratic and/or dose-dependent side-effect.

Sulfonamide-induced side-effects in dogs may be in part due to the dog's inability to metabolize the sulfonamides via acetylation (the major metabolic pathway for sulfonamides in people). The underlying pathophysiology is not well understood but in part involves immune-mediated mechanisms. For example, sulfonamide metabolites may play a role in triggering a T cell-mediated response to haptenated proteins.

Idiosyncratic sulfonamide hypersensitivity reactions in dogs occur at standard doses and have a reported incidence of 0.25%. Many body systems can be affected, including blood dyscrasias (immune-mediated hemolytic anemia, immune-mediated thrombocytopenia and/or neutropenia), acute hepatotoxicity, polyarthropathy (Doberman pinschers are overrepresented or predisposed to developing a sulfonamide-triggered arthropathy), cutaneous skin eruptions, keratoconjunctivitis sicca (KCS), and uveitis. Clinical symptoms occur at least 5–7 days after drug initiation and in many cases resolve with drug withdrawal. The specific clinical signs observed are dependent on the body system(s) affected but often include non-specific systemic signs, most commonly fever. These sulfonamide hypersensitivity reactions are much less common in cats and more likely include mucocutaneous ulceration and ulcerative dermatitis.

Dose-dependent side-effects of the potentiated sulfonamides in dogs include non-regenerative anemia and the inhibition of thyroid hormone synthesis. A normocytic, non-regenerative anemia may arise in dogs treated with high-dose, long-duration therapy (i.e., 30–60 mg/kg/day for eight weeks). The suspected mechanism for this non-regenerative anemia is a secondary folate deficiency arising from the simultaneous inhibition of folate synthesis by trimethoprim (inhibitor of dihydrofolate reductase) and sulfonamide (a folate analog). The degree of anemia tends to be mild to moderate and normocytic. In several species, including dogs, sulfonamides inhibit thyroid peroxidase, the enzyme needed for iodination and thyroid hormone production. Dogs undergoing prolonged therapy with a potentiated sulfonamide may be at risk for clinical hypothyroidism; however, the frequency in dogs appears variable and effects are reversible once the sulfonamide administration is discontinued.

Patients prescribed potentiated sulfonamide therapy should be monitored during therapy for adverse reactions. In addition, owners should be educated as to the clinical signs (decreased appetite, vomiting, diarrhea, lameness, lethargy, ocular changes or discharge, and dark to red urine) associated with an adverse effect to enable early intervention, including drug discontinuation. Ideally, a systemic work-up is indicated in any dog with clinical signs of a sulfonamide hypersensitivity during or following a course of therapy. Indicated diagnostics include a physical exam, ocular exam, complete blood count (CBC), biochemistry profile, urinalysis, and Schirmer test (STT). Prior to prescribing a potentiated sulfonamide to a dog, a baseline physical exam, CBC, biochemistry panel, and STT are recommended to avoid their use in dogs with KCS and to provide a baseline for comparison during and following therapy.

Tetracyclines

As a group, the tetracyclines are considered as relatively broad-spectrum antimicrobials, but the common gram-negative organisms (*E. coli*, *Klebsiella*, *Bacteroides*, *Enterobacter*, *Proteus*, and *Pseudomonas* species) develop resistance to the tetracyclines. In small animal veterinary medicine, doxycycline is the most common tetracycline used in the treatment of some tick-borne diseases, leptospirosis, or respiratory infections associated with *Bordetella bronchiseptica* or *Mycoplasma pneumoniae*.

Minocycline has previously had limited clinical use in veterinary medicine but its use may increase based on the current cost and availability of doxycycline. In people, minocycline is well tolerated, with gastrointestinal signs reported. Anecdotally, the clinical use of oral minocycline in dogs has been associated with more gastrointestinal upset (resulting in drug discontinuation) relative to doxycycline.

Minocycline has a spectrum of activity and pharmacokinetics similar to those of doxycycline. The exceptions are some MRSP isolates that are resistant to tetracycline but remain sensitive to minocycline. A tetracycline induction assay (which may not be available in all microbiology laboratories) is necessary to determine susceptibility of MRSP isolates to minocycline.

Side-effects associated with the tetracyclines may limit their use in some patient populations. Young dogs and cats may experience tooth enamel discoloration following therapy with a tetracycline. Tetracyclines have an affinity for polyvalent cations and are taken up by calcifying tissues (i.e., teeth and bone) as a fluorescent pigment. When tetracyclines are administered during tooth development, the tetracycline pigment is taken up by the enamel and dentin, resulting in permanent discoloration. Doxycycline appears to have a lower risk of tooth discoloration compared to other tetracyclines.

In cats, doxycycline has been associated with the development of esophageal strictures. In people, when capsules are retained in the esophagus, the acidity of doxycycline salts (hyclate or hydrochloride > monohydrate) can cause local esophagitis and ulceration, leading to stricture formation. A similar mechanism of stricture formation has been proposed in cats. Administering a liquid formulation versus capsules of doxycycline to cats is recommended to avoid stricture formation.

Clinically important drug interactions are also associated with orally administered tetracyclines. Tetracyclines administered in association with drugs or vitamins containing di- or tri-valent cations (e.g., calcium, magnesium, iron) result in dramatically lower oral absorption of tetracycline antimicrobials. Common drugs that contain aluminum and/or magnesium should not be co-administered with any of the tetracycline antibiotics,

including bismuth subsalicylate (Pepto-Bismol®), sucralfate, and many antacids. This interaction may be less clinically significant for doxycycline due to its lower affinity for calcium relative to other tetracyclines.

Additional Considerations

To optimize antimicrobial therapy, clinicians should have a working knowledge of the available drugs, including their spectrum of activity, clinically important side-effects, and drug–drug interactions. Prior to writing any antibiotic prescription, consideration of some important questions can help optimize clinical outcomes. Define the need for antimicrobial therapy. Is a bacterial infection suspected or identified? Define the spectrum of activity needed. Where is the site of infection? What is the most likely infecting bacterial pathogen(s)? Are additional diagnostics necessary such as culture and antimicrobial susceptibility testing? Define the patient characteristics which may limit efficacy or increase the risk for an adverse event or drug–drug interaction. Does my patient have underlying kidney or liver disease? What other drugs are being administered to this patient?

Often, in otherwise healthy patients with uncomplicated bacterial infections in which the infecting pathogen(s) are predictable (e.g., canine female lower urinary tract infections), empiric antimicrobial therapy is effective. However, bacterial culture and antimicrobial susceptibility become mandatory for any patient following their first empiric antibiotic therapeutic failure. Other clinical situations in which antimicrobial therapy becomes more complicated include patients with recurrent infections, multidrug-resistant infections, or in immunocompromised patients in which bacterial culture and antimicrobial susceptibility testing are critical to optimize efficacy and minimize further antimicrobial resistance. In cases of chronic recurrent or multidrug-resistant infection, repeating bacterial culture and antimicrobial susceptibility testing during therapy and/or following therapy becomes essential to confirm responsiveness to antimicrobial therapy and/or confirm the resolution of infection. Consensus guidelines for treatment of bacterial infections in dogs and cats are available at the International Society for Companion Animal Infectious Disease website (www.iscaid.org)

Further Reading

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115

Antifungal Therapy

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Until relatively recently, treatment of systemic mycoses was limited to intravenous amphotericin B and oral ketoconazole. However, in the last two decades, significant progress has been made in the development of first-generation triazole drugs, newer second-generation triazole drugs, and echinocandins.

New antifungal therapies are often constrained by the fact that fungal organisms are eukaryotic, and therefore greater potential exists for host toxicity. For example, traditional antifungal medications that target ergosterol, or its production, can cause toxicity in mammalian cells via inhibition of cholesterol production or damage to cell membranes. Newer therapies are being directed at components unique to fungal organisms, thereby sparing mammalian cells. Although *in vitro* testing frequently finds antifungal drugs to be fungicidal, most appear to be fungistatic *in vivo*, thus the host immune system must eliminate the organisms.

Amphotericin B

Since its discovery in 1956 and increased availability in the early 1960s, amphotericin B has become, and remains, the reference treatment for invasive fungal infections. Amphotericin B is a macrocyclic polyene antibiotic originally extracted from *Streptomyces nodosus*. This drug forms micelles with fungal ergosterol, which creates channels in the fungal membrane, alters cell permeability, and allows leakage of ions and cellular components from the fungal organism. The effectiveness of amphotericin B is due to its greater affinity for ergosterol, the major sterol of fungal cell membranes, relative to cholesterol.

Effective amphotericin B treatment requires intravenous (IV) administration, with the major limiting factor in its use being cumulative nephrotoxicity; however, the only absolute contraindication to use is anaphylaxis. The cause of nephrotoxicity remains incompletely understood, but is potentially related to both direct toxicity to epithelial cell membranes and renal vasoconstriction. In people, serum creatinine is monitored during treatment; a clinically significant increase is considered a new elevation above the normal range, or an increase of greater than 20% from the baseline value.

The inherent nephrotoxicity of the original amphotericin B formulation led to the development of three new formulations: liposomal preparation, lipid complex, and colloidal dispersion with cholesterol sulfate.

Liposomal amphotericin B (lip-amB) achieves higher plasma concentrations than the original formulation; this is thought to be due to decreased uptake by the reticuloendothelial system (RES). Liposomes containing amphotericin B fuse with the fungal cell membrane, leading to fungal cell death. Lip-amB has been evaluated for safety in healthy beagle dogs, and when dosed at 1 mg/kg/day for 29 days, no azotemia was noted, and minimal renal tubular necrosis was seen on histopathology.

Amphotericin B lipid complex (ABLC) is composed of a suspension of amphotericin B complexed with two phospholipids: dimyristoylphosphatidylcholine and dimyristoylphosphatidylglycerol. ABLC is taken up by the cells of the RES, and subsequently concentrates in the liver, lungs, and spleen. The lipid complexes are likely disrupted by phospholipases at sites of inflammation or infection, leading to the release of amphotericin B. Repeated dosing of up to 5 mg/kg/day in research dogs found ABLC to be 8–10-fold less nephrotoxic, on the basis of renal values and histology, than conventional amphotericin B. Importantly, although mean glomerular filtration rate (GFR) decreased over the course of treatment, only one of 10 dogs that received 8–12 mg/kg ABLC showed a decrease in GFR below the reference range.

The third lipid-incorporated preparation to be developed was amphotericin B colloidal dispersion (ABCD).

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This formulation is composed of amphotericin B inserted between cholesterol sulfate bilayers, creating a disc-like structure. Similar to ABLC, the RES rapidly takes up ABCD. In one canine study, ABCD led to high concentrations in the bone marrow, liver, and spleen in healthy dogs, while concentrations remained low in the kidneys and lungs.

All three modified amphotericin B preparations have greater hydrophobicity, which likely results in greater delivery to the site of infection, and decreased delivery to the kidneys. All three modifications appear to maintain efficacy relative to conventional amphotericin B, while decreasing nephrotoxicity in humans. Amphotericin B remains an important treatment option in veterinary medicine, as many of the newer drugs available for people are cost-prohibitive in veterinary patients.

Azoles

The azole drugs exert their effect by inhibition of lanosterol 14-alpha demethylase, leading to ergosterol depletion and accumulation of aberrant and potentially toxic sterols in the cell membrane. Azoles are classified as imidazoles or triazoles depending on whether they possess two or three nitrogen molecules within their azole ring. Individual azole drugs are summarized in Table 115.1.

Ketoconazole

Ketoconazole was the first azole released, and is the only imidazole antifungal agent remaining in use for the treatment of systemic mycoses. It is highly lipophilic, and is ~99% plasma protein bound in humans, which impairs distribution to the brain and cerebrospinal fluid. Ketoconazole shows optimal dissolution and absorption at an acidic gastric pH in both humans and dogs, and should not be given with antacids.

In dogs, ketoconazole has been used historically to treat various systemic mycoses, including blastomycosis and histoplasmosis. Although ketoconazole has been successful in treating systemic mycoses, it should be combined with amphotericin B to yield response rates that are comparable to itraconazole alone in dogs with systemic blastomycosis. When dosed at 5–10 mg/kg/day for three weeks, ketoconazole remains an inexpensive and effective treatment for *Malassezia* dermatitis in veterinary patients.

Gastrointestinal upset or decreased appetite account for over half of the adverse events reported in dogs

Table 115.1 Summary of azole antifungal drugs, including formulation, indications, and side-effects

Drug (trade name)	Class and formulation	Indications	Side-effects
Ketoconazole (Nizoral®)	Imidazole (oral, topical)	Topical mycotic infections *Malassezia* dermatitis Third-line treatment for systemic mycoses	GI upset Dose-dependent increases in ALT Potent CYP3A inhibitor Inhibitor of p-glycoprotein Absorption impaired by antacids
Fluconazole (Diflucan®)	First-generation triazole (oral, injectable)	Candidiasis and cryptococcosis Systemic mycoses with ocular or CNS involvement Possibly first-line treatment of blastomycosis	GI upset Dose-dependent increases in ALT Requires dosage reduction in renal failure
Itraconazole (Sporanox®)	First-generation triazole (oral)	First-line for nonlife-threatening systemic mycoses that do not involve CNS	GI upset Dose-dependent increases in ALT CYP3A inhibitor Absorption impaired by antacids
Voriconazole (Vfend®)	Second-generation triazole (oral, injectable)	Invasive aspergillosis Likely efficacious against most systemic mycoses	Visual and neurologic abnormalities CYP3A inhibitor Induces its own metabolism over time in dogs
Posaconazole (Noxafil®)	Second-generation triazole (oral)	Aspergillosis, candidiasis, and cryptococcosis Limited data but likely effective against other systemic mycoses	GI upset Headache Prolongation of QT interval CYP3A inhibitor
Clotrimazole	Imidazole (topical)	Sinonasal aspergillosis *Malassezia* otitis	Poor oral bioavailability
Enilconazole	Imidazole (topical)	Sinonasal aspergillosis	Poor oral bioavailability

treated with ketoconazole, with 7% of dogs exhibiting nausea or vomiting and 5% showing only inappetence; similar signs are seen in treated cats. Hepatotoxicity and cutaneous reactions are much less frequently observed. Hepatotoxicity from ketoconazole typically manifests as mild to moderate increases in alanine aminotransferase (ALT) that are reversible with drug discontinuation.

Ketoconazole is a potent inhibitor of both the P450 enzyme CYP3A and p-glycoprotein, and therefore has many potential drug interactions. For example, ketoconazole leads to increased plasma concentrations of ivermectin and midazolam in dogs, and cyclosporine in dogs and cats. It inhibits the adrenal production of many adrenal steroids such as cortisol and testosterone, and should be avoided in breeding animals.

Fluconazole

Fluconazole is a first-generation triazole drug that was initially released in 1990 for the treatment of candidiasis and cryptococcosis. Its *in vitro* susceptibility profile suggests low potency as an antifungal agent; however, it is relatively water soluble, minimally (~10%) protein bound, and distributes well throughout the body, leading to better efficacy *in vivo*. Fluconazole effectively penetrates the blood–brain barrier, as well as the blood–ocular and blood–prostate barriers, in both people and veterinary patients. Fluconazole absorption is not affected by concurrent use of antacids, and may be a better choice in patients requiring H2 blockers or proton pump inhibitor therapy. Fluconazole also does not require food for optimal absorption. As fluconazole is approximately 70% excreted unchanged in the urine, the dosage should be reduced in patients with compromised renal function.

As in humans, fluconazole has been recommended for veterinary patients with systemic mycoses affecting the central nervous system (CNS) or eyes. Fluconazole has been used successfully in dogs and cats with cryptococcosis and blastomycosis, and the introduction of generic fluconazole has significantly reduced its cost. Moderate, reversible ALT increases have been observed in dogs receiving fluconazole for treatment of blastomycosis. Fluconazole is a teratogen in animals, and should be avoided during pregnancy.

Fluconazole is empirically prescribed at a dosage of 5–10 mg/kg per day in dogs, while cats may receive a dosage of 50 mg per day. Because of its predictable pharmacokinetics, fluconazole does not require therapeutic drug monitoring.

Itraconazole

Itraconazole is another first-generation triazole that was released in 1992, and rapidly became the oral treatment of choice for both histoplasmosis and blastomycosis in humans. Today, itraconazole remains the preferred azole in people for nonlife-threatening systemic mycoses that do not involve the CNS. It is lipophilic and is highly protein bound (>99%). Like ketoconazole, the absorption of itraconazole is diminished in the presence of antacids so it is recommended that itraconazole be administered with food, and that antacids are avoided during itraconazole therapy.

Itraconazole has become the drug of choice for treatment of systemic mycoses in dogs and cats, and is effective for the treatment of blastomycosis, histoplasmosis, cryptococcosis, and coccidioidomycosis. Although itraconazole does not effectively penetrate the blood–brain or blood–ocular barriers, it may achieve adequate levels to treat CNS or ocular infection when there is associated inflammation and compromise of the barriers.

Itraconazole has been dosed at 5–10 mg/kg per day, and may be administered as a single dose or divided into twice-daily dosing. The most common side-effects are gastrointestinal upset and hepatocellular toxicity. Although a loading dose of itraconazole has been suggested when starting therapy, no difference has been found with or without an initial loading dose.

Substitution with generic itraconazole has been shown to reduce plasma itraconazole concentrations to the subtherapeutic range in people, and has led to recrudescence of infection. A recent study in dogs found that neither generic nor compounded itraconazole achieved bioequivalence with branded itraconazole.

As with ketoconazole, itraconazole is an inhibitor of CYP3A and has many potential drug interactions. It has been shown to increase the concentrations of cyclosporine, digoxin, and midazolam in people. Unlike ketoconazole, itraconazole does not appear to be a significant inhibitor of cortisol or testosterone synthesis at clinically relevant doses. Itraconazole is available as an oral capsule and solution.

Newer Triazoles

Voriconazole is a second-generation triazole that is structurally similar to fluconazole. It has become the drug of choice for treatment of invasive aspergillosis in humans. Despite its similarity to fluconazole, voriconazole is poorly water soluble and moderately protein bound.

Hepatotoxicity, skin rash or eruptions, and peripheral neuropathy have been reported. Like ketoconazole and itraconazole, voriconazole is a substrate inhibitor of CYP3A, and can increase plasma concentrations of other drugs in humans. It is also teratogenic in animals and should not be used during pregnancy. In dogs, voriconazole undergoes extensive metabolism; it also induces its own metabolism over time. The *in vitro*

potency of voriconazole against veterinary fungal isolates appears to be favorable when compared to itraconazole. Voriconazole is available as an oral tablet or solution, or as an IV preparation. The use of voriconazole has been reported in cats with unilateral orbital aspergillosis; however, it has also been reported to cause neurologic deficits in cats, including ataxia, hindlimb paralysis, and visual abnormalities.

Posaconazole is a lipophilic second-generation triazole derived from itraconazole. It was approved for use in people for prophylaxis of invasive *Aspergillus* and *Candida* infections and for treatment of oropharyngeal candidiasis. Posaconazole also appears to have efficacy against *Blastomyces*, *Histoplasma*, and *Coccidioides* spp. As with itraconazole, administration of posaconazole with a meal appears to improve bioavailability; however, like fluconazole, alterations in gastric acidity do not appear to affect posaconazole absorption.

The most common adverse effects reported in human patients are headache and gastrointestinal upset; hepatotoxicity and QT interval prolongation are reported but much less common. Although posaconazole appears to have a narrower drug interaction profile, inhibition of CYP3A4 has been demonstrated in humans. Posaconazole is available only in oral formulations.

Topical Azoles

Both clotrimazole and enilconazole are classified as imidazoles within the azole class of drugs; however, both drugs have minimal systemic bioavailability due to a high first-pass effect. These drugs are thus confined to topical use, such as clotrimazole in otic suspensions for the treatment of *Malassezia* otitis in dogs and cats. Both clotrimazole and enilconazole are effective, when instilled into the nasal passages, for treating sinonasal aspergillosis in dogs; clotrimazole has also been reported to be effective in cats with nasal aspergillosis. Although some dogs require multiple treatments, more than 85% of dogs can be cured with up to three treatments.

Echinocandins

Echinocandins are a relatively new class of antifungal medications; the first compound, caspofungin, was approved by the FDA in 2001. Echinocandins inhibit glucan synthase and prevent the synthesis of beta-1,3 glucan, an essential component of the cell wall in certain fungi. In susceptible fungi, the integrity of the cell wall is compromised, leading to cell lysis.

The clinical use of the echinocandins is limited to *Candida* and *Aspergillus* spp. in human patients; *Cryptococcus neoformans* and the zygomycetes are typically resistant. The mycelial forms of *Blastomyces dermatitidis* and *Histoplasma capsulatum* appear to be susceptible to the echinocandins, although the yeast forms are not, due to the predominance of alpha-glucan, which is not a target of echinocandins, in the yeast cell wall. Echinocandins have poor oral bioavailability and are only available in intravenous formulations. The side-effects associated with echinocandins are typically minimal, with fever, gastrointestinal signs, phlebitis, and headache being most commonly reported.

Terbinafine

Terbinafine belongs to the allylamine group of antifungal agents, and is most frequently used in people for the treatment of dermatophytoses and toenail onychomycosis. Its antifungal activity is mediated via noncompetitive inhibition of squalene epoxidase, an enzyme involved in fungal ergosterol synthesis, with more than 4000-fold selectivity for fungal versus mammalian P450 enzymes. Terbinafine is very well absorbed from the gastrointestinal tract and then rapidly diffuses from the bloodstream into the dermis and epidermis. Terbinafine is highly lipophilic, which leads to its high concentration in hair follicles, skin, nail plate, and adipose tissue, with levels in the stratum corneum exceeding those in plasma by a factor of 75 within 12 days of therapy.

Terbinafine has shown high *in vitro* efficacy against many dermatophytes, including *Trichophyton* and *Tinea* spp. It has also been combined with echinocandins or triazoles in a multimodal approach to systemic mycoses in people. Side-effects are generally limited to gastrointestinal upset and, rarely, hepatotoxicity. Terbinafine is currently available in tablet form as well as a topical cream or gel.

In dogs, terbinafine has *in vitro* activity against *Microsporum* and *Trichophyton* isolates, with little evidence of acquired resistance during treatment. Terbinafine appears to be equivalent or superior to ketoconazole for the treatment of *Malassezia* dermatitis in dogs, with a reduction in both yeast counts and pruritus.

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Part 4

Special Topics

116

Nosocomial and Multidrug-Resistant Infections

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Nosocomial infections, typically referred to as "hospital-associated (or healthcare-associated) infections" (HAIs), are infections acquired by patients during hospitalization and are an inherent risk in veterinary medicine. In human hospitals, HAIs are a well-recognized contributor to illness and death, with substantial associated financial costs. Although veterinary data for this field are limited, similar (or even higher) HAI rates have been reported compared to human studies. Between 2003 and 2008, 82% of veterinary teaching hospitals in North America and Europe reported at least one HAI outbreak. Many of these outbreaks required restricted patient admissions or hospital closure.

Animals suffering from HAIs may have an increased hospital stay and suffer permanent health consequences (including death). Some veterinary HA pathogens can be transmitted to staff or pet owners, resulting in human illness. A wide range of pathogens may be involved in HAIs, but most of the focus is on the emerging epidemic of multidrug-resistant bacteria because of dramatic increases in infections, limited antimicrobial options, and potential public health consequences.

Perhaps most important to this topic is the assumption in human medicine that 10–70% of all HAIs are preventable. The proportion of HAIs that are preventable in veterinary medicine is unknown, but likely to be similar. The routine use of simple infection prevention practices can reduce HAIs and related multidrug-resistant organisms (MDROs).

Identification of Hospital-Associated Infections

Early identification of HAIs is critical for effective disease control and prevention. It is not unusual for veterinary HAI outbreaks to go unnoticed because of a lack of centralized data reporting or communication. Key elements of early HAI identification include a hospital-specific surveillance program and routine use of diagnostic culture and susceptibility data to establish practice-specific levels of pathogen prevalence and antimicrobial resistance.

Surveillance programs allow for early recognition of HAI transmission and outbreaks. They also provide "benchmarking" data that can be used to identify changes in disease rates (e.g., understanding the background surgical site infection rate so that any increases can be promptly investigated). These programs can also provide important information for better understanding and responding to other disease occurrences, such as MDROs. The specifics of a surveillance program will be driven by the needs and disease risks of the practice.

There are three main types of surveillance: active, passive, and syndromic. Active surveillance involves collection of data specifically for infection control purposes. This type of surveillance is expensive and time-consuming and, given the small population of susceptible patients and unclear response, not typically justifiable in a veterinary hospital. As the prevalence of MDROs increases in the animal population and more is known about HAIs, active surveillance practices may become useful in some situations. Passive surveillance involves the use of data that are already available. For example, it may be used to monitor surgical site infections by reviewing case records for surgical patients after a procedure or collating susceptibility data from urinary *E. coli* to assess empiric antimicrobial choices. Syndromic surveillance involves detection of identifiable syndromes (e.g., coughing, diarrhea). It is an easy tool for identification of certain high-risk hospitalized cases and can also identify higher-risk patients prior to admission, so that specific infection control practices can be employed.

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Common Presentations and Risk Factors for HAIs

In veterinary medicine, urinary tract infections (UTIs), pneumonia, surgical site infections (SSIs), bloodstream infections (BSIs), and gastrointestinal disease (infectious diarrhea) are likely to be the most common presentations for HAIs.

Urinary Tract Infections

Catheter-associated UTIs are one of the more common HAIs in small animal veterinary medicine. Pathogens involved may be either endogenous to the patient, arising from the rectum or perineum, or from the hospital environment or people through contamination of the drainage system or bag. Biofilms (a complex structure of microorganisms and extracellular matrix) can be produced by bacteria on the surface of urinary catheters, resulting in poor antimicrobial penetration, antimicrobial resistance, and treatment failure. Catheter-associated UTIs are best prevented through careful attention to aseptic technique during placement and maintenance of urinary catheters as well as by avoidance of urinary catheterization unless necessary and at least daily reassessment of whether a urinary catheter is still required. Culture of catheters or urine from catheterized patients in the absence of clinical or cytologic evidence of disease is not recommended.

Pneumonia

Hospital-associated pneumonia has been minimally investigated in the veterinary field, in large part because of the limited use of mechanical ventilation (a major contributor in human medicine). Recumbent position, mechanical ventilation, use of endotracheal/nasogastric tubes, and factors that increase aspiration pneumonia (e.g., laryngeal or esophageal disorders and decreased mentation or recumbency) likely increase HAI risk. Recumbent, sedated, or debilitated patients may benefit from having the cranial portion of the body elevated.

Surgical Site Infections

Surgical site infections are an inherent risk of breaching the body's normal barriers and are estimated to occur in approximately 2–7% of veterinary surgical patients. Factors likely to increase SSI risk include longer duration of surgery or anesthesia, inappropriate antimicrobial therapy, greater contamination of the surgical site, endocrine disease, increased number of people in the operating room, and orthopedic surgeries and procedures with an implant. For most SSIs, the source of pathogens is the endogenous flora of the patient. Therefore, the pathogens responsible for SSIs will vary by type of surgery (e.g., gram-negative rods occurring in abdominal surgeries, staphylococci in orthopedic procedures). Methods such as clipping the patient immediately before surgery after induction, following strict aseptic technique, cleaning and care of clipper blades after each use, minimizing personnel flow in the operating room, and prudent use of antimicrobials are important in reducing the likelihood of SSIs.

Bloodstream Infections

In human medicine, most BSIs are associated with intravascular devices, with duration of catheterization being the most important risk factor. Despite this risk, studies have not found a decrease in the incidence of catheter-related (CR) BSIs with prophylactic catheter changes (e.g., every three days). The current recommendation is for catheters to be removed as soon as medically indicated, but for routine changes to be avoided, since a catheter that has remained free of complications for a few days may pose a lower risk than a newly placed catheter. A similar approach is appropriate in veterinary medicine.

Veterinary studies have revealed that jugular and intravenous catheters are frequently contaminated with enteric or environmental pathogens. Factors associated with intravenous catheter contamination in dogs and cats include longer duration of catheter placement and patient immunosuppression. Contamination may occur from the hands of people placing or handling the catheter, the patient's own flora, or the hospital environment. The use of aseptic technique, including appropriate skin preparation, hand hygiene immediately before placement, use of gloves, and minimal contact with the catheter site, is important to reduce CR HAIs. Culture of catheter insertion sites is not recommended since skin bacteria are expected to be present. As HAI outbreaks have been associated with contaminated materials used in skin preparation, all containers holding disinfectant and materials used for skin preparation should be routinely (i.e., daily to weekly) disinfected, sterilized or discarded, rather than continuously refilled.

Infectious Diarrhea

In small animal veterinary facilities, gastrointestinal HAIs may involve a number of pathogens, including *Salmonella* spp. Given the high frequency with which animals may subclinically shed gastrointestinal pathogens, efforts must be aimed at both early identification of animals at increased risk for shedding pathogens linked with HAIs (e.g., recent consumption of raw egg or meat products) and routine use of infection control practices.

Pathogens of Concern

In veterinary medicine, current knowledge of many aspects of the epidemiology of important MDROs and HA pathogens is unclear. Based on reported veterinary HA outbreaks or supposition from the human literature, several important pathogens responsible for HAIs (including MDROs) are identifiable (see later). Pathogens involved in HAIs are often opportunistic and found in healthy animals. The frequency of colonization with each pathogen likely varies with geography, animal species, and veterinary practice (in part influenced by antimicrobial use/pressure). Environmentally stable pathogens have a demonstrated clear "advantage," increasing the chance of transmission. Given the close interaction between veterinary staff and patients, as well as the often poor hand hygiene practices documented in veterinary practices, human commensals with zoonotic potential are important in veterinary HAIs. Finally, increased resistance to antimicrobials is a common feature. The specific resistance profiles and treatment options for common MDR pathogens have recently been summarized.

Staphylococcus spp.

Staphylococcus pseudintermedius and, to a lesser extent, *S. aureus* are frequently the cause of veterinary HAIs. As both are often carried in the nasopharynx, on the skin and in the gastrointestinal tracts of dogs and people (respectively), this is expected given the roles of endogenous bacteria and hands of healthcare workers in HAIs. The emergence of methicillin resistance in these species (MRSP and MRSA) has had profound implications for HAI prevention and control. Methicillin resistance is mediated by the *mecA* gene, which confers resistance to beta-lactam antimicrobials (penicillins, cephalosporins, and carbapenems); isolates are frequently resistant to additional antimicrobial classes.

Methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) has rapidly spread globally in canine populations, often with high levels of antimicrobial resistance, something that is of tremendous concern as *S. pseudintermedius* is the leading opportunistic pathogen in dogs (and to a lesser degree cats). Recent prior hospitalization and beta-lactam antimicrobial administration have been associated with MRSP infections, suggesting nosocomial transmission may be a factor in MRSP disease.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is less of an issue from a veterinary HAI standpoint, although its role as an important human pathogen increases concern for zoonotic transmission. Risk factors for MRSA colonization or infection in companion animals include antimicrobial use, prior hospitalization, ownership by veterinary or human healthcare workers/students, and longer hospitalization (>3 days). A high proportion of veterinarians and staff are colonized with MRSA compared to the general public, likely due to deficiencies in standard infection control and hygiene practices that allow for zoonotic transmission. As such, they may serve as a source for HAIs in their patients if infection control practices are not observed.

Escherichia coli

Escherichia coli is a common component of the commensal gastrointestinal microflora and is an important pathogen. Many community and hospitalized companion animals shed MDR *E. coli* in their feces. Factors associated with dogs shedding or acquiring MDR *E. coli* during hospitalization include duration of hospitalization (>3 days) and treatment with antimicrobials shortly before or while hospitalized. Of particular concern is the ability for some strains of *E. coli* to produce beta-lactamase, notably the extended-spectrum beta-lactamase (ESBL) producers, which provide resistance to a broad range of beta-lactam antimicrobials, including third-generation cephalosporins. Resistance to additional antimicrobial classes is not uncommon. ESBL-producing *E. coli* has been identified as the source of veterinary HAIs, occurring as SSIs and CR UTIs.

Carbapenemase-producing Enterobacteriaceae (or carbapenem-resistant Enterobacteriaceae; CRE) (including *E. coli*), conferring resistance to additional antimicrobial classes, have recently become a significant public health concern. CR *E. coli* have been identified in small animals, with suggested nosocomial transmission. This currently appears to be a rare occurrence, but one that is likely to increase as CREs increase in prevalence in the human population.

Enterococcus spp.

Enterococci are commonly found in the gastrointestinal tract of animals and humans. *E. faecium* and *E. faecalis* are most often involved in HAIs, notably in compromised hosts. Enterococci are inherently resistant to a number of antimicrobial classes, including cephalosporins, some penicillins, fluoroquinolones, clindamycin, and trimethoprim, and may acquire resistance to other antimicrobial classes. Vancomycin-resistant enterococci (VRE) are an increasing concern in human medicine. To date, VRE appear to be rare in companion animals; however, other MDR enterococci are regularly recognized and have been identified in HAIs. Enterococci are often identified as UTIs (including catheter-associated) although infections at other anatomic sites occur

(SSIs, BSIs, pneumonia). The high degree of antimicrobial resistance, ability to propagate for extended periods in small animal hosts as a commensal, and environmental persistence make enterococci particularly challenging when involved in HAIs.

Salmonella spp.

Salmonella has been identified as a source of sporadic illness and hospital-associated outbreaks in small animal hospitals. A notable concern with *Salmonella* HAIs is the occurrence of zoonotic transmission with accompanying human infections. Factors increasing the risk of *Salmonella* shedding in small animals include consumption of raw meat diets and exposure to livestock. As with *E.coli*, ESBL-producing strains are a concern for antimicrobial resistance and have been identified in small animals.

Acinetobacter spp and *Pseudomonas* spp.

As opportunistic pathogens in small animals and able to persist in the environment for extended periods, *Acinetobacter* and *Pseudomonas* are important in veterinary HAIs. Documented HAIs involving *A. baumannii* include intravenous and urinary catheters, surgical drain infections, SSIs, pneumonia, and BSIs. SSIs, including cardiovascular device infections, have been attributed to *P. aeruginosa*. Identification of hospital clusters of *Pseudomonas* infections should prompt investigation of potentially contaminated environmental, equipment (e.g., endoscope) or consumable (e.g., catheter preparation supplies) sources.

Management

Although complete prevention of HAIs and MDROs is our goal, given the nature of medicine, bacterial adaptation, and numerous mechanisms for antimicrobial resistance, it is inevitable they will continue to occur. Methods to manage MDR infections and reduce the risk of HAIs and nosocomial transmission are paramount (Box 116.1).

Efforts should be directed toward prompt identification, appropriate therapy, and infection control practices. Establishing and maintaining an infection control program is vital to integrating these efforts and protecting the health of pets and people.

Therapy

Antimicrobial therapy is an important part of the treatment of many MDROs and HAIs. Although available antimicrobial choices may be limited, the general principles of therapy are the same as for antimicrobial-sensitive pathogens: ensuring the appropriate drug (and dose) is selected based on the patient and infection. As infections caused by MDROs appear clinically identical to those caused by antimicrobial-susceptible bacteria, culture and susceptibility testing are fundamental in this process. Local therapy (e.g., topical therapy, antimicrobial-impregnated materials, intraarticular injection) is often overlooked, and in many cases can provide adequate drug levels for treatment and may be an alternative for drugs that are not an option for systemic therapy. However, the possibility of systemic absorption of locally administered drugs must be considered.

In addition to treating MDROs, it is important to prevent their development. Prudent antimicrobial use will help reduce the risk for HAIs at both the individual patient and hospital population levels. Clinicians should avoid using antimicrobials when a bacterial infection has not been confirmed by culture. Antimicrobials used in the initial treatment of an infection should be selected based on the effectiveness against the most likely organisms causing the infection and penetration into the body site affected. Guidelines are available to assist veterinarians in antimicrobial selection.

Box 116.1 Key methods to manage multidrug-resistant infections and reduce the risk of hospital-associated infections

Reduce the prevalence of MDROs in patients
- Prudent antimicrobial use
- Therapy directed by culture and susceptibility testing
- Withholding therapy (as appropriate) for patients only colonized and not infected
- Discontinue use of higher risk devices (e.g., urinary and intravenous catheters) when no longer medically required
- Infection control practices

Reduce within-hospital exposure
- Hand hygiene
- Environmental cleaning and disinfection
- Personal protective equipment (e.g., gloves, gowns)
- Cohorting patients with similar infectious disease risks
- Isolation of known or suspected infectious cases

Prompt recognition and response
- Culture and susceptibility testing
- HAI surveillance (e.g., passive surveillance for HAIs, reporting of pathogens and syndromes of interest)
- Education of staff and clients

HAI, hospital-associated infection; MDRO, multidrug-resistant organism.

Colonization versus Infection

Following exposure to an opportunistic pathogen, animals may become colonized (pathogen multiplies without tissue invasion/damage), infected (multiplies with tissue damage and often signs of clinical disease), both, or neither. In animals, decolonization therapy for MDROs has not been shown to be effective and unsuccessful attempts result in promotion of further resistance. As such, therapy should be reserved for animals with clinical disease, regardless of the MDRO involved. Animals without clinical signs of disease, assuming they are otherwise immunocompetent and expected to demonstrate clinical signs should infection occur, may be carefully monitored. Staff and clients should be informed of the colonization status of patients, as these patients may nonetheless shed the pathogen, serving as a source for HAIs or zoonotic infections.

Patient Housing

In order to protect other patients and clinic staff, attention to patient housing and animal flow is important in managing patients with MDROs. Patient cohorting entails housing together and maintaining a general flow (e.g., assigning waiting and examination areas) of patients that have similar infectious disease risks, including risk of shedding infectious organisms as well as vulnerability to infection. Additionally, animals infected or suspected to be infected with MDROs should be isolated. The specific protocols will vary with the pathogen, severity of disease, and facility, but should include use of personal protective equipment (PPE), cleaning and disinfection, and restricted personnel access. Materials and equipment used for isolation patients should be dedicated to the patient during its hospital stay, after which they should be cleaned and disinfected.

Hand Hygiene and Contact Precautions

Hand hygiene and use of PPE, such as nonsterile gloves and gowns, are simple techniques that can reduce the risk of HAIs. A number of studies indicate that veterinarians and staff typically do a poor job at performing hand hygiene between patients or using PPE when indicated; improvement in these areas is desperately needed.

Hand hygiene is described as the single most effective and underutilized infection control measure. Use of hand hygiene limits the spread of organisms between patients and between patients and staff. Biocidal soap and water and alcohol-based hand sanitizers (AHS) are most frequently used for this purpose. Individuals should ensure hands have soap or AHS contact for at least 15 seconds, paying attention to fingertips, between fingers, backs of hands and base of the thumbs, as these areas are often missed. Hand hygiene should occur before and after every animal contact and after removing gloves.

Appropriate PPE use reduces the risk of contamination of personal clothing, reduces exposure of skin and mucous membranes of veterinary staff to pathogens, and reduces transmission of pathogens between patients by veterinary personnel. The use of PPE is especially important when handling animals with known or suspected MDROs. This includes the use of a barrier gown (disposable or laboratory coat that is not worn elsewhere) and gloves. As animals with MDROs may be colonized or contaminated at locations distant to the infected site, these clothing precautions should be worn when having contact with any MDRO patient or its housing environment.

Cleaning and Disinfection

Evidence suggests environmental contamination in human hospitals increases the risk for HAIs and interventions that reduce environmental contamination reduce HAIs. This connection is less well established in veterinary medicine, but it is logical to assume that it exists. Examples of fomites that have been identified as reservoirs of HA pathogens include stethoscopes, computer keyboards, thermometers, examination tables, and floors. The role of these items in HAIs is not known but it is prudent to minimize contamination.

Several key steps must be taken to ensure a disinfectant is effective, including ensuring the surface/item is clean and the product is applied at the manufacturer's suggested dilution and contact time (amount of time the disinfectant is in contact with the item before being removed). Disinfectants should be selected based on a number of criteria including the product's spectrum of activity, susceptibility to inactivation by organic matter, and potential pathogens in the environment. Resources are available to guide disinfectant selection (see Chapter 117).

Antimicrobial resistance does not necessarily indicate further resistance to environmental disinfectants, although the consequences for inadequate removal/decontamination are greater. As such, it is prudent to consider the use of a "broad-spectrum" disinfectant (e.g., oxidizing agents), for contact surfaces of patients with HAIs or MDROs.

Zoonotic Concerns

During their careers, many veterinarians report a major animal-related injury resulting in lost work or hospitalization. Although not responsible for the majority of

these injuries, HAIs such as MDROs (e.g., MRSA, *Salmonella*) do occur. Educating staff and clients on zoonotic disease risks and enforcing hospital infection control protocols to reduce these risks will be beneficial to the health of people and patients.

Conclusion

Hospital-associated infections are reported in veterinary medicine and their frequency is likely to increase with the rise in intensive care practices. Prolonged hospitalization and the use of invasive devices and procedures increase the risk of HAIs. All staff members should be educated on the risks and signs associated with HAIs so that cases can be detected early and managed appropriately. A multifaceted approach is necessary to address HAIs and MDROs in small animal veterinary medicine, including prudent antimicrobial use, strengthening surveillance in companion animal species, improving infection control practices, instilling an infection control culture amongst veterinary staff, and improving healthcare worker and public education regarding antimicrobials.

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117

Management of Infectious Disease in Kennels and Multicat Environments: Creating a Culture of Compliance

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Dog kennels and multiple-cat environments exist in various types of venues. Whether a boarding facility, a cattery, dog breeding kennel, animal control shelter or humane society, challenges arise in minimizing and managing infectious disease in environments where multiple individuals co-habit in confined areas. Minimizing the risks, understanding modes of transmission, promoting prevention, taking a structured approach to disinfection, and, most importantly, creating a culture of compliance for established protocols can be helpful in the prevention and control of infectious disease in these settings. Not only will the health of the canine and feline residents be promoted, but such an approach protects the human caretaker from zoonotic disease transmission.

Risks

Some of the major risks for the spread of infectious disease include poor facility design, overcrowding, introduction of new individuals with undetermined health status, untrained/noncompliant staff, and lack of policy, procedures, and/or biologic risk management (BRM) protocols for managing infectious disease.

Overcrowding increases exposure through direct contact between animals and increases stress, which can lead to decreased immunity. Stress can also lead to reactivation of latent infection, which causes increased shedding, and increased infection across the population. The presence of younger individuals and others with naive immune systems (not fully vaccinated) makes the population more susceptible to disease outbreak. The housing of animals according to immune status should be implemented, with the naive individuals (young and/or unvaccinated) housed separately from the adults.

Minimum space requirements should be considered for each facility. The Humane Society of the United States and the Animal Welfare Act have set minimum standards to follow. Dogs in group housing should have a minimum of 4 ×4 feet of floor space per individual. Co-housed cats should have at least 10.8 square feet per cat and an additional 2.5 square feet for cats that are co-housed together. Ventilation is also important, with an optimum exchange rate of air inside a building replaced with fresh outside air 8–15 times per hour. Safe outside housing is ideal in terms of air circulation and has the added benefit of sunlight and ultraviolet light, as they reduce the number of microorganisms and can inactivate viruses, bacteria, fungi, and mycoplasma. The materials in the facility need to be nonporous to allow for proper cleaning and disinfection of surfaces.

Modes of Transmission

Understanding of the modes of transmission is helpful in determining the preventive measures that need to be taken. Aerosol transmission is affected by ventilation and distance between individuals. Oral ingestion of contaminated food/water and oral contact with inanimate objects (fomites) such as toys, cages, bedding, etc. are two of the most common routes of disease transmission. Direct contact or animal-to-animal contact (nose to nose) is also common. Vector transfer of disease via arthropods is another cause for concern. Environmental transmission necessitates proper sanitation protocols.

Prevention

Prevention is paramount to success in the management of infectious disease outbreaks. The staff and supervisors of facilities need to understand and identify the risks and then develop infection control policies and procedures for the facility and education and training protocols for the staff.

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Upon intake to a facility, animals must be evaluated via physical exam and checking of medical records in order to identify any problem(s) that may be present and develop a preventive health plan for each animal. Staff need to be aware of the clinical signs to look for, which diagnostic tests need to be run (e.g., FeLV/FIV test, SNAP® Parvo Test) and what preventive measures need to be taken (e.g., vaccination protocol followed). If a disease is diagnosed, it is neccessary to follow a protocol on how to treat and where to house ill animals, and how to monitor for additional spread in order to succeed in managing an outbreak.

Numerous pathogens need to be addressed and understanding the agent, mode of excretion, incubation, shedding, and carrier states is key to managing them. The Koret Shelter Medicine website is one valuable resource for providing specific profiles and protocols for addressing diseases (www.sheltermedicine.com).

Along with these management strategies, prevention involves vaccination and diagnostic testing protocols and the use of proper sanitation to prevent transmission. Improving immune status of individuals should be addressed via vaccination, good nutrition, and decreasing stress. Prevention is also accomplished by screening at a designated receiving area and establishing proper isolation and quarantine areas. Staff should understand that with most diseases, isolation of 14 days is a minimal holding time for ill animals. Less than seven days is of little benefit for most infectious diseases.

Vaccination

Vaccination provides an additional safeguard to the health and well-being of cats and dogs. The *2017 American Animal Hospital Association (AAHA) Canine Vaccine Guidelines* and the *2015 World Small Animal Veterinary Association (WSAVA) Guidelines for the Vaccination of Dogs and Cats* provide a comprehensive look at which vaccines are core and noncore, and how protocols may differ between canines seen in general veterinary practice and those in shelter housing (kenneled).

For felines, the *2013 American Association of Feline Practitioners Feline Vaccine Advisory Panel Report* is an excellent resource for the core, noncore, and not recommended feline vaccinations.

Timing can be critical. In shelters, core vaccines should be given as soon as possible and if vaccination status of an incoming animal is unknown, some might argue that it is best to assume that it is unvaccinated. In boarding kennels, proper timing of vaccination (such as *Bordetella bronchiseptica*) well in advance of boarding an individual is warranted. Understanding the role of maternal immunity and how it affects vaccination protocol and proper follow-up of additional boosters in puppies and kittens is crucial for adequate protection of these individuals.

Cleaning and Disinfection

The importance of sanitation is often underestimated and even though immunization for infectious disease is a valuable tool, it is good to remember that one "cannot vaccinate one's way out of an outbreak." If the pathogen load is great enough, a vaccinated animal can still succumb to disease.

It is important to know which disinfectants are the right choices for routine disinfection protocols and what is appropriate when an outbreak occurs. Determine whether broad-spectrum activity or targeting of a specific isolated organism is needed and then choose the appropriate disinfectant, correct concentration, application, and contact time. It is important to know which disinfectants are needed to kill bacteria, enveloped viruses, nonenveloped viruses, fungus/ringworm, parasite eggs, and spores. These are listed from easiest to hardest to kill. Disinfectant failure occurs for a number of reasons. Often, the wrong choice is made for a given pathogen or there is under- or overdilution of the product. Failure to rid a surface of organic material, lack of adequate application, wrong temperature, humidity and especially lack of contact time (no less than 10 minutes with most disinfectants) are additional pitfalls to avoid. The establishment of a "disinfection action plan" includes assessment, cleaning, washing, disinfection, and evaluation. Washing is considered to be the most crucial step in the disinfection process and can result in the removal of 99% of bacteria present in a contaminated area.

Hand washing cannot be overemphasized. Human hands play a major role in the transmission of infectious disease. A "bare below the elbows" policy allows all individuals an easier opportunity to wash the hands, wrists, *and* forearms after contact with animals. Running water and soap should be provided in as many areas of a facility as possible, especially in isolation areas. Understanding the limitations of hand sanitizers is important. These alcohol-based products do not kill nonenveloped viruses like canine parvovirus and panleukopenia and are easily deactivated in the presence of organic material on unclean hands. However, the World Health Organization (WHO) recommends that these alcohol-based products are currently "the only means for rapidly and effectively inactivating a wide array of potentially harmful microorganism on hands." Personal protective equipment (PPE) is also important for staff at animal facilities as clothing is a common fomite. Using gloves, lab jackets or a designated uniform and proper disposal or decontamination of these

items are crucial to preventing the spread of pathogens. This is especially important when handling sick animals or when working in a designated isolation area.

Quaternary compounds are commonly used and some of the brand names are misleading in terms of what organisms they are effective against. The Center for Food Security and Public Health (www.cfsph.iastate.edu) provides charts of both the characteristics and antimicrobial spectrum of various products. These should be routinely used as a reference when decisions about appropriate disinfectant choice are needed. In general, quaternary compounds are *not* effective against canine parvovirus and panleukopenia, both nonenveloped viruses that can have fatal consequences for individuals in kennels and catteries respectively. The hydrogen peroxide-based oxidizing agents are effective against some of these microbes.

Bleach can be very effective but only if proper dilution, length of efficacy after mixing, and proper application protocols are followed. Concentrations greater than 1:32 can be harmful to mucous membranes, thus increasing susceptibility to disease. When cleaning and disinfecting cages, feline patients should be removed from the area when deep cleaning is involved. It is considered a standard of care to remove dogs from kennel runs when they are being sprayed down. Phenolic disinfectants ("Lysol") should not be used in catteries as they are toxic to felines.

Managing Outbreaks

Recognizing an outbreak as early as possible provides the best prevention. Controlling the outbreak requires isolation, proper diagnosis, and treatment. In an outbreak situation, an isolation area can help prevent cross-infection between animals. Separate equipment needs to be stored in this area and the correct PPE and protocols need to be followed by staff. Protective outer equipment should be used when cleaning, and it should be cleaned and changed daily. Disposable shoe covers are used when heavy infection load is suspected and thrown away after use.

Culture of Compliance

One of the biggest risks to proper disease control in kennels and multicat facilities is the lack of an established policy and procedure and the lack of staff compliance with established protocols. Staff need to be aware that their hands and fomites like clothing and equipment may be the biggest risk to the spread of disease in a facility. Outbreaks can be avoided and/or their impact minimized if good protocols exist. However, if there is no compliance from the staff, even the best protocols will be ineffective. Many protocols are ready to follow and the staff has the ability to perform them. Their motivation to do so, on the other hand, may or may not result in compliance.

The idea of establishing an "infection control culture" may be fundamental in providing effective infectious disease control. What people "read, hear, see, and talk about on a regular basis" are what characterize the idea of "culture." The "read" component would be the establishment of a written infection control manual which would be used to train new staff and which existing staff could refer to when needed. The "hear" component comes from supervisors in terms of staff updates about protocol changes and encouraging conversation about the protocol during regular staff meetings. Posters about hand washing and use of hand sanitizers, for example, help as a visual reminder. Additionally, supervisors and senior staff can serve as an example to follow, further supporting the "see" component of the equation. Giving the staff adequate time to perform hand hygiene, proper cleaning and disinfection, changing PPE and other tasks demonstrates the importance that is placed on these practices, and thereby contributes to the infection control culture. The concept of compliance is a critical factor here. As per the *Compendium of Veterinary Precautions*, "a written checklist, which specifies the frequency of cleaning, disinfection procedures, products to be used, and the staff responsible, should be developed for each area of the facility…".

Protection from Zoonotic Pathogens

The emergence of new or evolving pathogens in kennels and catteries will remain a challenge to managing disease. For example, in kennels, *Streptococcus zooepidemicus* is one such pathogen and clinical signs are similar to those of kennel cough. The bacterium is able to spread between dogs as outbreaks at kennels often affect large numbers of animal within a short time. No vaccine exists but good husbandry and isolation of infected individuals are a must. Again, early detection, isolation, and disinfection provide the best management practice and have been found to be fundamental for the control of *S. zooepidemicus* outbreaks. Good hygiene standards will also minimize the risk of transmission of *S. zooepidemicus* to dog handlers.

Conclusion

When following effective protocols for managing infectious disease in kennels and multicat environments, the outcome is not only reduced transmission from animal to animal but also the reduction of potential zoonotic transmission. Again, *S. zooepidemicus* provides an

excellent example. In order to improve control of this disease, it is crucial to raise awareness, to ensure that cases are recognized early. This will allow the implementation of suitable protocols to minimize the spread of infection along with measures to protect staff from zoonotic infection. The National Association of State Public Health Veterinarians has produced the *Compendium of Veterinary Standard Precautions* (www.nasphv.org), which provides a resource for PPE, environmental infection control, and isolation of animals with infectious diseases. Extensive resources are readily available to enhance the management of infectious disease in kennels and multicat environments. With the establishment of an infection control culture as well as a culture of compliance, the spread of infectious disease can be minimized, thus protecting the health of cats and dogs as well as their human caretakers.

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Section 10

Renal and Genitourinary Disease

118

Disorders of Sodium and Water Homeostasis

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Sodium (Na) and water disorders traditionally have been viewed by veterinarians as difficult concepts. An appreciation of the basic physiology underlying these concepts will facilitate their understanding. The objectives of this chapter are to review the pathophysiology of changes in volume and composition of the body fluid compartments associated with hyponatremia and hypernatremia as well as a clinical approach to fluid therapy that takes into account these changes in sodium concentration.

Water Balance Made Easy

Imagine two compartments separated by a semipermeable membrane. Each compartment has the same osmolality (number of solute particles per kilogram of solvent). If solute (without water) is added to compartment #1 without changing the volume of the compartment, the concentration of osmoles in that compartment will increase transiently. The increase in osmolality in compartment #1 will result in movement of water (by osmosis) from compartment #2 to compartment #1 until the osmolality of the two compartments is equalized. The final osmolality will be the same in both compartments, and higher than the initial osmolality.

The same concept will apply if the volume of water or number of sodium ions in body fluids is changed: water will flow from one compartment to the other in order to maintain the same osmolality in both compartments. Thus, there are only four ways to change serum sodium concentration: adding free water, removing free water, adding sodium, or removing sodium.

Hyponatremia is the most common sodium disturbance in small animals. It can result from an excess of free water (e.g., excessive water consumption, intravenous fluid therapy with hypotonic fluids, antidiuretic hormone [ADH] secretion) or from loss of sodium (in excess of water), which is rare because sodium usually is followed by water. Rare examples include salt-losing nephropathy and cerebral salt-wasting syndrome. Hyponatremia usually means that an excessive amount of water is present in body fluids, and the generalization "hyponatremia means too much water" applies in most situations. Treatment of hyponatremia requires understanding and resolution of the primary process. Conversely, the generalization "hypernatremia means not enough water" also is true most of the time. Hypernatremia may arise either as a consequence of loss of free water (i.e., evaporation from the skin or respiratory tract) or hypotonic fluid, or by the addition of sodium (e.g., intravenous fluid therapy with 0.9% saline or hypertonic saline). Treatment of hypernatremia mainly is based on slow volume replacement to avoid detrimental transcellular shifts of water, as will be discussed later.

Sodium and Water Disturbances: A Little Physiology Goes a Long Way

The Darrow–Yannet diagram (Figure 118.1) illustrates the partition of total body water (TBW) into compartments. Although some variation exists due to species, age or sex, it is estimated that:

- total body water is 60% of body weight (BW)
- total body water is divided into two compartments:
  - intracellular fluid (ICF): approximately 2/3 of TBW – 40% of body weight
  - extracellular fluid (ECF): approximately 1/3 of TBW – 20% of body weight
  - ECF is further subdivided into the interstitial compartment (3/4 of ECF) and the intravascular compartment (IV) (1/4 of ECF).

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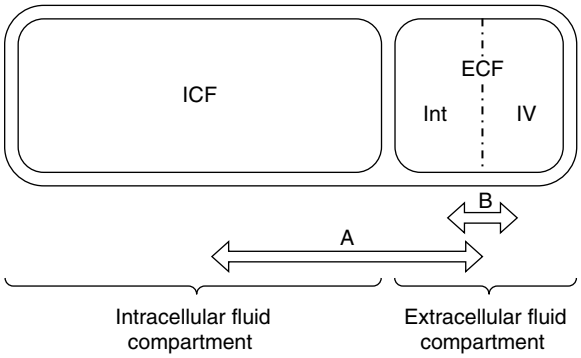


Figure 118.1 Partition of total body water (TBW) into body compartments. See text for details.

To understand changes in serum sodium concentration, it is important to remember that movement of water between ICF and ECF (arrow A on Figure 118.1) depends on osmolality, whereas movement of water within the ECF (arrow B on Figure 118.1) depends on Starling's forces, which will not be reviewed here. An estimation of osmolarity is given by the following equation:

$$\text{Plasma osmolarity}\left(\text{mOsm/L}\right) = 2\left(\text{Na}+\text{K}\right) + \text{BUN}\left(\text{mg/dL}\right)/2.8 + \text{glucose}\left(\text{mg/dL}\right)/18$$

It is noteworthy that osmolality is a function of the number of solute particles and not their molecular weight. If using international units (mmol/L) for BUN or glucose, the dividing factors shown above are not necessary. The dividing factors convert conventional units into international units by dividing the conventional units by molecular weight (i.e., 28 g/mol for urea or 180 g/mol for glucose) and multiplying by 10 to convert deciliters (dL) to liters (L). A very abundant molecule such as albumin (mean plasma concentration of 4.5 g/dL) has a minimal effect on osmolality because its molecular weight is very high (66 000 Da equivalent to a molar mass of 66 000 g/mol), which makes the particle number relatively low. Albumin contributes only approximately 0.75 mOsm/kg to plasma osmolality. By the same token, colloid osmotic pressure refers to the osmolality due to proteins, and contributes approximately 1–2 mOsm/kg. The osmolarity calculated by the equation above and expressed in mOsm/L is always lower than the osmolality measured by freezing point depression osmometry and expressed in mOsm/kg. The so-called osmolal gap is the contribution of osmoles other than sodium, potassium, urea, and glucose and usually is <10 mOsm/kg. If the osmolal gap is increased, it may be due to a large quantity of unmeasured osmoles such as mannitol or ethylene glycol and its metabolites.

Osmoregulation and Volume Regulation

Serum sodium concentration is regulated by changes in water balance, and not by changes in sodium or volume. Similarly, it is important to understand the difference between plasma osmolality and serum sodium concentration, as well as their regulation. Plasma osmolality is regulated by changes in water excretion and intake mediated by ADH secretion and thirst, whereas sodium balance is regulated by changes in sodium excretion via skin, urine, fecal, and respiratory losses. Overall, there is no predictable relationship between serum sodium concentration and ECF volume. However, serum sodium concentration and serum osmolality vary in parallel, except when a large number of *effective osmoles* is present (e.g., glucose). (Effective osmoles are those that do not move across a semipermeable membrane and thus have the potential to initiate water movement by osmosis.)

Serum osmolality is regulated by hypothalamic osmoreceptors that trigger ADH release and stimulate thirst. Antidiuretic hormone secretion in response to changes in osmolality is very sensitive, and a change of just 1% in serum sodium concentration (1–2 mEq/L) will stimulate ADH release. This very sensitive trigger means that a small change, even of 1 mEq/L, in serum sodium concentration can be abnormal for an individual patient despite being within the reference range for a patient population. Antidiuretic hormone secretion increases water reabsorption in the collecting tubules of the kidneys. In addition to hyperosmolality sensed by osmoreceptors, ADH secretion also is triggered by hypovolemia when a decrease in ECF volume is sensed by the baroreceptors (actually stretch receptors) situated in the aortic arch and carotid sinus.

Multiple receptors and effectors are involved in volume regulation. The most pertinent to sodium regulation are the natriuretic peptides and ADH. Natriuretic peptides (e.g. atrial natriuretic peptide [ANP] and brain natriuretic peptide [BNP]) are released by the atria in response to hypervolemia and promote renal sodium excretion. Antidiuretic hormone release has been described above. The renin-angiotensin-aldosterone system (RAAS), although a very potent volume regulator, does not lead to changes in serum sodium concentration. The RAAS endpoint is the release of aldosterone, which triggers isotonic fluid reabsorption in the kidneys in response to hypovolemia. Thus, aldosterone release does not lead to a change in serum sodium concentration. However, some cross-talk occurs between the RAAS and ADH secretion, with angiotensin II triggering ADH release.

Thirst is a commonly overlooked modifier of serum sodium concentration. Thirst is triggered by a variety of factors, including hypovolemia and increased plasma osmolality. Thirst mainly is regulated centrally, with some input from the cerebral cortex which influences nonessential intake (i.e., social drinking in humans), and also by the sensation of a dry mouth. The sensation of thirst is so powerful that normal subjects do not become hypernatremic despite intake of a large amount of sodium as long as they have access to enough water to drink. This is true even in patients with central diabetes insipidus (CDI), which explains the fact that such patients usually are presented with signs of polydipsia and polyuria with normal serum sodium concentration unless they lack access to water (e.g., freezing of the water source or a spilled water bowl).

Hypovolemia triggers both isotonic (via aldosterone) and hypotonic (via ADH) fluid reabsorption. Theoretically, hypotonic fluid reabsorption would generate a hypoosmolar state which would turn off ADH release, in order to maintain plasma osmolality. However, although ADH release due to changes in osmolality is very sensitive, ADH release in response to hypovolemia is very powerful, and restoration of volume will proceed at the expense of osmoregulation (i.e., hyponatremia will ensue). From an evolutionary perspective, it likely was advantageous to survival of the animal to preserve volume over normal osmolality.

Hyponatremia

Causes of Hyponatremia

Hyponatremia is a common electrolyte disorder in critically ill and hospitalized patients. It can be divided into three categories, based on osmolality and volume status (Table 118.1).

Pseudohyponatremia may occur when serum sodium concentration is determined by flame photometry, an obsolete technique by which serum sodium concentration is measured in a defined plasma volume (water and solids such as proteins and lipids). If there is a high concentration of lipids or proteins, the measured serum sodium concentration will be artificially low. This also is true if the serum sodium concentration is measured by indirect potentiometry, which is common in reference laboratories. This does not occur if an ion-selective electrode (i.e., direct potentiometry) is used, which is commonly used in point-of-care instruments.

Most hyponatremic patients fall into the hypovolemic, hypoosmolar category, with the notable exception of patients suffering from diabetes mellitus (see later). Hypovolemia causes reduction of effective circulating volume, triggering ADH secretion and free water retention. Hypovolemia occurs after gastrointestinal losses (i.e., vomiting and diarrhea), renal losses, hypoadrenocorticism, and other causes of hypovolemia.

Patients in congestive heart failure (CHF) or advanced liver failure with ascites also have decreased effective circulating volume although they have excessive total body fluid volume and are hyponatremic. In CHF, decreased "effective stroke volume" secondary, for example, to valvular disease triggers ADH release and thirst, leading to hyponatremia despite hypervolemia. The same is true in the liver failure patient, where portal hypertension leads to ascites and decreased venous return, stimulating ADH release and water retention.

Patients suffering from diabetes mellitus can have normoosmolar hyponatremia. In diabetes mellitus, the hyperosmolality resulting from a high blood glucose concentration induces a shift of water from the ICF compartment to the ECF compartment and results in serum sodium concentration dilution. This is the primary reason why hyponatremia occurs in diabetes mellitus, contrary to the common belief that it is due to a loss of sodium. Actually, osmotic diuresis leads to loss of water in excess of sodium, and potentially to hypernatremia.

Table 118.1 Categories of hyponatremia

Hypoosmolar		
Hypovolemic	**Normovolemic**	**Hypervolemic**
Addison's disease	Syndrome of inappropriate ADH secretion	Acute/chronic renal failure
Salt-losing nephropathy	Hypotonic fluid administration	Nephrotic syndrome
Cerebral salt wasting	Hypothyroidism	Congestive heart failure
Hypovolemic states:	Glucocorticoid insufficiency	Hepatic cirrhosis
Gastrointestinal loss	Psychogenic polydipsia	Accidental ingestion/injection of water
Third space loss	Reset osmostat	
Shock		
Diuretics		
Renal insufficiency		

A correction factor can be applied to correct the serum sodium concentration in diabetic patients. Traditionally, that correction factor has been reported to be 1.6–1.7 mEq/L, such that for each 100 g/dL increase in blood glucose concentration above normal, the serum sodium concentration will decrease by 1.6–1.7 mEq/L. This correction factor has been challenged in human medicine, and the correction factor may be closer to 2.4 mEq/L, and also the association between sodium and glucose concentrations is nonlinear, with a correction factor that can be up to 4.0 mEq/L if blood glucose concentration is above 400 mg/dL. The appropriate correction factor for dogs and cats is unknown.

For example, a patient with a blood glucose concentration of 1100 g/dL and serum sodium concentration between 105 and 125 mEq/L would have a "corrected serum sodium" concentration of 145 mEq/L (i.e., normal) if a correction factor of 2–4 mEq/L is used. This patient therefore is actually not suffering from hyponatremia. Alternatively, the same patient with a measured serum sodium concentration of 135 mEq/L would have a "corrected serum sodium" concentration between 155 and 175 mEq/L. Thus, such a patient actually is suffering from free water loss and should be treated accordingly. Similarly, when monitoring the changes in serum sodium concentration in diabetes mellitus, the "corrected serum sodium" concentration should be used to judge the risk of overly rapid osmotic shifts of water, because these shifts are due to changes in osmolality and should take into account the blood glucose concentration.

The syndrome of inappropriate ADH secretion (SIADH) is a common disorder in critically ill human patients and also has been described in dogs. It is common in neurologic or oncologic patients as well as after major surgery (Table 118.2). The syndrome refers to secretion of ADH that is inappropriate for the physiologic state (i.e., not secondary to hypovolemia or hyperosmolality). It is characterized clinically by normovolemia, low serum sodium concentration, and decreased urine output. The urine osmolality is high and urine sodium concentration is >20 mEq/L, indicating that the patient is not in a sodium-retaining state (i.e., not hypovolemic) and that the ADH secretion is in fact inappropriate (see Table 118.2). The decreased urine output will not respond to fluid administration, which is the first indication for the clinician faced with a patient with decreased urination, and measurements of urine sodium concentration and osmolality are necessary for the diagnosis of SIADH. The usual treatment for SIADH is fluid restriction and treatment of the primary cause, allowing the body to reset its ADH trigger (usually within 24–72 hours). Most criticalists will treat patients with SIADH using a low dosage (e.g., 0.2–0.5 mg/kg) of furosemide.

Clinical Manifestations of Hyponatremia

It is not possible to predict serum sodium concentration based on history and physical examination. Measurement of serum sodium concentration is needed as well as some other clinicopathologic data to rule out pseudohyponatremia. Clinical signs of hyponatremia are nonspecific (e.g., nausea, vomiting), and related to dysfunction of the central nervous system, such as lethargy, disorientation, and diminished reflexes. Most human patients do not manifest clinical signs until serum sodium concentration is below 125 mEq/L, although rapid decrease in serum

Table 118.2 Syndrome of inappropriate ADH secretion summary

Identify appropriate trigger • Postoperative nausea • Pain or stress • Neoplasia (common) • Pulmonary disease • Neurologic disease • Trauma • Drugs (e.g., NSAIDs, narcotics, vincristine)	Diagnosis • Plasma hypoosmolality • Normovolemia[a] (i.e., absence of hypovolemia) • Increased urine specific gravity/osmolality (>100 mOsm/kg) • Urine sodium concentration >20–40 mEq/L indicating absence of an RAAS trigger (i.e., absence of hypovolemia)[b]
Treatment • Stop/decrease fluid therapy • Treat primary trigger • May provide small dose of furosemide	Notes • Low urine output not responsive to fluid therapy • Age is a risk factor in humans • Case reports of SIADH have been published in veterinary medicine

NSAID, nonsteroidal antiinflammatory drug; RAAS, renin-angiotensin-aldosterone system; SIADH, syndrome of inappropriate ADH.
[a] Spot urine sodium concentration can be influenced by administration of steroids or diuretics, osmotic diuresis (e.g., glucosuria, mannitol administration, postobstructive diuresis), chronic kidney disease and bicarbonaturia (e.g., proximal renal tubular acidosis).
[b] A weight gain is common in SIADH (author's personal observation).

sodium concentration can lead to clinical signs such as seizures, coma, respiratory arrest or brainstem herniation.

Consequences of Chronic Hyponatremia

Maintenance of (relatively) constant serum sodium concentration and plasma osmolality is essential for maintenance of cell volume, as explained above. This is especially relevant for brain volume. If hyponatremia develops acutely (i.e., a few hours) due to rapid, massive ingestion of water, for example, an osmotic gradient will develop and water will move rapidly into the brain, increasing brain cell volume and creating severe acute brain edema and eventually death. If a similar degree of hyponatremia develops over several days, the brain cells will release electrolytes (e.g., sodium and potassium) and idiogenic osmoles (also known as osmolytes). Loss of these idiogenic osmoles, such as amino acids (e.g., glutamine, glutamate, taurine), polyols (e.g., myoinositol), and methylamines (e.g., phosphocreatinine) creates an osmotic effect that shifts free water back out of brain cells and slowly allows them to reequilibrate their volume, although it does not completely correct brain hypoosmolality. It takes hours to days for these osmolytes to be effective.

This concept is very important in the correction of hyponatremia. Actually, the major in-hospital deleterious consequence of chronic hyponatremia is mismanagement of the problem. If too rapid, the increase in serum sodium concentration provokes osmotic water movement out of the cells and brain cell shrinkage. Brain shrinkage can cause vascular rupture, leading to cerebral bleeding, and be responsible for acute neurologic signs such as seizures, impaired mental state, and even death. In addition to the immediate changes, overly rapid correction of hyponatremia (as well as rapid hypernatremia) may cause a delayed syndrome, called osmotic demyelination syndrome (ODS) or central pontine demyelination (CPD). This syndrome is characterized by irreversible neurologic damage including ataxia, paresis, dysphagia or coma and has been described in veterinary medicine.

Principles of Management of Hyponatremia

The goal of correction of chronic severe hyponatremia or hypernatremia is to minimize the change in serum sodium concentration to 0.5 mEq/L/h or a maximum of 10–12 mEq/L per day.

Acute hyponatremia can be corrected relatively quickly (1–2 mEq/L/h or more rapidly), if the clinician is certain the change is acute (e.g., acute water or salt intoxication, iatrogenic hypo- or hypernatremia). Furthermore, severe clinical signs (e.g., seizures) due to hyponatremia also can be corrected rapidly, with the goal of increasing serum sodium by 3–7 mEq/L in 1–2 hours and stopping clinical manifestations such as seizures, before resuming a slower rate of sodium correction. The rate of correction of hyponatremia should be decreased as soon as severe clinical signs have resolved (usually when serum sodium concentration is above 125–130 mEq/L).

When presented with a hyponatremic patient, it is very important for the clinician to review causes of hyponatremia, because treating the underlying cause of hyponatremia is the most important part of correcting it. The indiscriminate use of 0.9% NaCl or 3% NaCl is not warranted in all cases of hyponatremia.

History and physical examination, focused on assessment of volume status, are important. Volume status, plasma osmolality, blood glucose concentration, assessment of adrenal function, urine osmolality and urine sodium concentration will help assess the cause of hyponatremia. Urine electrolyte concentrations and urine osmolality are of paramount importance to discriminate between unrecognized low effective circulating volume (i.e., occult hypovolemia) and SIADH (see Table 118.2).

The majority of patients with hyponatremia have an associated depletion of ECF volume (i.e., loss of total body sodium). Such patients require appropriate volume replacement with isotonic fluids. Although 0.9% NaCl can be used, a balanced electrolyte solution (e.g., lactated Ringer's solution, Plasmalyte® 148) is more physiologic than 0.9% NaCl and will avoid the hyperchloremia and mild metabolic acidosis associated with administration of a large volume of 0.9% NaCl. Patients with hypoadrenocorticism should be treated with fluid therapy and mineralocorticosteroid replacement.

Only patients with symptomatic hyponatremia without evidence of hypovolemia should be treated with 0.9% NaCl and diuretics such as furosemide, combined with water restriction. This approach is used primarily in patients with liver failure. The combination of mannitol and furosemide for treatment of symptomatic hyponatremia also has been described. Patients with CHF should be treated with furosemide alone.

Sodium Deficit Calculation

The next step in management of the patient is calculation of the sodium deficit. Most clinicians use the following equation:

$$\text{Sodium deficit} = \text{body weight}\,(\text{in kg}) \times 0.6 \times (\text{normal Na} - \text{patient Na}) \quad \text{Eqn 1}$$

The sodium deficit (in mEq) should be replaced over several hours with a goal of 0.5 mEq/L/h. Sodium

replacement can be accomplished using 0.9% NaCl ([Na]= 154 mEq/L), 3% NaCl ([Na]= 513 mEq/L), 7.5% NaCl ([Na]= 1300 mEq/L) or 23.4% NaCl ([Na]= 4000 mEq/L).

For example, a 10 kg dog has a serum sodium concentration of 100 mEq/L and it is the clinician's goal to increase it to 140 mEq/L over 80 hours at a rate of 0.5 mEq/L per hour. Using Equation 1, we can calculate:

$$\text{Sodium deficit} = 10 \times 0.6 \times (140 - 100)$$

$$\text{Sodium deficit} = 240\,\text{mEq}$$

This 240 mEq of sodium should be replaced over 80 hours or at a rate of 3 mEq/hour. Using 3% NaCl, this corresponds to an infusion rate of 6 mL/h or 19.3 mL/h if 0.9% NaCl is used.

This formula is very basic and necessitates a good understanding of how to replace the sodium deficit. A number of clinicians use the following equation which provides a rate of infusion in mL/h that depends on the sodium goal, the fluid used, and the speed of correction:

$$\text{Rate of infusion}\,(\text{mL/h}) = [0.6 \times \text{body weight}\,(\text{kg}) \times (\text{desired Na} - \text{Na measured}) \times 1000] / (\text{Na content of the fluid}\,[\text{mEq/L}] \times \text{hours})$$

In the example of a 10 kg dog with a sodium deficit of 240 mEq corrected over 80 hours with 3% NaCl, this rate of infusion becomes:

$$\text{Rate of infusion}\,(\text{mL/h}) = (0.6 \times 10 \times 40 \times 1000) / (513 \times 80)$$

$$\text{Rate of infusion}\,(\text{mL/h}) = 240000 / 41040$$

$$\text{Rate of infusion}\,(\text{mL/h}) = 5.85$$

Some clinicians recommend the use of the Adrogué–Madias equation that calculates the change in sodium with the infusion of a liter of a given fluid. This equation can be used for both hyponatremia and hypernatremia:

$$\text{Change in serum Na} = (\text{Na} + \text{K in 1 L of solution} - \text{patient Na}) / (0.6 \times \text{body weight}\,[\text{kg}] + 1)$$

In our case example above (10 kg dog with a serum sodium of 100 mEq/L) using 3% NaCl, this becomes:

$$\text{Change in serum Na} = (513 - 100) / (0.6 \times 10 + 1)$$

$$\text{Change in serum Na} = 413 / 7$$

$$\text{Change in serum Na} = 59\,\text{mEq}$$

One liter of 3% NaCl will increase the patient's serum sodium concentration up to 159 (= 100 + 59) mEq/L. The goal being 140 mEq/L, the clinician will use 678 mL given over 80 hours, or an infusion rate of 8.5 mL/h. Please note that the result is slightly different than that determined by the first two equations.

For asymptomatic patients, complications may arise from the correction of hyponatremia, usually due to overzealous correction of hyponatremia and brain shrinkage. Careful calculation and monitoring of serum sodium concentration (up to every hour) are warranted to avoid such complications. If complications arise, administration of hypotonic fluids is indicated.

Hypernatremia

Hypernatremia reflects a relative excess of sodium compared to water, arising either by loss of water or from addition of salt, the latter being less common (i.e., thirst prevents development of hypernatremia after ingestion of salt as long as the animal has access to drinking water). Loss of water can be a consequence of pure water loss or hypotonic fluid loss (i.e., more water than salt).

Causes of Hypernatremia

Hypernatremia can be classified according to volume status, and in unusual circumstances according to osmolality (Table 118.3).

Hypernatremia typically is associated with water loss in excess of sodium (most common) or a salt gain (occasionally, almost always with concurrent restriction of access to water). For example, although fluid losses in diarrhea can be isosmotic overall, the combined sodium and potassium concentration of diarrhea fluid is lower than that of plasma (typically around 40–100 mEq/L of sodium and potassium combined). Thus, more free water is lost than sodium and the patient becomes hypernatremic, a very common clinical scenario. The same applies for renal losses. Loss of free water by osmotic diuresis or ADH dysregulation also is common. Usually, ADH will be released, thirst will be stimulated, and hypernatremia and hyperosmolality will be corrected.

Clinical Manifestations of Hypernatremia

The clinical signs of hypernatremia usually are vague, and neurologic in nature, including lethargy, confusion, and decreased mentation. Acute hypernatremia (e.g., ingestion of a large amount of salt water or hypertonic saline administration) can lead to seizures and death due to acute brain shrinkage. As stated earlier, if the thirst mechanism is intact and water is readily available, the animal will ingest water and not become hypernatremic. Most patients presented with severe, chronic hypernatremia have a neurologic problem that has either altered

Table 118.3 Causes of hypernatremia

Hyperosmolar			Hypoosmolar[a]
Hypovolemia	**Normovolemia**	**Hypervolemia**	**Hypoproteinemia (hypolipidemia)**
Renal losses Gastrointestinal losses (vomiting or diarrhea) Burns Osmotic diuresis • Diabetes mellitus[b] • Diabetic ketoacidosis[b] • Hyperosmolar nonketotic syndrome[b] • Mannitol infusion • Postobstructive diuresis	Hypodypsia (very rare) Diabetes insipidus (DI) (with decreased water intake) • Central DI • Congenital nephrogenic DI • Acquired nephrogenic DI Fever Decreased access to water	Salt intoxication • Iatrogenic • Sea water ingestion Hypertonic saline infusion Sodium bicarbonate infusion Primary hyperaldosteronism Hyperadrenocorticism	

[a] Pseudohypernatremia may occur when serum sodium concentration is measured by flame photometry, an obsolete technique, or indirect potentiometry, which is common in reference laboratories. These concerns are not relevant if an ion-selective electrode (direct potentiometry) is used to measure serum sodium concentration.
[b] Use corrected sodium concentration (previously discussed).

their thirst mechanism or prevented their ability to obtain and independently drink water. In patients with decreased access to water, intense thirst may be the only clinical sign, and it may subside with chronicity.

Consequences of Chronic Hypernatremia

Similarly (although in the opposite direction) to what happens in chronic hyponatremia, chronic hypernatremia induces increased production of osmolytes, leading to normalization of brain cell volume. This explains why only acute or subacute hypernatremia leads to important clinical signs. Also, clinical signs may arise after acute normalization of serum sodium concentration in patients with chronic hypernatremia, because rapid lowering of the serum sodium concentration may cause brain edema and associated clinical signs. In such cases, administration of hypertonic fluid and mannitol may be warranted.

Principles of Management of Hypernatremia

A thorough history and complete physical examination, including questions about access to water and water consumption, and careful assessment of volume status are the starting points. Ruling out diabetes mellitus is easy and inexpensive. Determination of urine osmolality is important to assess the body's response to ADH. Concentrated urine suggests extrarenal (usually gastrointestinal) water loss, whereas hypoosmolar urine indicates that the kidney is the source of free water loss, usually secondary to diabetes insipidus.

Although usually easily identified, understanding and addressing the underlying cause of hypernatremia are important. Correcting hyperosmolality usually requires slow free water administration. As mentioned earlier, chronic hypernatremia must be corrected slowly to avoid adverse cerebral fluid shifts. The recommended rate for correction of hypernatremia is identical to the correction of hyponatremia, with a maximum rate of 10–12 mEq/L per day, and a goal of 0.5–1 mEq/L per hour. Correction of hypernatremia is achieved by free water replacement.

Water Deficit Calculations

Several equations exist, but the classic water deficit equation is:

$$\text{Water deficit} = 0.6 \times \text{body weight}\,(\text{kg}) \times \left[\left(\text{Plasma Na} / \text{Normal Na}\right) - 1\right]$$

For example, for a 10 kg patient with a normal serum sodium concentration of 145 mEq/L and a current serum sodium concentration of 175 mEq/L:

$$\text{Water deficit} = 0.6 \times 10 \times \left[\left(175/145\right) - 1\right] = 1.2\,\text{L} = 1200\,\text{mL}$$

This formula estimates the amount of free water required to return this patient's serum sodium concentration to normal (i.e., 145 mEq/L). In chronic hypernatremia, the serum sodium concentration should be corrected no more rapidly than 0.5–1 mEq/L/h. The patient described earlier should receive the 1200 mL over 30–60 hours, with a free water fluid rate of of 20–40 mL/h.

As mentioned earlier, the Adrogué–Madias formula that calculates the change in serum sodium concentration with infusion of a liter of a given fluid also can be used:

$$\text{Change in serum sodium concentration} = \left(\text{Na} + \text{K content in 1 L of solution} - \text{Na measured}\right) / \left(0.6 \times \text{body weight [kg]} + 1\right)$$

In the example of a 10 kg dog and using 5% dextrose:

$$\text{Change in serum Na} = \left(0 - 175\right) / \left(0.6 \times 10 + 1\right)$$

$$\text{Change in serum Na} = -175 / 7$$

$$\text{Change in serum Na} = -25$$

This formula indicates that 1 L of 5% dextrose in water will decrease the serum sodium concentration by 25 mEq/L. To decrease it to normal (i.e., 145 mEq/L) from 175 mEq/L, 1.2 L of 5% dextrose in water will be necessary, given over 30–60 hours (at a rate of 0.5–1 mEq/L/h) and thus the infusion rate should be 20–40 mL/h.

The water deficit formula has been challenged for several reasons and may underestimate the true water deficit by as much as 50%. First, it assumes that total body water remains unchanged during hyponatremic states. Also, it does not account for low solute fluid losses (i.e., hypotonic fluids), such as urine and gastrointestinal secretions (i.e., it only accounts for free water loss). Likewise, it does not account for any ongoing hypotonic losses. The Adrogué–Madias equation results in the same volume of free water, and thus also has been challenged. The important clinical implication is that serial monitoring (q4–6h) is necessary to reevaluate serum sodium concentration and serum osmolality, and adjust the fluid infusion rate, which is invariably necessary. Ongoing losses of hypotonic fluid also can persist and make the calculation unpredictable. Some clinicians (personal communication, Dr Steve Haskins) use the quick rule of thumb that "3.7–mL/kg/h of free water will decrease the serum sodium concentration by 1 mEq/L per hour" and reassess the serum sodium concentration after 4–6 hours. For the example above, the animal would have received 37 mL/h.

As mentioned previously, acute changes in serum sodium concentration (e.g., accidental sodium loading in parenteral fluids) can be corrected more rapidly. This is also true for patients with severe clinical signs due to chronic changes in serum sodium concentration, when the serum sodium concentration can be corrected rapidly until clinical signs resolve, before adopting a more chronic approach.

The approach described earlier does not account for any isotonic fluid losses or for the patient's maintenance fluid requirement. If 0.45% NaCl is used (sodium concentration of 77 mEq/L), the rate should be adjusted because only half of this solution represents free water. The patient above should receive 36–71 mL/h, which represents a substantial volume and potentially could worsen brain edema. Thus, the lowest tonicity fluid (and hence volume) is always recommended.

If 5% dextrose in water is contraindicated (e.g., hyperglycemic patients) and only if a central venous catheter is in place, some clinicians have advocated using intravascular sterile water. When administered through a central intravenous catheter, sterile water does not cause clinically relevant intravascular hemolysis.

Shock Resuscitation of the Chronically Hypernatremic Patient

Resuscitation of volume-depleted hypernatremic patients, or those with concomitant isotonic fluid losses, should be done carefully, with the sodium content of the fluid matching the animal's serum sodium concentration within 10 mEq/L to avoid decreasing the serum sodium concentration too rapidly. Consider again the 10 kg dog with a serum sodium concentration of 175 mEq/L, and add the clinical situation of hypovolemic shock.

If lactated Ringer's solution (LRS) is used and the dog requires administration of 1 L of LRS over a one-hour period, we can calculate the impact of 1 L of LRS on the patient's serum sodium concentration. LRS has a sodium concentration of 132 mEq/L, so 75% (i.e., 132/175) of the solution is isotonic to the patient's plasma and 25% is free water. With the administration of 1000 mL of LRS, the patient actually will receive the equivalent of 250 mL of free water, decreasing its serum sodium concentration from 175 to 168 over one hour and possibly leading to cellular swelling, brain edema, seizures, and coma. The use of a fluid isotonic to the patient is necessary for shock resuscitation of a chronically hypernatremic patient. If LRS is used, the addition of 10 mL of 23.4% NaCl (4 mEq/mL of Na) to a liter of LRS will create a balanced electrolyte solution with a sodium concentration of 172 mEq/L (= 132 + 10 × 4) that will be very close to the patient's serum sodium concentration of 175 mEq/L. Once shock is treated, the clinician can focus on the free water deficit. A similar approach also can be used for shock resuscitation of the chronically hyponatremic patient.

Conclusion

A good understanding of sodium and water balance is necessary to appropriately identify and treat chronic and acute changes in serum sodium concentration in small animal patients. The proper approach is always the one of the conscientious clinician: a thorough history and complete physical examination, appropriate diagnostic

tests (including serum sodium concentration and urine electrolyte concentrations if needed), appropriate calculation of sodium (or water) deficit, and careful monitoring of changes in the serum sodium concentration and osmolality in order to avoid deleterious effects of treatment. With these concepts in mind, sodium and water balance becomes both exciting and challenging at the same time.

Further Reading

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119

Disorders of Phosphorus and Magnesium

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Phosphorus

Phosphorus is vital for many physiologic roles within the body, including skeletal development and structure, cell metabolism and acting as a urinary and intracellular buffer. Disorders of phosphorus homeostasis are identified with relative frequency in clinical practice and warrant consideration of their underlying etiology, careful monitoring and, in certain circumstances, will require therapeutic intervention.

Phosphorus can be found in the body in two forms: organic and inorganic (orthophosphoric and pyrophosphoric acid). Approximately 85%, of total body phosphorus is found in an organic form as hydroxyapatite ($Ca_{10}(PO_4)_6OH_2$) in bone and as fluorapatite ($Ca_5(PO_4)_3F$) in teeth. Only 14% of total body phosphorus is found intracellularly and 1% within the extracellular fluid (ECF) compartment.

Phosphorus is the principal anion in cells where it is a component of phospholipids and phosphoproteins and incorporated in the structure of nucleic acids and nucleotides. Phospholipids (e.g., phosphatidylcholine, phosphatidylserine) are an important part of the lipid bilayer of cell membranes and are required for platelet aggregation. Phosphorus can also be found in cyclic adenosine monophosphate (cAMP), which is required for intracellular signaling pathways and is incorporated in the high-energy phosphate bonds of adenosine triphosphate (ATP) and guanosine triphosphate (GTP). Within red blood cells, phosphorus is found in 2,3 diphosphoglycerate (2,3 DPG) which is responsible for the release of oxygen from hemoglobin at the tissue level.

Intracellular organic phosphorus can be readily converted to the inorganic form. Rapid translocation between the intracellular fluid and the ECF space can occur, resulting in substantial alteration in ECF concentrations. In the ECF, 70% of plasma phosphorus is in an organic form circulating as phospholipids. The remaining 30% of plasma phosphate exists in an inorganic form where it may be protein bound (10%), complexed to sodium, calcium and magnesium (5%) or circulating free as anions (85%; HPO_4^{2-}, $H_2PO_4^-$).

Regulation of Phosphorus

Homeostasis of calcium and phosphorus is intrinsically linked with many of the hormones recognized in the control of calcium also important in the regulation of phosphorus. Traditionally, it was considered that calcium was tightly regulated and that phosphorus concentrations were maintained in a reciprocal arrangement. However, it is now appreciated that independent regulation of phosphorus is also important.

Phosphorus homeostasis involves three major body organ systems: intestines, bone, and kidneys (Figure 119.1). Plasma phosphorus concentration is the composite effect of dietary phosphorus intake, gastrointestinal absorption, cellular translocation, and renal excretion. In a neutral state of phosphorus balance, daily dietary intake of phosphorus will be countered by renal excretion such that total body phosphorus concentrations vary little.

The main hormones traditionally cited in the regulation of phosphorus are parathyroid hormone (PTH) and calcitriol ($1,25(OH)_2$ cholecalciferol) (Figure 119.2). Recently, further important hormones referred to as phosphotonins have been identified. Phosphotonins, such as fibroblast growth factor 23 (FGF23), play an important role regulating renal handling of phosphorus. In a similar manner to PTH, FGF23 increases renal tubular excretion of phosphorus. However, FGF23 has an opposing action to PTH by inhibiting production of calcitriol and therefore indirectly reducing release of phosphorus from bone and decreasing absorption of phosphorus from the intestinal tract.

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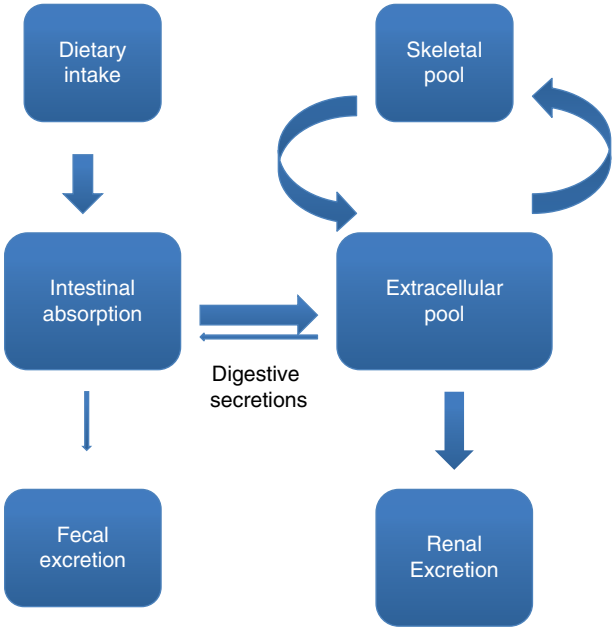


Figure 119.1 Phosphorus homeostasis in the body.

Dietary phosphorus is the main source of phosphorus for the body. Efficient absorption of phosphorus occurs in the small intestine. Phosphorus absorbed from the intestine enters the extracellular pool, with a small quantity excreted back to the intestine within digestive secretions. The skeletal and extracellular phosphorus pools are in a constant state of flux, allowing maintenance of phosphorus concentrations. Excess phosphorus absorbed from dietary intake, in health, is balanced by renal excretion in order to maintain total body phosphorus concentrations.

Regulation of phosphorus is intrinsically linked to the regulation of calcium. However, phosphorus itself has a number of direct regulatory effects.

- Increased phosphorus concentrations, by the law of mass action, result in a relative decline in ionized calcium concentration, driving production of PTH from the parathyroid gland. Phosphorus can also have a direct stimulatory effect on the parathyroid glandm increasing production of PTH.
- PTH acts on the kidney to decrease absorption of phosphate. Given that a driving factor for the production of PTH is a decrease in calcium concentration,

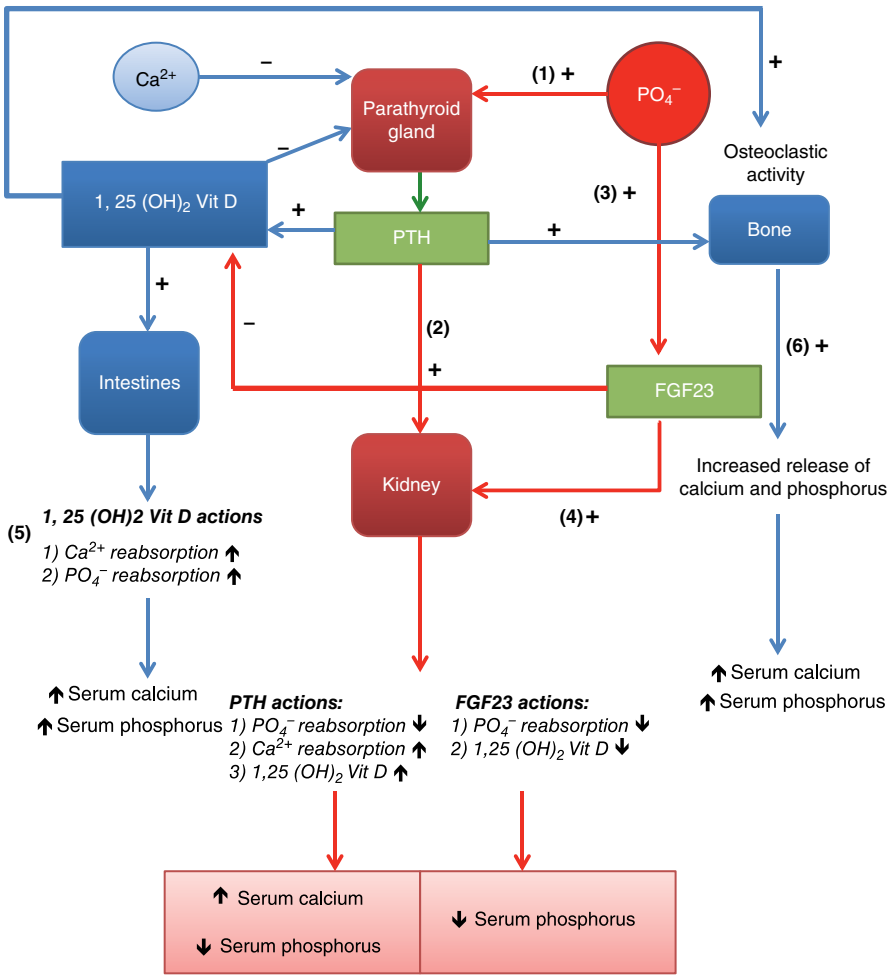


Figure 119.2 Hormonal regulation of phosphorus in health. 1,25 $(OH)_2$ Vit D, calcitriol; Ca^{2+}, calcium; FGF23; fibroblast growth factor 23; PO_4^-, phosphate; PTH, parathyroid hormone.

PTH also increases renal absorption of calcium and stimulates production of calcitriol. The net effect of PTH on the kidney is therefore a reduction in plasma phosphate and an increase in plasma calcium.

- Increased phosphorus concentration also directly stimulates osteocytes to produce the phosphotonin FGF23.
- FGF23 acts on the kidney in a similar manner to PTH, decreasing tubular absorption of phosphorus.
- Calcitriol increases absorption of both calcium and phosphorus from the small intestine. This process is facilitated indirectly by PTH, which increases renal production of calcitriol. FGF23 has an opposing action, inhibiting calcitriol production and therefore decreasing absorption of phosphorus from the intestinal tract.
- Calcitriol and PTH also increase reabsorption of calcium and phosphorus from bone.

Meat, bone, and fish are food sources high in phosphorus and dietary intake is therefore a major source of phosphorus for the body. Typical commercial canine and feline diets have a phosphorus concentration of 0.8–1.6% on a dry matter basis with a calcium to phosphorus ratio of 1.2–2.1. Most organic phosphate is hydrolyzed in the gastrointestinal tract to inorganic phosphate for absorption. Phosphate is absorbed via paracellular pathways in all regions of the small intestine. However, approximately 30% of intestinal absorption is active and occurs in the duodenum, utilizing a sodium-phosphorus co-transporter (NaPi2b). Expression and insertion of the NaPi2b co-transporter are under the control of calcitriol. A decrease in intestinal phosphate or an increase in calcitriol will increase intestinal absorption of phosphate.

Once absorbed, inorganic phosphate within the extracellular pool is exchangeable with the skeletal stores under the influence of both PTH and calcitriol. However, because proportionally only a very small amount of phosphorus is found in the ECF, measurement of plasma phosphorus concentrations does not always provide a good reflection of total body phosphorus.

Inorganic plasma phosphate that is not bound to protein is freely filtered at the glomerulus. Approximately 85% of filtered phosphate is reabsorbed by active transport in the proximal tubule, with a small amount also absorbed in the distal nephron. However, during periods of low dietary intake, efficiency can increase until almost 100% of filtered phosphate is reabsorbed. Active transport occurs via sodium-phosphate co-transporters (NaPi2a and NaPi2c) located in the brush border of proximal tubular cells. Expression of the NaPi2a co-transporter is under the control of PTH, FGF23, and intestinal phosphate absorption (Box 119.1).

Box 119.1 Regulation of phosphate handling by the kidney

In periods of phosphate excess, increase in PTH concentration favors internalization and lysosomal degradation of the NaPi2a co-transporter, thus limiting phosphate reabsorption and increasing phosphate excretion in the urine. Conversely, in periods of hypophosphatemia, decrease in PTH concentrations has a permissive role, favoring insertion and maintenance of the NaPi2a co-transporter in the proximal tubular brush border and increasing phosphate reabsorption. PTH is therefore a phosphaturic hormone promoting excretion of phosphate in the urine.

FGF23, produced by osteocytes in response to increased phosphorus concentration, also acts as a phosphaturic factor. FGF23 in conjunction with its co-factor klotho decreases expression and activity of NaPi2a co-transporter in the proximal tubular cells, thus decreasing tubular reabsorption and increasing renal excretion of phosphorus.

Other factors which can modulate and increase renal tubular phosphate reabsorption include growth hormone, thyroid hormone, insulin, insulin-like growth factor 1 (IGF-1) and 1,25 $(OH)_2$ cholecalciferol. Reabsorption can be reduced by parathyroid hormone-related protein (PTHrP), glucocorticoids, calcitonin, and atrial natriuretic peptide.

Laboratory Assessment of Phosphorus

Circulating inorganic phosphorus (Pi), which can be either free or complexed to calcium, magnesium or sodium, is the component routinely quantified by diagnostic laboratories. Serum phosphate concentrations are slightly higher than plasma phosphate concentrations due to release of phosphate from cells and platelets during the clotting process. Normal phosphate reference intervals will be laboratory dependent but values of approximately 2.5–5.5 mg/dL (0.8–1.8 mmol/L) are reported for dogs and 2.5–6.0 mg/dL (0.8–1.9 mmol/L) for cats.

It is widely recognized that young animals demonstrate elevated plasma phosphorus concentrations. This is likely to be the consequence of increased growth hormone facilitating renal tubular reabsorption of phosphate and also increased concentrations of calcitriol. In puppies up to 8 weeks of age, plasma phosphate concentrations up to 10.8 mg/dL (3.4 mmol/L) can be considered normal. However, an age-related difference in phosphorus concentrations can be present until 1 year of age. This difference is more marked in the dog than the cat.

Phosphate concentrations can be factitiously increased by lipemia, hyperproteinemia, and hemolysis and can be increased postprandially, particularly after a high-protein meal. Patients should therefore ideally be fasted for

8–12 hours prior to measurement. A number of drugs may influence plasma phosphate concentrations either as a desired therapeutic effect (e.g., intestinal phosphate binders) or as a secondary consequence of their administration (e.g., antacids including sucralfate, insulin, and dextrose).

Hypophosphatemia

Hypophosphatemia can be defined as a plasma phosphorus concentration <2.5 mg/dL (0.8 mmol/L) and can occur as a result of three main mechanisms: increased renal excretion, reduced intake or intracellular movement of phosphorus. As only ~1% of total body phosphorus is present in the ECF compartment, transcellular movement can result in marked change in plasma phosphorus concentrations which may not always accurately reflect total body phosphorus.

Clinical Signs

Patients with mild hypophosphatemia can be asymptomatic or show nonspecific signs of weakness, lethargy, and inappetence. However, severe hypophosphatemia can result in more dramatic clinical consequences including anemia, cardiac arrhythmias, depression, coma, seizures, rhabdomyolysis, and respiratory compromise. At plasma phosphorus concentrations <1 mg/dL (0.3 mmol/L), red cell hemolysis becomes a significant clinical concern due to increased fragility and decreased ATP availability.

In total body phosphate depletion, reduction in phospholipid production, loss of cell membrane integrity, decreased cellular enzyme and energy production (ATP), and loss of ion gradients maintained by Na+K+ATPases affect cellular function. This change in cellular function is not restricted to red blood cells and can cause abnormal membrane potentials, resulting in cardiac arrhythmias and neurologic dysfunction. Leukocytes may demonstrate reduced chemotactic, bactericidal, and phagocytic activity, and platelet function may also be impaired. Decreased production of 2,3 DPG can result in decreased release of oxygen from hemoglobin, causing tissue hypoxia. Decreased muscle contractility, particularly affecting the diaphragm, can lead to ventilatory compromise or in extreme hypophosphatemia, disruption of myocytes can result in rhabdomyolysis. Inappetence, nausea, and vomiting may occur as a consequence of ileus.

Conditions associated with hypophosphatemia are outlined in Box 119.2. Mild hypophosphatemia may be identified in patients at diagnosis of diabetes mellitus as a consequence of increased muscle and fat catabolism and diuresis. However, in the diabetic patient and in particular patients with diabetic ketoacidosis, the period of greatest concern with regard to hypophosphatemia is during initiation of therapy. Intravenous fluid therapy, insulin, and bicarbonate administration can all cause intracellular translocation of phosphate. Total body phosphate concentrations may be normal or reduced, but during the acute phase of therapy, severe hypophosphatemia can develop. Plasma phosphate concentrations should be closely monitored during treatment and appropriate intravenous supplementation started in order to prevent secondary consequences of severe hypophosphatemia such as hemolysis.

Box 119.2 Causes of hypophosphatemia

- Increased renal excretion
  - Diabetes mellitus*
  - Primary hyperparathyroidism*
  - Diuretic administration (carbonic anhydrase inhibitors)
  - Renal tubular disorders, e.g., Fanconi syndrome
  - Eclampsia
  - Hyperadrenocorticism
  - Hyperaldosteronism
  - Early stages of hypercalcemia of malignancy
- Decreased phosphorus intake
  - Vomiting and diarrhea
  - Malabsorption, e.g., primary intestinal disease
  - Administration of phosphate binders
  - Vitamin D deficiency (dietary imbalance, rickets)
- Transcellular shifts
  - Insulin administration and treatment of diabetic ketoacidosis*
  - Parenteral glucose administration*
  - Refeeding syndrome/total parenteral nutrition
  - Respiratory alkalosis/hyperventilation
  - Bicarbonate administration
  - Hypothermia
  - Sepsis

* Commonly identified in clinical practice.

Primary hyperparathyroidism (PHPTH) is a relatively uncommon condition in clinical practice. Clinical signs in hyperparathyroidism are often occult and when identified, usually relate to the presence of hypercalcemia or the secondary development of urolithiasis. However, plasma phosphate concentrations within the lower half or below normal reference interval are reported in 30–100% of dogs with PHPTH as a result of PTH-mediated inhibition of renal tubular phosphate reabsorption. Primary hyperparathyroidism is rare in cats and hypophosphatemia is an inconsistent finding.

Hypophosphatemia as a consequence of low dietary intake is uncommon unless there has been a period of prolonged anorexia or dietary deficiency. Rarely,

hypophosphatemia may be identified secondary to hypovitaminosis D (rickets or osteomalacia). Malabsorptive conditions, for example inflammatory bowel disease or exocrine pancreatic insufficiency, or those patients with vomiting and/or diarrhea may have increased intestinal phosphate loss. In such patients, mild hypophosphatemia can be identified but it is uncommon for marked deficiencies to be identified. Oral administration of antacid medications such as sucralfate, or intestinal phosphate binders, can effectively complex dietary phosphate within the intestine. Whilst during periods of hyperphosphatemia this may be the desired effect, inappropriate or overzealous administration can result in hypophosphatemia.

After a sustained period of anorexia, reintroduction of food without adequate phosphorus supplementation and, in particular, introduction of a high-calorie, carbohydrate-dense diet can result in refeeding syndrome. During periods of inadequate nutrition, phosphate may redistribute to the ECF in order to maintain normal plasma phosphate concentrations and hence cell membrane potentials. With refeeding, increased glucose and insulin concentrations potentiate the translocation of phosphate to the intracellular compartment with a resultant decrease in ECF phosphate concentration. Hypophosphatemia in this situation can be extreme and result in hemolysis, rhabdomyolysis, seizures, and neurologic disorders. Refeeding syndrome may be of particular concern for anorexic cats with primary or secondary hepatic lipidosis.

Treatment of Hypophosphatemia

Treatment of hypophosphatemia requires thorough assessment of the patient in order to identify and, where possible, rectify the underlying etiology. For patients where only mild hypophosphatemia is identified and further decrease is unlikely, treatment of the underlying condition, ensuring adequate nutritional intake and continued monitoring, may be sufficient.

However, phosphorus supplementation is recommended for all patients with clinical signs or hematologic abnormalities (e.g., hemolysis) associated with hypophosphatemia. Supplementation should also be considered prophylactically in those patients that are at high risk for developing severe hypophosphatemia, such as patients with diabetic ketoacidosis or those at risk of refeeding syndrome. In these situations, supplementation can be provided intravenously with either sodium phosphate or potassium phosphate as a continuous rate infusion (CRI) at 0.01–0.06 mmol/kg/h.

During intravenous phosphorus supplementation, calcium and phosphorus concentrations should be carefully monitored q6–8h and CRI dose adjusted in order to initially reach low normal phosphate concentrations (>2.0 mg/dL, >0.6 mmol/L) and subsequently to bring phosphate concentrations to the lower end of the normal reference interval. Due to concern regarding precipitation of calcium phosphate, phosphorus-containing fluids should be diluted in saline for administration. Response to supplementation is individual but gradual correction can usually be achieved over a period of hours to days.

Patients should be closely monitored for the development of hypocalcemia, tetany, and hyperphosphatemia. Hyperphosphatemia may be of particular concern during the initial phase of supplementation when pathophysiologic mechanisms that have been activated to ensure maximal phosphate retention and reduction in renal tubular excretion during a period of phosphorus repletion have not yet adapted. In patients receiving phosphorus supplementation, if the calcium:phosphorus product exceeds 60–70 mg^2/dL^2 (4.8–5.6 $mmol^2/L^2$), soft tissue mineralization and renal failure become a concern. In patients with diabetic ketoacidosis where there is evidence of both hypokalemia and hypophosphatemia, supplementation with potassium phosphate may be preferred. In this situation, approximately quarter of potassium supplementation can be administered as potassium phosphate with the remainder as potassium chloride.

Hyperphosphatemia

Hyperphosphatemia can occur as a consequence of three main mechanisms: impaired renal excretion, excessive intestinal absorption, and transcellular shift from tissue/bone to the ECF (Box 119.3).

Clinical signs as a direct consequence of hyperphosphatemia are rarely observed but can relate to relative hypocalcemia, such as weakness, neuromuscular tetany, and seizures. Hyperphosphatemia may also contribute to the risk of soft tissue mineralization if the calcium:phosphorus product exceeds 60–70 mg^2/dL^2 (4.8–5.6 $mmol^2/L^2$).

Impaired renal function, as a consequence of either chronic kidney disease (CKD) or acute kidney injury (AKI), is the most common clinical cause of hyperphosphatemia. Reduction in glomerular filtration rate (GFR) and loss of functioning nephrons result in decreased excretion of phosphorus by the kidney. In the early stages of CKD, initial phosphorus retention is countered by increased production of FGF23, reduction in calcitriol concentrations and, in later stages, increased PTH production. These compensatory mechanisms initially maintain plasma phosphate concentrations within the reference interval by promoting tubular phosphate excretion in remaining nephrons. However, with progressive loss of nephrons and decline in GFR, the compensatory mechanisms are exceeded and hyperphosphatemia ensues.

Box 119.3 Causes of hyperphosphatemia

- Impaired renal excretion
  - Renal*
    - Prerenal causes, e.g., hypoadrenocorticism
    - Renal causes, e.g., chronic kidney disease or acute kidney injury
    - Postrenal causes, e.g., uroabdomen, urinary tract obstruction
  - Hypoparathyroidism
  - Hyperthyroidism
  - (Acromegaly)
- Increased phosphorus intake
  - Gastrointestinal absorption
    - Vitamin D toxicosis: rodenticide poisoning, e.g., cholecalciferol; psoriasis creams, e.g., calcipotriene
    - Phosphate-containing enemas
  - Intravenous
    - Administration of phosphorus-containing fluids
- Transcellular shifts
  - Cellular breakdown
    - Tumor lysis syndrome
    - Hemolysis
    - Rhabdomyolysis
    - Tissue trauma or hypoxia
- Physiologic
  - Young animal*
  - Postprandial*
- Laboratory error
  - Hyperlipemia
  - Hyperproteinemia
  - Hemolysis

* Commonly identified in clinical practice.

In both dogs and cats, the prevalence of hyperphosphatemia increases with advancing stages of CKD. A study in cats demonstrated that 20% of cats with compensated CKD, 49% with uremic CKD and 100% with end-stage CKD were hyperphosphatemic. Findings were similar in a group of dogs: 18% with International Renal Interest Society (IRIS) stage 1, 40% stage 2, 92% stage 3, 100% stage 4. In AKI, decline in renal function can occur without sufficient time for adequate compensatory mechanisms to develop. Severe hyperphosphatemia may therefore be identified in AKI and may be proportionally greater for the degree of reduction in GFR than identified with CKD.

Any prerenal or postrenal causes of reduced GFR, for example hypoadrenocorticism or uroabdomen/urinary tract obstruction respectively, which decrease filtration fraction and renal excretion of phosphorus, can result in hyperphosphatemia.

Studies suggest that up to 43% of cats with hyperthyroidism are hyperphosphatemic at diagnosis. In cats that remain nonazotemic, with successful treatment and return of euthyroidism, phosphorus concentrations return to normal. The exact cause of hyperphosphatemia in feline hyperthyroidism has not been fully elucidated. Thyroxine is known to directly increase renal tubular absorption of phosphate. In addition, increased bone isoenzyme alkaline phosphatase and osteocalcin as a marker of osteoblastic activity suggest that altered bone metabolism may contribute. However, in those cats that are revealed to be azotemic after return of euthyroidism, phosphate concentrations do not significantly change and in such patients reduced renal function may also be contributing.

Growth hormone can directly increase renal tubular absorption of phosphate and therefore may theoretically contribute to hyperphosphatemia in acromegaly. However, recent studies evaluating the clinicopathologic abnormaltities in larger cohorts of cats with acromegaly have not confirmed this finding.

In dogs with hypoparathyroidism, reduction in PTH concentration favors insertion of renal tubular NaPi2a co-transporters and therefore reabsorption of phosphorus. Studies suggest that ~30–100% of dogs with hypoparathyroidism demonstrate hyperphosphatemia. Hyperphosphatemia has also been reported in cats with idiopathic hypoparathyroidism although this is a rare condition. However, clinical signs in primary hypoparathyroidism usually relate to marked hypocalcemia rather than any concurrent hyperphosphatemia.

Increased intestinal absorption of phosphorus is an uncommon clinical cause of hyperphosphatemia. Ingestion of excess vitamin D, either in rodenticides containing cholecalciferol or from psoriasis creams containing calcipotriene, can cause increased release of calcium and phosphorus from bone and absorption from the intestinal tract. Absorption of phosphorus from phosphate-containing enemas has been reported to cause hyperphosphatemia in dogs and cats.

Phosphorus is found at high concentrations intracellularly. Any process that results in marked cell destruction has the potential to increase plasma phosphate concentrations. For example, hyperphosphatemia is one of a number of electrolyte abnormalities identified during tumor lysis syndrome (hyperphosphatemia, hypocalcemia, hyperkalemia, hyperuricemia, oliguric AKI). Administration of chemotherapy to a patient with a large tumor burden, that is highly sensitive to the chemotherapeutic agent or radiation dose administered, results in rapid lysis of tumoral cells and release of intracellular phosphorus to the ECF. Acute tumor lysis syndrome has previously been reported in dogs and cats with lymphosarcoma. A similar situation can occur during hemolysis, with release of phosphorus from red blood cells or during rhabdomyolysis, tissue infarction or severe crush

injuries. In rhabdomyolysis, marked myoglobinuria may cause AKI and therefore reduced renal function may also contribute to hyperphosphatemia.

Treatment of Hyperphosphatemia

Similar to the management of hypophosphatemia, the first step in the management of hyperphosphatemia is determining and, when possible, correcting the underlying etiology. Renal excretion of phosphorus should be optimized with correction of any prerenal or postrenal component. Intravenous fluid therapy to correct hypovolemia and/or dehydration and to provide mild expansion of ECF may improve renal excretion of phosphorus. In patients with AKI, dialysis may offer a way to correct electrolyte imbalances including hyperphosphatemia.

However, in those patients with CKD, restricting intestinal absorption of phosphate can control hyperphosphatemia. In early CKD (IRIS stage 2), this can be achieved using a phosphate-restricted diet. However, with advancing CKD, addition of intestinal phosphate binders may be required to achieve phosphate targets, such as aluminum hydroxide, calcium carbonate +/- chitosan, calcium acetate, lanthanum carbonate, and sevelamer hydrochloride. Dietary phosphate restriction is achieved by feeding a low-protein, low-phosphorus diet. Intestinal phosphate binders complex with dietary phosphate, producing an insoluble, nonabsorbable compound, which is excreted in the feces. For maximum efficacy, phosphate binders should therefore be administered with every meal and used in conjunction with phosphate-restricted diets.

Aluminum hydroxide is a commonly used and well-tolerated phosphate binder in canine and feline patients with CKD (30–100 mg/kg/day). Side-effects can include constipation and in human patients with end-stage kidney disease or undergoing hemodialysis, aluminum toxicity and neurotoxicity are reported. Caution is warranted when using calcium-containing phosphate binders, such as calcium carbonate, due to the potential for development of hypercalcemia, an elevated calcium phosphorus product and dystrophic mineralization. Side-effects of calcium-containing phosphate binders can also include nausea and constipation. Sevelamer hydrochloride (30–40 mg/kg PO q8h) is a resin-based phosphate binder that contains neither aluminum nor calcium. Sevelamer binds to the mucosal surface of the intestine, allowing extended periods of phosphate binding. However, its expense, gastrointestinal side-effects, and potential to bind other substances (e.g., vitamins, bile acids and cholesterol) may make it a less desired product. Lanthanum carbonate (dogs 6.25–12.5 mg/kg PO q12h; cats 400–800 mg/cat/day divided according to feeding schedule) is another nonaluminum, noncalcium-based phosphate binder, which is capable of binding phosphate at both low and high pH, being effective therefore in both the stomach and small intestine. Lanthanum undergoes biliary excretion and therefore should not accumulate in patients with compromised renal function.

Interventions to control hyperphosphatemia should be carefully monitored by serial measurement of plasma phosphate concentrations. For patients with CKD, the IRIS provides stage-specific targets for phosphate control. The effect of either introducing a phosphate-restricted diet or phosphate binder or altering dosage of a phosphate binder in patients with CKD can be relatively slow in onset due to whole-body phosphate retention. Assessment of plasma phosphate concentration after ~2–4 weeks is therefore likely to be adequate.

Magnesium

Until recently, magnesium has received relatively little attention in small animal medicine. However, magnesium is known to play a vital part in many cellular functions and the clinical consequences of alteration in magnesium homeostasis are receiving increased recognition in small animal patients, particularly within a critical care setting.

Distribution in the Body

Greater than 99% of the body's magnesium is located intracellularly, with less than 1% found within the ECF. Of the intracellular stores, ~70% is present in bone, ~20% in muscle, and ~10% other soft tissues. Within the ECF, ~55% of magnesium is ionized or free and considered the biologically active component, with a further 20–30% protein bound and 15–20% complexed to anions (e.g., phosphate or bicarbonate). The relatively smaller proportion of protein-bound magnesium in comparison to calcium means that magnesium concentrations are less likely to be influenced by changes in albumin concentration.

Biologic Importance of Magnesium

Magnesium is required in the mitochondria of cells for oxidative phosphorylation and for anaerobic metabolism of glucose. It also plays a role in the synthesis and degradation of DNA, ribosomal binding to RNA, nucleotide synthesis, and production of intracellular messengers such as cAMP.

Magnesium is an important regulator of intracellular calcium cycling in both smooth and cardiac myocytes and is therefore important for cardiac excitability, contraction, and conduction mechanisms. In vascular smooth muscle, intracellular magnesium concentrations

may contribute to peripheral vascular resistance; increased intracellular smooth muscle magnesium concentrations enhance vasorelaxation whilst conversely decreased concentrations facilitate vasoconstriction.

Magnesium is important in neuromuscular transmission and severe magnesium deficiency results in increased neuronal excitability and neuromuscular transmission. The classic neuromuscular clinical signs of hypomagnesemia are more frequently appreciated in large animal internal medicine where severe muscle tetany and seizure are identified in cattle with "grass staggers."

Magnesium is also a vital co-factor for ATP. Given that ATP is the critical energy source for many cellular ion pumps, such as Na+K+ATPase, HCO_3^-ATPase, and Ca^{2+}ATPase, variation in magnesium availability may influence the concentration of intracellular electrolytes such as calcium and potassium.

Regulation of Magnesium

Magnesium homeostasis is incompletely understood but, in a similar manner to calcium and phosphorus, gastrointestinal absorption, renal reabsorption/excretion, and exchange with skeletal stores are important factors in maintaining total body and extracellular magnesium concentrations. Absorption of magnesium in the intestine primarily occurs in the ileum, with further absorption in the jejunum and colon. Intestinal absorption of magnesium is via either a passive paracellular or active transcellular route. Active transport of magnesium in the gut is likely to involve specific magnesium transport proteins, including those from the transient receptor potential (TRP) family such asTRPM6 and TRPM7. Magnesium is freely filtered at the glomerulus but in contrast to other electrolytes, the primary site for reabsorption is the loop of Henle (60–70%), with lesser contributions in the proximal tubule (15%) and distal convoluted tubule (10–15%).

Hormonal regulation of magnesium absorption in the intestine and kidney likely occurs but remains incompletely understood. Parathyroid hormone, calcitonin, glucagon, antidiuretic hormone, aldosterone, and insulin can all increase absorption of magnesium whilst prostaglandin E2, hypokalemia, hypophosphatemia, and acidosis may all reduce magnesium reabsorption.

Laboratory Assessment of Magnesium

Making an assessment of total body hypomagnesemia can be challenging due to the high proportion of magnesium that is present within an intracellular location. Currently there is no consensus with regard to the optimal methodology to assess total body magnesium status.

Quantification of either total or ionized magnesium concentrations can be performed. However, total serum or plasma magnesium concentrations do not correlate well with signs of hypomagnesemia and may not correlate with ionized concentrations. Other factors such as albumin concentrations, sample handling, and acid–base status may influence measured total serum magnesium concentrations. As ionized magnesium equilibrates rapidly across cell membranes, it may be a more representative measure of intracellular magnesium but uncertainty exists as to whether it provides a true reflection of total body magnesium. Quantification of magnesium within red or white blood cells or muscle tissue, and assessment of renal handling of magnesium (e.g., 24-hour urinary excretion or evaluation of magnesium retention) may give further information regarding magnesium status but these methodologies are not routinely available as clinical diagnostic tests.

In those patients where clinical signs are compatible with hypomagnesemia, a low total or ionized magnesium concentration will provide support that clinical signs may be attributable to hypomagnesemia. However, it should be appreciated that intracellular hypomagnesemia can be present with normal serum total or ionized magnesium concentrations.

Hypomagnesemia

A number of clinical causes of hypomagnesemia can be identified (Box 119.4) reflecting increased gastrointestinal loss, reduced intestinal absorption, redistribution between the intracellular and extracellular compartments, or increased renal excretion. The clinical consequences of hypomagnesemia can include electrolyte and neuromuscular abnormalities and cardiac arrhythmias. However, with mild hypomagnesemia, clinical signs can be vague and attributable to general illness.

In human medicine, hypomagnesemia is a commonly reported electrolyte abnormality in critical care populations and is an independent risk factor for mortality. Studies suggest that in veterinary medicine, between 28% and 50% of cats and dogs in a critical care setting also demonstrate hypomagnesemia but information regarding any association with survival, morbidity or mortality is lacking. Other aspects of illness often identified in a critical care setting (e.g., sepsis) or associated treatments (e.g., blood transfusions due to citrate administration, intravenous fluid therapy, insulin administration) may increase a patient's predisposition to develop hypomagnesemia.

Hypomagnesemia has perhaps received most attention for the role it plays in concurrent electrolyte disturbances. Magnesium facilitates potassium leaving the intracellular compartment and enhances renal loss of

Box 119.4 Common clinical conditions associated with hypomagnesemia

- Gastrointestinal loss
  - Anorexia
  - Malabsorption/severe diarrhea
  - Short bowel syndrome
- Renal loss
  - Diabetes mellitus/diabetic ketoacidosis
  - Chronic kidney disease
  - Renal tubular acidosis
  - Drugs: loop diuretics
  - Renal transplantation
- Miscellaneous
  - Eclampsia
  - Redistribution
    - Severe pancreatitis
    - Sepsis
    - Refeeding syndrome
    - Catecholamine excess (pheochromocytoma)
    - Large-volume resuscitation with magnesium-replete fluid

potassium such that hypomagnesemia and hypokalemia occur simultaneously. Clinical signs in this situation usually reflect hypokalemia but potassium deficiency may prove refractory to therapy until magnesium levels have also been corrected. Hypocalcemia has also been reported in conjunction with hypomagnesemia.

In human patients, magnesium deficiency has been reported to contribute to the development and severity of atrial fibrillation, supraventricular tachycardia, and ventricular tachyarrhythmias. Information regarding hypomagnesemia in dogs and cats with cardiac disease is limited and the clinical importance is therefore uncertain. However, certain drugs commonly used in cardiac patients such as digoxin and loop diuretics increase magnesium loss. Patients with cardiac disease that develop hypomagnesemia may be at risk of cardiac arrhythmias, decreased cardiac contractility, and refractory hypokalemia. Consideration could therefore be given to assessment of magnesium concentrations in these situations.

Magnesium deficiency due to reduced dietary intake is unlikely, particularly if commercial diets are being fed, but could occur in patients with prolonged anorexia or severe gastrointestinal disease such as chronic diarrhea, malabsorptive disease, and short bowel syndrome. Hypomagnesemia has previously been reported in dogs with protein-losing enteropathy (PLE) and as a component of refeeding syndrome when increased cellular demand occurs in addition to chronic depletion secondary to prior anorexia.

Hypomagnesemia has also been reported in association with a number of endocrine conditions, for example, in cats with hyperthyroidism, diabetes mellitus, and diabetic ketoacidosis. However, the clinical significance of these associations is still uncertain and a study evaluating magnesium concentrations in dogs with diabetes mellitus did not find an association.

Hypomanesemia may be identified in lactating bitches although is rarely clinically significant in the healthy bitch. The prevalence of hypomagnesemia in bitches with eclampsia has been reported to be 44%.

Treatment of Hypomagnesemia

Magnesium supplementation should be considered when a patient's clinical signs are attributable to hypomagnesemia. Supplementation may also be indicated in those patients with refractory hypokalemia or hypocalcemia despite appropriate potassium and calcium supplementation respectively.

Intravenous magnesium supplementation is usually provided as magnesium sulfate or magnesium chloride. Typical dosages reported are 0.03–0.04 mEq/kg/h administered as a CRI diluted in 5% dextrose or 0.9% saline. Magnesium salt concentrations >20% should not be administered and magnesium salt solutions are not compatible with calcium- or bicarbonate-containing fluids. Careful monitoring should be performed during administration to avoid inadvertent overdosage and supplementation continued until low normal concentrations have been achieved and maintenance magnesium requirements can be provided via the patient's daily dietary intake. Caution should be exercised when providing magnesium supplementation, particularly in those patients with reduced renal function where risk of development of hypermagnesemia is increased. The value of chronic supplementation is uncertain in veterinary medicine but oral supplementation with magnesium oxide (1–2 mEq/kg/day) has been reported.

Reports of magnesium supplementation in the veterinary literature have also included patients with tetanus where supplemental magnesium may aid in reducing muscle spasm and sedative requirements, and in patients with cardiac arrhythmias where hypomagnesmia is deemed contributory.

Hypermagnesemia

The kidney excretes excess magnesium. Hypermagnesemia may occur with any marked reduction in GFR. It is rare for dogs and cats to demonstrate clinical signs associated with mild to moderate hypermagnesemia. Clinical signs reported with severe hypermagnesemia can include depression, weakness, lethargy, flaccid paralysis, and decreased reflexes. Hypotension may be

documented secondary to decreased total peripheral resistance. Bradycardia may be identified associated with prolongation of the QRS complex and an increased P-Q interval. Untreated, severe hypermagnesemia will result in ventricular fibrillation, asystole, and death.

Iatrogenic hypermagnesemia has been reported in human medicine in children associated with excessive use of magnesium-containing laxative agents and antacids. In veterinary medicine, iatrogenic hypermagnesemia has been reported in a dog and a cat due to oversupplementation. These patients demonstrated magnesium concentrations 7–9 times the normal reference interval and clinical signs including hypotension and bradycardia. This emphasizes the need for careful dose calculation and monitoring during magnesium supplementation. Increased magnesium concentrations have also been reported in dogs with hypoadrenocorticism and after surgery/anaesthesia although these changes were not clinically significant.

Treatment of hypermagnesemia depends on severity and should involve discontinuation of any supplementation being provided. Saline diuresis and administration of loop diuretics may increase magnesium renal excretion. In an acute situation with arrhythmias secondary to hypermagnesemia, calcium gluconate should be administered (50–150 mg/kg) as a bolus over 20–30 minutes to reverse cardiac toxicity. In human medicine, in certain clinical situations, dialysis may also be used for correction of hypermagnesemia.

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120

Acute Kidney Injury

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Etiology/Pathophysiology

Acute kidney injury (AKI) has classically been categorized into hemodynamic (prerenal), renal parenchymal (intrinsic), and postrenal etiologies. Hemodynamic causes include decreases in renal perfusion and/or excessive vasoconstriction, and are characterized as rapidly reversible if the inciting cause is eliminated shortly after occurrence. It is questionable whether hemodynamic changes resulting in azotemia represent true renal injury or an appropriate physiologic attempt to conserve fluid volume as a response to a reduced effective circulating blood volume. Neurohumoral responses to reductions in effective circulating volume result in a reduction in renal blood flow and, thus, glomerular filtration rate (GFR) as a means of conserving fluid volume. Regardless of whether the hemodynamic changes represent pathology or physiology, it is generally accepted that prolonged ischemia can contribute to renal parenchymal injury.

Intrinsic causes of AKI include infectious diseases, toxins, and systemic diseases with renal manifestations. Removal of the inciting cause of parenchymal injury is often the only means of directly addressing this type of insult. Postrenal AKI is due to obstruction or diversion of urine flow, including urethral obstruction, bilateral ureteral obstruction or unilateral obstruction with a nonfunctional contralateral kidney, or rupture of any portion of the urinary tract. Restoration of urine flow may rapidly reduce the concentrations of circulating uremic toxins. However, prolonged obstruction of urine flow may lead to renal parenchymal injury.

During the diagnostic evaluation for AKI, it is important to recognize that (1) the classic etiologies of AKI frequently produce insults that encompass more than one of the hemodynamic, intrinsic, or postrenal processes and (2) an etiologic cause of AKI is frequently not identified. Table 120.1 provides an extensive, but not exhaustive, list of etiologies for canine and feline AKI.

The pathophysiologic process of AKI is often multifactorial, with overlapping ischemic, inflammatory, toxic, and septic components. Classically, the clinical course of AKI proceeds through four phases. These phases are defined by experimental models of ischemic acute kidney injury and may not be representative of the multifactorial nature of the disease.

The *initiation* phase is characterized by the first stages of renal injury. Intervention at this phase may prevent progression to more severe injury, but injury at this stage occurs on a subcellular level and may not be biochemically evident. During the *extension* phase, cellular injury progresses to cell death. At this stage, biochemical derangements and clinical manifestations of disease manifest. During the *maintenance* phase, both cell death and regeneration occur simultaneously, and the potential for and length of recovery from this phase may be determined by the balance between these processes. Removal of the initiating cause at this stage does not alter the existing damage, but may allow for the balance to shift in favor of parenchymal regeneration. The *recovery* phase is characterized by improvement in GFR and tubular function; this final phase may last weeks to months.

Epidemiology

The epidemiology of AKI has not been thoroughly characterized in veterinary medicine. The difficulty in establishing the population characteristics of this disease is primarily related to the lack of a standard definition for AKI and the wide spectrum of disease (ranging from clinically undetectable, subcellular damage to fulminant, excretory failure). This problem previously

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Table 120.1 List of etiologies for canine and feline acute kidney injury

Nephrotoxins

Antimicrobial agents
Aminoglycosides
Aztreonam
Carbapenems
Cephalosporins
Penicillins
Polymyxins
Quinolones
Rifampin
Sulfonamides
Tetracyclines
Vancomycin

Antifungal agents
Amphotericin B

Antineoplastic drugs
Cisplatin and carboplatin
Doxorubicin
Methotrexate

Antiviral agents
Aciclovir
Foscarnet

Antiprotozoal agents
Dapsone
Pentamidine
Sulfadiazine
Thiacetarsamide
Trimethoprim-sulfamethoxazole

Immunosuppressive drugs
Azathioprine
Calcineurin inhibitors (e.g., ciclosporin, tacrlimus)
Interleukin-2

Miscellaneous therapeutic agents
Acetaminophen
Allopurinol
Angiotensin enzyme converting inhibitors
Antidepressants
Apomorphine
Cimetidine
Deferoxamine
Dextran-40
Diuretics
epsilon-Aminocaproic acid
EDTA
Lipid-lowering drugs
Lithium
Methoxyflurane
Nonsteroidal antiinflammatory drugs
Penicillamine
Phosphorus-containing urinary acidifiers
Streptokinase
Tricyclic antidepressants
Vitamin D analogs

Endogenous compounds
Hemoglobin
Myoglobin (e.g., trauma/rhabdomyolysis)

Heavy metals
Antimony
Arsenic
Bismuth salts
Cadmium
Chromium
Copper
Gold
Lead
Mercury
Nickel
Silver
Thallium
Uranium

Organic compounds
Carbon tetrachloride and other chlorinated hydrocarbons
Chloroform
Ethylene glycol
Herbicides
Pesticides
Solvents

Miscellaneous nontherapeutic agents
Bee venom
Diphosphonate
Calcium antagonists
Gallium nitrate
Grapes or raisins
Illicit drugs
Lilies
Mushrooms
Radiocontrast agents
Snake venom
Sodium fluoride
Superphosphate fertilizer
Vitamin D-containing rodenticides, "Jerky treats"

Nonnephrotoxic insults

Decreased cardiac output/ischemia
Volume depletion
Congestive heart failure
Arrhythmias
Cardiac arrest
Cardiac tamponade
Fluid overload
Deep anesthesia/extensive surgery
Renal vessel thrombosis
Hyperviscosity – polycythemia
Hepatorenal syndrome

Infectious
Bacterial/fungal
Pyelonephritis
Leptospirosis
Borreliosis
Feline infectious peritonitis
Babesiosis
Leishmaniasis
Bacterial endocarditis

Immune-mediated inflammatory
Acute glomerulonephritis
Systemic lupus erythematosus
Renal transplant rejection
Vasculitis
Systemic inflammatory response syndrome
Sepsis
Disseminated intravascular coagulation

Obstructive
Ureteral obstruction
Urethral obstruction

Miscellaneous
Lymphoma
Blood transfusion reactions
Heatstroke/hyperthermia
Malignant hypertension
Neoplasia
Hypercalcemia

existed in human medicine, but has largely been overcome by the development of standardized classification schemes. The most widely accepted schemes are the Risk Injury Failure End Stage Kidney Disease (RIFLE) scheme, the Acute Kidney Injury Network (AKIN), and the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury. Both sets of criteria appear to perform equally well when both sensitivity for detection of AKI and predictive ability of adverse outcomes are evaluated and, therefore, these schemes have become accepted within the human nephrology community as the standard means of defining AKI for epidemiologic characterization.

There is considerable difficulty, however, with application of these criteria to veterinary AKI because both RIFLE and AKIN schemes primarily rely on relative changes in serum or plasma creatinine concentrations. In contrast to human medicine, in which most cases of AKI are hospital acquired and as such, relative changes in serum or plasma creatinine concentrations are more easily measured, most cases of veterinary AKI currently recognized are community acquired, and a baseline serum or plasma creatinine concentration is not available. Additional criteria for identification and staging of AKI exist within these schemes, but these criteria also have limitations (e.g., lack of baseline value for GFR and practical considerations of indwelling urinary collection system for monitoring of urine output). Nonetheless, recently published retrospective data collected from hospitalized dogs, utilizing a scheme similar to AKIN (Table 120.2), suggest that an association between small changes in plasma creatinine concentration (≥0.3 mg/dL) and mortality may exist.

Due to the limitations associated with defining and staging AKI based on relative changes in serum or plasma creatinine, Cowgill recently proposed a veterinary staging scheme based primarily on absolute serum or plasma creatinine concentrations (Table 120.3). This proposed scheme is being validated in a prospective study that is currently under way.

Table 120.2 Veterinary Acute Kidney Injury (VAKI) staging scheme for dogs

VAKI stage	Criteria
Stage 0	Creatinine increase <150% from baseline
Stage 1	Creatinine increase of 150–199% from baseline OR Creatinine increase of 0.3 mg/dL from baseline
Stage 2	Creatinine increase of 200–299% from baseline
Stage 3	Creatinine increase of ≥300% from baseline OR An absolute creatinine value of >4.0 mg/dL

Table 120.3 International Renal Interest Society grading scheme for acute kidney injury (AKI) (dogs and cats)

Grade	Creatinine	Clinical description
Grade I	<1.6	**Nonazotemic AKI** – Documented AKI: historical, clinical, laboratory, or imaging evidence of acute kidney injury, clinical oliguria/anuria, volume responsiveness[a] and/or – Progressive *nonazotemic* increase in serum creatinine ≥0.3 mg/dL (≥26.4 µmol/L) within 48 hours – Measured oliguria (<1 mL/kg/h) or anuria over 6 hours
Grade II	1.6–2.5	**Mild AKI** – Documented AKI and static or progressive azotemia – Progressive azotemic increase in serum creatinine ≥0.3 mg/dL (≥26.4 µmol/L) within 48 hours, or volume responsiveness[b] – Measured oliguria (<1 mL/kg/h) or anuria over 6 hours
Grade III	2.6–5.0	**Moderate to severe AKI** – Documented AKI and increasing severities of azotemia and functional failure
Grade IV	5.0–10.0	
Grade V	>10.0	

[a] Volume responsive is an increase in urine production to >1 mL/kg/h over 6 hours and/or decrease in serum creatinine to baseline over 48 hours.
[b] Each grade of acute kidney injury is further substaged on the basis of current urine production as oliguric (O) or nonoliguric (NO) and on the requirement for renal replacement therapy (RRT).

Signalment

To date, there are no studies that document an age, sex, or breed predisposition for acute kidney injury. Within certain etiologies, however, predispositions based on signalment may exist. For example, epidemiologic studies have shown an increased risk for positive *Leptospira* serology in male dogs and herding dogs, hounds, working dogs, and mixed breed dogs. German shepherds, in particular, appear to be overrepresented for leptospirosis manifesting clinical signs. Risk factors for AKI based on signalment and etiology may be more readily identified once a standard definition/classification scheme for AKI has been established.

History and Clinical Signs

Common historical findings include lethargy, vomiting, diarrhea, and anorexia, but these signs are nonspecific and may be the result of a variety of extrarenal diseases. Oliguria, anuria, or polyuria may be reported. When a patient is polyuric, compensatory polydipsia may be present, or water intake may be reduced due to anorexia.

When patients are severely affected, reports of seizures, syncope, and dyspnea may overshadow more classic presenting signs associated with AKI.

Physical examination yields few findings specific to AKI, aside from enlarged, painful kidneys. Renomegaly and renal angina are inconsistently present, however, and for some cases in which underlying chronic kidney disease is present, the kidneys are small. Dehydration is a common finding at the time of initial presentation. However, inaccurate assessment of hydration status by physical examination parameters is common, and many euhydrated and overhydrated patients are erroneously categorized as dehydrated. Other findings may include halitosis, oral ulceration, tongue tip necrosis, scleral injection, bradycardia, cutaneous bruising, peripheral edema, and melena/diarrhea. These findings may be secondary to uremia or associated with the primary disease process resulting in AKI (e.g., disseminated intravascular coagulation [DIC], vasculitis). Hypothermia is a frequent finding and, in the absence of circulatory shock, is typically associated with alteration of the hypothalamic thermoregulatory set point. Normothermia or hyperthermia may be suggestive of an infectious, inflammatory, or immune-mediated etiology.

Diagnosis

Acute kidney injury is typically diagnosed on the basis of a combination of history, physical examination findings, and the results of laboratory and imaging tests. For some patients that present with azotemia and clinical signs associated with uremia, discrimination between AKI, chronic kidney disease, or an acute kidney injury superimposed on chronic kidney disease may be difficult. For many cases in which the chronicity of disease is not readily apparent, previous laboratory work is not available for establishment of baseline renal function and imaging discloses no renal abnormalities. Therefore, subtle findings in the clinical history, physical examination, and laboratory work may prove vital in determining chronicity, which has a large influence on the appropriate diagnostic, therapeutic, and prognostic algorithms.

Laboratory Tests

The complete blood count may show hemoconcentration or anemia secondary to gastrointestinal (GI) blood loss, hemolysis, or hemodilution. The platelet count may be normal or low, although platelet count alone should not be used to determine functionality of primary hemostasis, as uremia and various infectious diseases (e.g., leptospirosis) induce a thrombocytopathy. An infectious or immune-mediated etiology should be suspected when severe leukocytosis is present.

The serum/plasma biochemistry panel may show changes specific to renal dysfunction (e.g., azotemia and hyperphosphatemia) or changes associated with multisystemic disease. The severity of azotemia depends on the etiology and duration of AKI. The ratio of blood urea nitrogen to creatinine can be high from GI bleeding or dehydration, or it can be low in early stages of AKI. The degree of hyperphosphatemia typically mirrors that of hypercreatinemia with a few exceptions (e.g., acute ethylene glycol intoxication, juvenile growing animal, refeeding syndrome). Ionized calcium concentrations are normal or low (provided that hypercalcemia is not a cause of AKI). Ethylene glycol intoxication causes a profound ionized hypocalcemia, due to both severe hyperphosphatemia and chelation of calcium by oxalate.

The anion gap is usually high secondary to retained organic and inorganic acids, but can be normal early in the course of disease, or if hypoalbuminemia is present. A high anion gap without (or prior to) the presence of azotemia is supportive of intoxication in cases of suspected ethylene glycol exposure. The anion gap is calculated by the formula:

$$\text{Anion gap} = \left(Na^+ + K^+\right) - \left(HCO_3^- + Cl^-\right)$$

where Na^+ = sodium, K^+ = potassium, HCO_3^- = bicarbonate, and Cl^- = chloride. The normal anion gap is approximately 12–26 mEq/L, with the average anion gap being 5 mEq/L higher in cats than dogs.

Urinalysis can provide information regarding the etiology and severity of AKI. Care must be taken, however, to examine urine shortly after collection to avoid artifactual changes in biochemical and cellular composition. The urine specific gravity is frequently isosthenuric (1.007–1.015) in cases of intrinsic failure. A urine dipstick may reveal any combination of glucosuria (without hyperglycemia), proteinuria, bilirubinuria, and hemoglobinuria, depending on the underlying etiology. Glucosuria is frequently present in cases of leptospirosis and AKI associated with jerky treat ingestion. Proteinuria is frequently present, but qualitative (dipstick) and quantitative (protein:creatinine ratio) severity can vary within a specific etiology. The urine pH is usually acidic, unless there is a concurrent bacterial urinary tract infection. Careful microscopic assessment of urine sediment may disclose dysmorphic red blood cells (suggestive of glomerular disease), pyuria (suggestive of nephritis), or casts (most frequently granular, but red and white blood cell casts are uncommonly observed). In human medicine, eosinouria has historically been associated with acute interstitial nephritis (secondary to a drug reaction). However, more recent publications have shown that this finding lacks the satisfactory test characteristics to make it useful in the identification of this specific etiology. Calcium oxalate crystals if present in large numbers are supportive of

ethylene glycol intoxication, although a few oxalate crystals may be present in the urine of healthy patients (crystalluria is a common *in vitro* artifact that is secondary to prolonged storage of urine prior to analysis). An in-house variation of a Romanowsky stain is frequently useful for detailed assessment of red and white blood cell morphology, as well as for the identification of bacteria. A bacterial urine culture is important to confirm the presence of a urinary tract infection and to guide antimicrobial therapy.

Imaging

Survey abdominal radiographs may show a normal renal silhouette or renomegaly, but hydronephrosis cannot be detected by radiography. Nephroliths or ureteroliths may be apparent, provided they are above the limit of detection. Although radiography and ultrasonography are typically complementary (ureteral calculi that may be obscured by gas or ingesta during ultrasonography frequently can be detected by radiography), ultrasonography typically provides more information.

Abdominal ultrasonography usually shows normal or enlarged kidneys with normal parenchymal architecture. Perirenal fluid is commonly seen with a variety of etiologies. It is important to note, however, that many (especially geriatric) patients with AKI may have underlying chronic kidney disease, which may manifest as ultrasonographic changes such as decreased corticomedullary definition, cysts, infarcts, small size, and irregular renal contour. The presence of ultrasonographic changes consistent with chronic kidney disease does not preclude the possibility of an acute injury superimposed on chronic kidney disease. Likewise, normal ultrasonographic renal architecture does not rule out the possibility of chronic kidney disease.

Oxalate crystal deposition in the kidneys increases the echogenicity with ethylene glycol intoxication, making the renal cortices and, to a lesser extent, the medulla hyperechoic. Obstruction is characterized by renal pelvic dilation or hydronephrosis. Historically, pyelonephritis has been associated with renal pelvic dilation. However, this ultrasonographic sign is associated with a variety of other lesions and is not pathognomonic for renal infection. An intravenous pyelogram can aid in the identification of pelvic, ureteral, and cystic disease processes, especially obstructive renal lesions that are not readily apparent with survey radiography or ultrasound. In addition, it can provide information regarding renal function in the contralateral kidney (i.e., if uptake of radiocontrast is not detectable in the renal parenchyma or collecting system, the likelihood of a substantial GFR in that kidney is low). If the GFR in an obstructed kidney is below a certain threshold, an intravenous pyelogram will result in inadequate study quality due to poor uptake of contrast. Antegrade pyelography may be a better choice for ureteroliths, as this technique does not rely on an adequate GFR for proper distribution of contrast material. Computed tomography or magnetic resonance imaging can add information about renal architecture and better characterize obstruction, but are infrequently utilized.

Other Diagnostic Modalities

Measurement of GFR (e.g., iohexol clearance, endogenous creatinine clearance, scintigraphy) can be expensive and some techniques are not readily available. These studies have limited applicability in the initial treatment of AKI, as the degree of impairment in GFR is almost always detectable by surrogate markers, such as serum or plasma creatinine concentration. Typically, following a diagnosis of AKI with serum or plasma creatinine and urea concentrations, no additional tests are useful in confirming that renal impairment is present or further characterizing the degree of impairment.

Leptospira serology detects antibodies produced in response to organism or vaccine exposure. There are multiple limitations to the application of this test. While there is considerable cross-reactivity among different *Leptospira* serovars, most available assays test a maximum of seven serovars and, due to the large number (>250) of potentially pathogenic serovars, this limitation may lead to false-negative test results. Titers may also be negative within the first 7–10 days of illness; a fourfold rise after 2–4 weeks is used to confirm exposure when initial titers are negative. A single titer of 1:800 or greater, with appropriate clinical signs and in the absence of recent vaccination, is also suggestive of *Leptospira* spp. exposure. However, there is a high degree of discordance in interpretation of leptospirosis among different commercial laboratories, potentially affecting interpretation of borderline results. A strong clinical suspicion for leptospirosis must be present with titers in excess of 1:800 for serovar Autumnalis, as titers often increase parallel to vaccinal serovars and with other diseases. While the microscopic agglutination test remains the gold standard for leptospira serology, new antibody detection kits are now commercially available that allow more rapid and inexpensive detection of circulating antibodies. These newer assays do not disinguish serovars.

Polymerase chain reaction assays for both blood and urine have been developed for rapid, early diagnosis in dogs, but data on their clinical utility are lacking.

Serologic tests for other infectious diseases known to cause AKI, such as Rocky Mountain spotted fever (*Rickettsia rickettsii*), *Ehrlichia canis*, Lyme disease (*Borrelia burgdorferi*), *Babesia* spp., or *Leishmania* spp., may be useful in certain areas or when there are other consistent clinical or pathologic signs, although a positive titer does not prove causality of AKI.

Cytology of tissue acquired by fine needle aspirates has limited utility in cases of AKI, but can aid in detection of an infiltrative etiology. Cytology for the diagnosis of renal lymphosarcoma may produce false-negative results. Therefore, for cases in which lymphosarcoma is suspected, histopathologic assessment of tissue may be necessary to rule out this etiology. Diagnosis of amyloidosis and feline infectious peritonitis requires special cytologic techniques (e.g., Congo red staining or coronavirus immunocytochemistry, respectively), and these diagnostic techniques have not been rigorously assessed. The risk of bleeding secondary to fine needle aspiration of the kidneys is low but possible, especially when platelet dysfunction is present.

Histopathologic samples can be obtained by percutaneous, ultrasonographically guided needle biopsy, laparoscopy, or surgical wedge biopsy. Histopathology may confirm a suspected etiology (e.g., ethylene glycol intoxication, renal lymphosarcoma) or it may disclose nonspecific findings. When AKI cannot be clinically distinguished from end-stage chronic kidney disease, histopathology (particularly Masson's trichrome stain) can aid in assessment of the severity of fibrosis and provide insight into the potential for renal recovery. The risk of significant hemorrhage secondary to renal biopsy is high when uremia is severe and platelet dysfunction is present.

Ethylene glycol intoxication is an emergency situation requiring immediate, specific therapy, which makes accurate and timely diagnosis crucial. Commercially available in-house test kits are available.

Therapy

Treatment of AKI is primarily aimed at addressing the underlying cause (if it can be identified and treated) and supportive measures to minimize the clinical sequelae of uremia. This section provides treatment recommendations for cases of severe AKI, in which severe uremic manifestations and abnormalities of acid–base, electrolyte, and fluid balance dominate the clinical picture. Specific doses for many of the drugs discussed are listed

Table 120.4 Indications, doses, adverse effects, and comments for drugs frequently used in cases of acute kidney injury

Drug	Indication	Dose	Adverse effects	Comments
Furosemide	Fluid overload, oliguria/anuria, hyperkalemia	2–5 mg/kg IV bolus, may be repeated up 3–5 times; 0.5–1 mg/kg/h CRI if urine production increased following bolus	Ototoxicity; volume depletion (unlikely if patient is monitored)	Results are frequently not satisfactory in cases of severe AKI, but adverse effects minimal so use in anuric AKI
Regular insulin	Hyperkalemia	0.5 units/kg IV or IM, may be repeated q4–6h provided hypoglycemia is avoided	Hypoglycemia	Hypokalemic effect modest and transient; IV dextrose must be administered concurrent with and following insulin administration
Dextrose	Hyperkalemia; avoidance of hypoglycemia following insulin administration	IV bolus of 2 g/unit of insulin administered; bolus followed by CRI (dextrose concentration and administration rate are dependent on serial blood glucose concentrations, patient's fluid status, and accessibility of central line)	Hyperglycemia, hyperosmolarity, hyponatremia, phlebitis with high dextrose concentrations	Dextrose should be diluted to avoid phlebitis; frequent changes in dextrose CRI often necessary based on serial blood glucose measurements
Calcium gluconate (10%)	Hyperkalemia; symptomatic hypocalcemia	0.5–1.5 mL/kg of 10% solution or 50–150 mg/kg IV slowly, to effect, while monitoring ECG, may be repeated	Worsening bradycardia and ECG changes; hypercalcemia; soft tissue mineralization	ECG should be monitored during administration; will not affect extracellular potassium concentration; effective in rapidly normalizing ECG, but results transient; administration of large volumes may contribute to soft tissue mineralization
Sodium bicarbonate	Severe acidemia	1/4 to 1/3 of the base deficit over 30–60 min followed by an additional 1/4 over the next 4–6 hours; additional dosing based on serial blood gas analyses	Paradoxic central nervous system acidosis; hypernatremia; fluid overload; hypochloremia; may cause or exacerbate hypokalemia if patient is polyuric; may exacerbate hypocalcemia	Requires close monitoring of blood gases and electrolytes for effective treatment and avoidance of adverse effects

CRI, continuous rate infusion; ECG, electrocardiogram; IM, intramuscular; IV, intravenous.

in Table 120.4. While renal replacement therapy (dialysis) is referenced, it is discussed in greater detail in Chapter 126.

Fluid Therapy

To ensure adequate tissue perfusion, extracellular fluid deficits should be corrected with a balanced polyionic solution. Ultimately, the type of fluid administered must be guided by monitoring of serum or plasma concentration of electrolytes because the degree of solute and free water balance varies widely in patients with AKI. Colloidal support may also be considered to reduce the total amount of fluid administered, if oliguria or anuria is suspected, although no benefit over crystalloid therapy has been documented in human or veterinary medicine. Goal-directed therapy to restore surrogate markers of perfusion (e.g., blood pressure, venous lactate concentration, venous oxygen saturation) should be employed with endpoints set to be reached within 24 hours. If oliguria or anuria persists despite achievement of normal surrogate markers of perfusion, additional fluid administration is more likely to result in fluid overload than urine production. Avoidance of fluid overload (typically defined as fluid accumulation >10% of baseline body weight) is essential, as there is ample evidence documenting the association between fluid overload and worse clinical outcomes.

Maintenance fluid administration (both volume and composition) should be guided by the volume and composition of urine produced, as well as ongoing sensible losses (vomitus, diarrhea, and yield from gastric suction) and insensible loss (respiration, formed stool). Urine volume can be determined by a variety of methods, including:

- indwelling urinary catheter and closed collection system
- collection of naturally voided urine
- metabolic cage
- weighing cage bedding and litter pans (1 mL of urine = 1 g)
- using body weight prior to and immediately following urination.

Urine production can be categorized as anuria (none to negligible amount), oliguria (<0.5 mL/kg/h), or polyuria (>2 mL/kg/h). Insensible losses can be estimated between 12 and 29 mL/kg/day and are dependent on a variety of factors, such as species, patient activity, and body temperature. Careful attention must be given to serial changes in the patient's body weight, as peracute fluctuations in weight are most likely due to changes in fluid balance rather than changes in lean muscle or fat content.

Once the patient's fluid deficit has been corrected, care must be taken to maintain a neutral fluid balance, as well as normal surrogate markers of perfusion. Consideration of the fluid load with enteral and parenteral nutrition and medication, as well as intravenous catheter flushes, is essential to avoidance of fluid overload, and the fluid volume administered with these treatments should be incorporated into the fluid plan. High-maintenance fluid rates have been historically advocated for cases of AKI based on the rationale that high-volume fluid administration beyond that which is necessary to restore normal volume status will improve GFR. However, there is no evidence supporting this claim and, in the author's experience, this practice is often futile in restoring GFR and frequently results in fluid overload.

Maintenance fluid therapy for an anuric, euhydrated patient should consist of replacement of insensible losses only. Frequently, this fluid requirement is achieved in excess by administration of medications, nutrition, and catheter flushes alone and the administration of these treatments may promote fluid overload. If the patient is diagnosed with fluid overload, all fluid therapy should be withheld. Fluid overload with concurrent oliguria or anuria is a clear indication for dialysis.

Monitoring fluid status is an ongoing process that must be repeated frequently. Efforts should be made to adhere to objective monitoring parameters (e.g., body weight, venous lactate concentration, urine production) of fluid status because subjective parameters, (e.g., skin turgor, saliva production) are inaccurate and often affected by variables other than hydration status. Body weight should be measured at least twice daily to assess for trends in fluid accumulation or deficit. Central venous pressure measurement has traditionally been recommended as a surrogate marker of cardiac preload, and thus fluid status. However, a thorough understanding of the limitations of this technique is necessary for appropriate interpretation, as the correlation between central venous pressure and clinical manifestations of fluid overload is increasingly recognized as flawed.

Diuretics

The use of diuretics in the treatment of AKI is a controversial topic in both human and veterinary medicine. Many of the benefits of the most commonly used diuretics in veterinary AKI, furosemide and mannitol, have only been theorized or demonstrated in experimental models of AKI. In fact, there is little or no clinical evidence in human or veterinary medicine that diuretics improve outcome in established AKI. It has been postulated that the ability to respond to diuretics is a marker of less severe renal injury associated with a better prognosis. However, an increase in urine output after diuretic administration does not necessarily coincide with an increase in uremic solute excretion and, therefore, does not preclude the need for dialysis if severe uremia or acid–base and electrolyte abnormalities persist.

In veterinary medicine, because dialysis is not readily available, diuretic administration plays a large role in volume management. Conversion from an oliguric or anuric state to normal urine production or polyuria may enhance the clinician's ability to prevent or manage fluid overload and thus allow administration of necessary parenteral medications and nutrition that would otherwise contribute to fluid overload. No class of diuretics has been proven to be superior to another. However, the use of loop diuretics predominates in both human and veterinary AKI due to the relatively high efficacy and safety margin of these drugs, compared to the osmotic diuretics. For this reason, the author does not recommend the use of mannitol as a diuretic for AKI.

Acid–Base Balance

Metabolic acidosis is a frequent complication in AKI of varying severities, and is due to the damaged nephron's inability to excrete hydrogen ions and reabsorb bicarbonate ions, as well as lactic acidosis secondary to compromised tissue perfusion (i.e., either volume deficit or excess). Once perfusion has been restored, provision of supplemental alkali, usually in the form of parenteral sodium bicarbonate, should be considered if severe acidemia (pH <7.2, bicarbonate <12 mmol) persists. The bicarbonate dosage can be calculated from the formula:

$$0.3 \times \text{body weight}\ (\text{kg}) \times \text{base deficit} = \text{bicarbonate}\ (\text{mEq/L})$$

where the base deficit = 24 mEq/L – (patient bicarbonate concentration). One-fourth to one-third of the dose should be given intravenously as a slow bolus, and an additional one-fourth over the next 4–6 hours. Subsequent doses should be based on serial venous blood gas analyses.

Bicarbonate administration to a hypoventilating patient can further increase the partial pressure of carbon dioxide and can lead to paradoxical central nervous system (CNS) acidosis. This phenomenon is due to the ability of carbon dioxide to diffuse across the blood–brain barrier, while the charged bicarbonate molecule diffuses across this barrier less readily. An additional drawback to parenteral sodium bicarbonate administration is that most formulations have high osmolality (e.g., 8.4% solution = 1 mEq/mL = 2000 mosm/L). Therefore, this solution must be diluted prior to administration, and the total volume administered must be factored into the fluid therapy plan. Provision of bicarbonate during dialysis is as effective in restoring extracellular acid–base status as sodium bicarbonate infusion, and has the added advantage of avoiding the fluid load necessary with the latter treatment. While there is no evidence in the form of randomized controlled trials supporting supplementation of alkali in human AKI, it is recommended in veterinary AKI when dialysis is not available.

Electrolyte Balance

Hyperkalemia can be an immediately life-threatening complication of AKI and is secondary to a decline in renal excretory function. Excitable cells become refractory to repolarization, thus resulting in decreased conduction of both cardiac and neuromuscular tissue. Typical electrocardiographic changes include bradycardia, tall T-waves, shortened QT intervals, wide QRS complexes, and small, wide, or absent P-waves. Severe hyperkalemia can lead to sine waves, ventricular fibrillation, or standstill. There are a variety of pharmacologic treatments available for emergent hyperkalemia, but these therapies act to translocate potassium to the intracellular space or increase the resting membrane potential to allow repolarization of excitable cells, rather than enhance excretion of potassium. The efficacy of these treatments is typically modest and transient. Only provision of dialysis or restoration of native renal excretory function can significantly reduce the potassium burden in fulminant AKI.

Expansion of the extracellular space with a nonpotassium-containing fluid (e.g., 0.9% sodium chloride) may be sufficient to at least partially correct hyperkalemia. This maneuver should be implemented in cases of suspected volume depletion, but should be used with caution or not at all if a patient is anuric or has volume overload.

Administration of regular insulin is a common pharmacologic treatment for hyperkalemia. Insulin upregulates synthesis of subunits of the Na+/K+ATPase pump, recruits the pump to the plasma cell membrane, and activates those pumps already located in the plasma membrane to stimulate intracellular translocation of potassium. The potassium-lowering effect of regular insulin may be observed within 20 minutes, but the effect is typically modest (decline of 1–2 mmol/L) and transient (redosing is frequently necessary within 4–6 hours). A potentially catastrophic adverse effect associated with regular insulin administration is hypoglycemia, so dextrose must be administered concurrently with regular insulin. If fluid overload is not present, the administration of a continuous rate infusion of dextrose, following the initial bolus, is recommended. Frequent assessment of blood glucose concentrations is imperative, as dextrose is metabolized more rapidly than insulin, and redosing of dextrose is often required.

Calcium salts are frequently administered intravenously to increase the threshold potential of polarized

cells, thus allowing depolarization at high extracellular potassium concentrations. The membrane-stabilizing effects of calcium salts are rapid and dramatic but the beneficial effects are even more transient than those of regular insulin. Readministration is typically necessary within 1–4 hours. The patient should be monitored with an electrocardiogram during administration to identify worsening bradycardia, a shortened QT interval, a widened T-wave, or alterations in the ST amplitude. If any of these changes are recognized, the calcium infusion should be discontinued. Calcium gluconate is favored over calcium chloride, due to the severe extravasation injuries that can occur with calcium chloride administration. It should be noted, however, that calcium gluconate can also cause extravasation injuries (albeit less severe), so care must be taken to ensure intravenous catheter patency prior to administration.

Lastly, theoretical concerns regarding promotion of calcium-phosphorus/phosphate precipitation and soft tissue mineralization exist with repeated administration of calcium salts.

Alternative treatments for hyperkalemia exist, but each has limitations in efficacy and side-effects, compared with provision of dialysis. These treatments include beta-2 agonist drugs, polystyrene sodium sulfonate, sodium bicarbonate, and loop diuretics.

While ionized hypocalcemia occurs frequently in AKI, clinical signs (e.g., tetany) associated with this problem are rare. When manifestations of hypocalcemia do occur, the minimum dose of supplemental calcium that controls clinical signs should be used to minimize precipitation with phosphorus. As with the treatment of hyperkalemia, the electrocardiogram should be monitored closely during infusion.

Additional electrolyte abnormalities may be present or develop during the course of disease, the most common of which are hyponatremia and hyperphosphatemia. Hyponatremia may be the result of gastrointestinal or urinary losses, with or without the contribution of decreased excretion of free water. Hyponatremia, if severe (<120 mmol/L), may result in neurologic sequelae. Hyperphosphatemia contributes to acidosis and renal secondary hyperparathyroidism. However, the use of phosphate-binding drugs has not been shown to improve outcome in human or veterinary cases of AKI. Furthermore, administration of aluminum hydroxide (the most commonly used phosphate-binding drug in veterinary medicine) may result in acute aluminum intoxication, which manifests as encephalopathy, a condition which may not be readily recognizable in a patient severely affected with AKI. Therefore, aluminum-containing phosphate-binding drugs should be used with caution in cases of AKI.

Nutritional Support

Nutritional support is an important component of supportive care for AKI. Enteral feeding is the preferred method of nutrient delivery, but is often limited by vomiting and ileus. For those patients that are not vomiting, esophageal, gastric, and jejunal feeding devices can be used. If vomiting cannot be controlled, partial or total parenteral nutrition should be considered. In patients which are anuric or oliguric, the volume and osmolality of nutritional product, whether administered enterally or parenterally, must be taken into consideration and may constitute a relative contraindication unless there is a method of excess fluid and solute removal (e.g., dialysis).

The optimal dietary composition for veterinary AKI patients has not been determined. The author is unaware of any particular diet that is appropriate in all scenarios of AKI. Rather, each individual patient should be evaluated for the following factors, as each may influence the choice of diet to be fed: degree of uremia, availability of dialysis, volume status and volume of urine produced, electrolyte balance, and availability of assisted feeding (e.g., esophagostomy or gastrostomy tube). Patients with severe uremia may benefit from a protein-restricted diet because a reduced protein content may decrease the endogenous production of uremic toxins. However, a negative protein balance may hinder renal repair/recovery. Patients treated with dialysis may actually require more protein than patients with extrarenal disease, due to loss of amino acids in dialysate. Patients with feeding tubes that are prone to volume overload should be fed the most calorically dense diet that will pass through the tube to minimize the amount of fluid administered. Some commercially available recovery diets have caloric contents of approximately 2 kcal/mL and easily pass through most 14 Fr red rubber catheters or feeding tubes. These diets typically have a high protein and potassium content, the latter of which may be problematic in hyperkalemic patients. There are multiple appropriate, commercially available diets from which to select, depending on the individual patient's clinical status.

However, a common misconception among veterinary personnel is that commercial renal diets, formulated and marketed for patients with chronic kidney disease, are also appropriate for patients with AKI. While these diets have reduced protein content, which may be desirable in certain situations, they require dilution and blending with water, which reduces their caloric density and increases the amount of fluid that must be administered with each feeding. Furthermore, these diets have a low sodium content, which is reduced even further when they are diluted with water. Many

patients with AKI are hyponatremic due to gastrointestinal and renal losses, so administration of large volumes of hypotonic enteral fluid in the form of a diluted renal diet may exacerbate hyponatremia and cause severe neurologic sequelae. Lastly, many feline commercial renal diets have a high potassium content which, as with recovery diets, can be problematic for hyperkalemic patients. For these reasons, the author typically refrains from administration of renal diets to tube-fed patients with AKI. Consideration is given to transition to a renal diet once renal recovery is presumed to be complete and it has been confidently established that the patient has residual chronic kidney disease.

Renal Replacement Therapy/Dialysis

Renal replacement therapy (referred to as dialysis) is discussed (in the context of AKI, as well as other disease states) in Chapter 126. Dialysis is the most efficient means of managing uremic, acid–base, electrolyte, and fluid-related sequelae of AKI. In fulminant cases, available pharmacologic therapies are, at best, incompletely effective at reversing the aforementioned complications, and their effects are transient. The cost and limited availability of dialysis, however, make it impractical for many owners and veterinarians.

Additional Treatment Considerations

Antiemetic therapy is recommended for all patients with severe AKI, regardless of whether they are vomiting. Metoclopramide is frequently used for this purpose, but reduced clearance associated with compromised renal function, and resultant adverse effects (primarily neurologic) must be considered. Furthermore, metoclopramide was found to be inferior to the 5-HT3 antagonist ondansetron in prevention of vomiting and nausea in uremic human patients.

The use of antisecretory drugs (e.g., H2 receptor antagonists, proton pump inhibitors) has historically been recommended for patients with AKI. Although uremic gastritis and stress-related mucosal disease are concerns in human AKI patients, gastric acid output and intragastric pH are not compatible with a hypersecretory state. Nonetheless, due to the high incidence of hemorrhage from the gastrointestinal tract in human AKI patients (presumably related to a combination of uremic injury and stress-related mucosal disease) and its association with mortality, antisecretory drugs should be considered in high-risk patients. A recent metaanalysis showed superiority of proton pump inhibitors versus H2 receptor antagonists in the prevention of stress-related mucosal bleeding. These results, in combination with the potential for accumulation of H2 receptor antagonists in patients with diminished renal function, favor the use of proton pump inhibitors. Sucralfate is frequently used for gastroprotection, but human data show that even short-term administration of this drug to patients with AKI can result in toxic aluminum concentrations.

Some human physicians advocate the use of diltiazem in the treatment of posttransplant AKI and the prevention of AKI following cardiovascular surgery, and there are data describing its use in dogs with AKI secondary to leptospirosis. While results of the canine study suggested a favorable trend with the use of diltiazem, evidence is insufficient to recommend its routine use.

Dopamine is a pharmacologic treatment for AKI that has fallen into and out of favor with both human and veterinary nephrologists. Stimulation of intrarenal dopamine receptors (DA-1, DA-2) results in vasodilation and natriuresis and diuresis, which have historically been regarded as favorable events in AKI. However, it is unclear whether reduced renal blood flow is a significant contributor to the initiation and maintenance of AKI. Furthermore, at higher doses, dopamine has inotropic and chronotropic cardiac effects that result in increased cardiac output, which may not be desirable if cardiac output is otherwise sufficient. Because of the difficulty in selecting appropriate dosing strategies for individual patients that target the desired receptors, dopamine is not currently recommended for the treatment of AKI. The use of fenoldopam, a selective DA-1 agonist, may favor activation of intrarenal dopamine receptors over adrenergic receptors, which may result in more desirable outcomes. However, there is currently insufficient evidence to recommend the routine use of fenoldopam for its vasodilatory and natriuretic effects.

Prognosis

The approximate mortality rate for AKI in cats and dogs is 50%; this figure is unchanged when assessing cats and dogs treated with intermittent hemodialysis. If it is acknowledged that patients treated with dialysis are more likely to have a greater severity of renal dysfunction and more complications associated with AKI, it can be deduced that dialysis offers a survival benefit in these cases. In those that survive, approximately 50% recover normal renal function.

Certain subsets of patients have better prognoses. Dogs with leptospirosis have survival rates approaching 80–90%. Patients with polyuria typically have a better outcome than those with oliguria or anuria. Azotemic AKI caused by ethylene glycol intoxication, however, has a poor prognosis, with approximately 80% of dogs requiring dialysis for the remainder of their lives.

Further Reading

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121

Glomerular Disease

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Etiology/Pathophysiology

Glomerular disease is a leading cause of renal disease in dogs but appears to be less common in cats. Accordingly, most of the content of this chapter is in reference to dogs.

Historically, glomerular diseases have been classified as being either primary or secondary. Primary glomerular diseases arise in the kidney and secondary diseases occur when the glomeruli are injured as part of a systemic disorder. Secondary glomerular injury is generally the result of damage that is either sustained following immune complex deposition (e.g., membranous glomerulonephritis, membranoproliferative glomerulonephritis, proliferative glomerulonephritis) or due to systemic factors affecting the glomeruli (e.g., amyloidosis, focal segmental glomerulosclerosis, minimal change disease).

Recently, an alternative approach to classification has been suggested in veterinary medicine where, on the basis of renal biopsy evaluation, three broad categories of disease are used: amyloidosis, immune complex-mediated glomerulonephritis (ICGN), and non-ICGN. This system should greatly facilitate the clinical management of dogs and cats with glomerular disease by separating out those that might benefit the most from a thorough search for a systemic disorder and therapy with immunosuppressive drugs. In a study of renal biopsies from 501 dogs with glomerular disease, 48% had ICGN and 15% had amyloidosis, leaving 37% with a variety of non-ICGN.

Because of the strong association between glomerular injury and immune complex deposition or systemic inflammation, glomerular diseases are often linked to systemic disease processes – specifically neoplastic, infectious, or noninfectious inflammatory (NIN) disorders. Published studies have suggested that approximately 50% of dogs with glomerular disease have an identifiable NIN. The categorization of biopsies from the previously mentioned 501 dogs suggests that as many as 63% of dogs with glomerular disease have undergone renal damage secondary to a disorder occurring elsewhere in the body. A NIN disorder may not be obvious at first presentation because it is either resolved or occult. Because occult NIN disorders may become overt months after initial presentation for proteinuria, continued observation and scrutiny of the dog and cat with glomerular disease are necessary.

Familial glomerulopathies have been reported in several breeds of dogs and can cross most of the before mentioned categories (Table 121.1).

Hereditary nephritis is the result of defective collagen synthesis and has been reported in bull terriers, English cocker spaniels, Dalmatians, Samoyed, and mixed breed dogs. An inherited podocytopathy is the cause of familial protein-losing nephropathy of soft-coated wheaten terriers. Shar-peis develop familial renal amyloidosis following episodes of recurrent fever and swollen joints. The etiopathogenesis of many of the remaining disorders is unknown.

Signalment

Glomerular diseases can develop at any age but may be more common in middle-aged to older dogs. The reported average from 876 dogs in six different studies was 7.4 years of age. In general, male and female dogs are nearly equally represented among dogs with glomerular disease. The average age and gender predilection seen with specific glomerular diseases will vary somewhat from the overall averages.

Any breed can be affected by glomerular disease. However, Labrador retrievers, golden retrievers, and Yorkshire terriers may be predisposed based on reported higher incidence of glomerular disease in these breeds; however, it is also possible that this increased representation reflects the popularity of these breeds. Amyloidosis may be overrepresented in Chinese shar-peis and English bulldogs.

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Table 121.1 Select breeds of dogs with familial glomerulopathies

Breed	Glomerular disease(s)
Beagle	Amyloidosis, primary glomerulopathy
Bernese mountain dog	Mesangiocapillary glomerulonephritis
Bull mastiff	Glomerulosclerosis
Bull terrier	Hereditary nephritis
Dalmatian	Hereditary nephritis
Doberman pinscher	Glomerulosclerosis, cystic glomerular atrophy
English cocker spaniel	Hereditary nephritis
English foxhound	Amyloidosis
Greyhound	Glomerular vasculopathy and necrosis
Newfoundland	Glomerulosclerosis
Pembroke Welsh corgi	Glomerulosclerosis, cystic glomerular atrophy
Rottweiler	Atrophic glomerulopathy
Samoyed	Hereditary nephritis
Shar-pei	Amyloidosis
Soft-coated wheaten terrier	Podocytopathy

History and Clinical Signs

Dogs and cats with glomerular disease can present with a variety of clinical signs, determined by the severity of proteinuria or renal disease and the presence or absence of any systemic disorders. They may be asymptomatic, have nonspecific signs (e.g., anorexia, weight loss, lethargy) or have signs of more advanced renal disease (e.g., polyuria, polydipsia, vomiting, diarrhea, halitosis). Animals with severe urinary protein loss may develop nephrotic syndrome and have evidence of fluid retention (e.g., abdominal enlargement consistent with ascites, peripheral edema). Animals also may develop clinical signs from thromboembolism (e.g., dyspnea, loss of limb function), or hypertension (e.g., acute blindness, or recent onset of neurologic signs or cardiac murmur). When glomerular disease is suspected, the history should include questions about the environment, possible exposure to infectious diseases as well as relevant drug or dietary exposure.

Complete physical examinations should be performed on dogs and cats with suspected glomerular disease, including body condition score, retinal and rectal examinations. Physical examination is often unremarkable. Poor body condition or poor hair coat may be nonspecific evidence of systemic disease. Animals with advanced renal disease may have oral ulcerations, pale mucous membranes, or dehydration. Subcutaneous edema or ascites, or both, are sometimes noted and consistent with nephrotic syndrome. Occasionally, there is physical evidence of thromboembolic disease, such as dyspnea or a decreased or absent peripheral pulse. Evidence of a predisposing inflammatory, infectious, or neoplastic process may be detected during the physical examination. The kidneys of affected animals are variable in size. Animals with chronic kidney disease often have small, firm, irregularly shaped kidneys, whereas those with less severe or long-standing disease often have normal-sized or, occasionally, enlarged kidneys.

Diagnosis

When proteinuria is detected, there are three key elements that need to be assessed: localization, persistence, and magnitude. Although proteinuria is the hallmark of glomerular disease, it can also occur secondary to prerenal, postrenal or renal tubular causes. The magnitude of proteinuria is generally assessed via the urine protein:creatinine ratio (UPC). Persistent renal proteinuria that is of high magnitude (i.e., UPC >2) is most likely of glomerular origin; however, there is no range of numbers that is diagnostic for any one renal disease and the overlap in expected ranges is too broad to be clinically reliable. In fact, glomerular lesions have been seen in dogs without proteinuria. Urine albumin can also be used to assess proteinuria. Microalbuminuria may develop before the UPC is increased. It therefore seems reasonable to conclude that a dog or cat with persistent microalbuminuria of increasing magnitude should be assessed as having an injurious process to the glomerular filtration barrier and may eventually develop overt proteinuria.

Once glomerular disease is suspected, a comprehensive diagnostic evaluation is recommended for all dogs and cats which includes urinalysis, serial UPC measurements, completed blood count, biochemical profile, and blood pressure measurement. Urine culture is warranted if there is pyuria, hematuria, bacteriuria, dilute urine (e.g., urine specific gravity <1.025) or concurrent diseases which might predispose the patient to urinary tract infection (e.g., hyperadrenocorticism). Animals with potential exposure to infectious diseases should undergo the appropriate testing. Any concominant extrarenal disease should be evaluated further (e.g., aspriation cytology of cutaneous masses, appropriate testing for hyperadrenocorticism). If proteinuria is of high magnitude (i.e., UPC >3.5), associated with hypoalbuminemia, azotemia, or hypertension, or progressive or nonresponsive to treatment, additional diagnostics including but not limited to abdominal ultrasound, thoracic radiographs, more extensive evaluation for infectious

diseases, and assessment of the coagulation system are indicated.

The results of this comprehensive evaluation will vary considerably in affected animals. Hypoproteinemia due to hypoalbuminemia develops in many dogs and cats with glomerular disease but is more likely in animals with heavy proteinuria. Azotemia, hyperphosphatemia, and metabolic acidosis, consistent with renal failure, may be present in animals with severe disease, although as many as 50% of affected animals will be nonazotemic. Nonregenerative anemia, secondary to renal failure or a systemic disease, is observed in many affected animals.

Other hematologic abnormalities also may reflect concurrent and possibly underlying systemic diseases. Thrombocytosis and hyperfibrinogenemia are common findings in dogs with glomerular disease. The nephrotic syndrome of hypoalbuminemia, proteinuria, hypercholesterolemia, and edema, although pathognomonic for glomerular disease, will only be present in a small proportion of dogs with glomerular disease (i.e., 10–15%). Because fluid retention can sometimes be cavitary, thoracic radiographs and abdominal ultrasound can be used to help detect edema. However, incomplete nephrotic syndrome (i.e., without edema or ascites) occurs in about half of affected dogs. The nephritic syndrome is a term that has primarily been used in people to describe a set of signs that develop secondary to renal inflammation, generally acute, that extends into the glomeruli. In people, this syndrome is characterized by hematuria and red blood cell (RBC) casts with one or more of the following: subnephrotic proteinuria, edema, hypertension, azotemia, oliguria. Although the nephritic syndrome has not been fully characterized in dogs, perhaps because of the probable low prevalence of acute glomerulonephritides in dogs, it is possible that dogs with acute inflammatory glomerular diseases (e.g., Lyme nephritis) may present with a nephritic-like syndrome. Isosthenuria is a variable finding in dogs and cats with glomerular disease and as many as 40% of affected dogs with glomerular disease will maintain renal concentrating ability, achieving urine specific gravities in excess of 1.035.

The finding of concurrent renal azotemia, concentrated urine, and proteinuria is indicative of glomerular disease. Cylindruria is common in dogs with glomerular disease; casts are most often hyaline but can be granular, waxy, or fatty. When affected animals are imaged, the kidneys may appear normal or small and irregular; some animals may have abnormally enlarged kidneys. Increased echogenicity of the cortex and loss of corticomedullary distinction may also be noted during abdominal ultrasound. The renal pelvis may be mildly dilated if polyuria is present or if fluids are being administered.

Renal biopsy should be considered under certain circumstances: proteinuria is of high magnitude (UPC >3.5, with or without concurrent hypoalbuminemia), progressive, or unresponsive to standard therapy; immunosuppressive therapy is being considered; medical contraindications to biopsy are not present; the renal biopsy can be collected, prepared and interpreted by experienced personnel; and, the sample can be submitted for evaluation using standard light microscopy but also electron microscopy and immunofluorescence. Medical contraindications to biopsy include advanced chronic kidney disease (i.e., IRIS stage 4), coagulopathy, cystic disease, hydronephrosis, pyelonephritis, perirenal abscess, uncontrolled hypertension, severe anemia, and pregnancy.

Electron microscopy is essential if a renal biopsy is to be evaluated and was required to confirm or rule out ICGN in 27.4% and 23.1% of biopsies, respectively, from one study. Light microscopy alone was 94% sensitive and 77% specific in identifying ICGN when specimens were evaluated by highly experienced nephropathologists; it is unlikely that pathologists without nephropathology training would achieve these same results.

Therapy

Standard Therapy

Standard therapy is the foundation for the care that should given to all dogs with glomerular disease, regardless of the inciting cause, and includes inhibition of the renin-angiotensin-aldosterone system (RAAS), and management of dietary intake, hypercoagulability, systemic hypertension, and body fluid volume (Box 121.1).

Evidence suggests that UPC >1.0 is associated with negative patient outcomes and when the UPC is reduced to <0.5, the outcome is improved. Therefore, it is recommended that standard therapies be considered when the UPC is persistently >0.5. However, standard therapy rarely leads to complete resolution of the renal lesions.

Inhibition of RAAS

Hemodynamic forces influence the transglomerular movement of proteins. The RAAS can be therapeutically targeted to alter renal hemodynamics, leading to a reduction in proteinuria. Decreased efferent glomerular arteriolar resistance leads to decreased glomerular transcapillary hydraulic pressure, which ideally leads to a reduction in proteinuria. Other proposed mechanisms include reduced loss of glomerular heparan sulfate, decreased size of the glomerular capillary endothelial pores, improved lipoprotein metabolism, slowed glomerular mesangial growth and proliferation, and inhibition of bradykinin degradation.

Box 121.1 Management of glomerular disease in dogs

Inhibition of renin-angiotensin-aldosterone system
Angiotensin-converting enzyme inhibitors (e.g., enalapril, benazapril)
Angiotensin receptor blockers (e.g., telmisartan)
Aldosterone receptor blockers (e.g., spironolactone)

Modified dietary intake
Increased n-3 polyunsaturated fatty acids
Modified protein content
Reduced sodium chloride

Antithrombotic therapy
Aspirin
Clopidogrel

Antihypertensive therapy
Angiotensin-converting enzyme inhibitors (e.g., enalapril, benazapril)
Angiotensin receptor blockers (e.g., telmisartan)
Calcium channel blocker (i.e., amlodipine)

Manage body fluid volume
Careful fluid therapy when fluid deficit present
Diuretics for fluid excesses that are contributing to respiratory distress

Immunosuppressive therapy for immune complex-mediated glomerulonephritis

Angiotensin-converting enzyme inhibitors (ACEi; e.g., enalapril, benazapril), angiotensin receptor blockers (ARB; e.g., telmisartan), and aldosterone receptor blockers (e.g., spironolactone) are the agents that target RAAS.

For most dogs with glomerular-range proteinuria, an ACEi is the initial agent used. Typically, an ACEi is given once daily initially, but more than half of the dogs will eventually need twice-daily administration and perhaps additional dosage escalations. Although worsening azotemia is a concern regarding the use of ACEi, severe worsening (i.e., >30% increase from baseline) due to ACEi administration alone seems uncommon and dogs that are dehydrated may be at highest risk. Less is known about the use of an ARB in dogs with glomerular disease although they have been extensively studied in people. The ARB that has historically been used in dogs with glomerular disease is losartan, although it has not always been effective. Recently, telmisartan has been shown to be very effective in some dogs and may prove useful as the initial line of therapy. Telmisartan has a more profound effect on lowering blood pressure than ACEis and should be used carefully in dogs that have low basal blood pressures (e.g., systolic <140 mmHg).

Because neither an ACEi nor an ARB as a single agent provides complete blockade of the RAAS, there may be an added benefit to combined therapy; however, this approach should be used with caution as it has been associated with a higher risk of kidney failure and death in people. Serum aldosterone increases over time (i.e., aldosterone escape) in people treated even with maximal dosages of ACEi and ARB; prolonged hyperaldosteronism may have adverse effects on the heart, systemic blood vessels, and glomeruli. People with hyperaldosteronism may have a greater reduction in proteinuria when an aldosterone receptor antagonist is added to their therapy. Spironolactone has been used most commonly in dogs; however, there are few data that support the efficacy of this drug in dogs in the management of glomerular disease. Spironolactone should only be effective if serum aldosterone concentrations are increased. This drug could be tried in animals that have high serum aldosterone concentrations and persistent proteinuria in spite of treatment with an ACEi, ARB or both, with the understanding that its efficacy in reducing proteinuria has not been established.

All dogs that are being treated for glomerular disease via RAAS inhibition should be monitored at least quarterly by a minimum of UPC, urinalysis, systemic arterial blood pressure and serum albumin, creatinine and potassium concentrations. The UPC, serum creatinine, serum potassium, and blood pressure should be evaluated 1–2 weeks after an ACEi or ARB has been added or altered. The desired therapeutic effect is a reduction in proteinuria without a severe worsening of renal function (i.e., >30% increase in serum creatinine), a critical increase in serum potassium or the unlikely development of hypotension. Changes in the magnitude of urine protein are most accurately measured by assessing trends in the UPC over time. Day-to-day variations in the UPC occur in most dogs with glomerular proteinuria, with greater variation occurring in dogs with UPC >4. Consideration should be given to either averaging 2–3 serial UPC or measuring a UPC in urine that has been pooled from 2–3 collections. The target for reduction is a UPC of <0.5 without inappropriate worsening of renal function; however, when that is not possible, a partial response with a reduction in the UPC of 50% or more is the alternative target.

Dogs with serum potassium concentrations of >6 mEq/L should be monitored closely and therapy should be modified when serum potassium concentrations are >6.5 mEq/L. Before modifying treatment, pseudohyperkalemia, due to the high potassium content of some blood cells which may occur in dogs with glomerular disease, should be eliminated as a cause by measuring the potassium concentration in lithium heparin plasma. True hyperkalemia can be managed by reducing the ACEi or ARB drug dosage, discontinuing spironolactone administration, or by feeding

diets that are reduced in potassium or administering an intestinal potassium binder (e.g., kayexelate). If the target reduction in UPC is not achieved and the dog does not have the before mentioned adverse effects, the dosages may be increased every 4–6 weeks.

Modified Dietary Intake

Modification of dietary intake has a central role in the management of all dogs with kidney disease and has been associated with delaying spontaneous progression of kidney disease and reducing the magnitude of proteinuria. It is well known that fat content of a diet can affect renal outcome. Most commercially available renal diets are modified with respect to polyunsaturated fatty acids (PUFA) content with the goal of slowing progression and reducing proteinuria. The consensus recommendation is that dogs with glomerular disease should be fed a diet with a reduced n-6:n-3 PUFA ratio of approximately 5:1. It is unknown if there is any additional benefit of supplementing n-3 PUFA when this ratio is already being provided via the diet. If supplementation is chosen, care should also be taken to provide adequate antioxidants (e.g., vitamin E). Dogs with glomerular disease should be fed modified protein diets because this has been shown to reduce proteinuria and slow progression.

Lastly, the sodium chloride content should be reduced in diets fed to dogs with glomerular disease. Salt restriction may enhance the beneficial effects of agents used to inhibit RAAS and help reduce fluid retention.

Antithrombotic Therapy

Hypercoagulability is a complication of protein-losing glomerular diseases and thromboembolism can occur in as many as 25% of dogs with glomerular disease. The pathogenesis of hypercoagulability in glomerular disease is complex and incompletely understood. Urinary loss of antithrombin has long been given as the explanation but in reality, the pathogenesis is more complex than this and probably includes vascular stasis as well as increased platelet aggregation, plasma procoagulant factors, and fibrinogen concentrations. Unfortunately, serum albumin concentrations, antithrombin activity, and UPC cannot be used in isolation to predict hypercoagulability in individual patients. It follows then that it remains unclear when to implement thromboprophylaxis. Consensus recommendations call for the daily administration of low-dose aspirin (1–5 mg/kg/day) in dogs with protein-losing glomerular diseases. Clopidogrel may be an effective alternative.

Antihypertensive Therapy

All dogs with glomerular disease should undergo repeat evaluation for systemic hypertension. This evaluation should not only include measurement of systemic blood pressure but also assessing the patient for target organ damage, evaluating for conditions that may contribute to hypertension and determining if any concurrent conditions that may complicate antihypertensive therapy are present. Personal preference and experience should dictate how the blood pressure is measured; however, the substaging by arterial blood pressure system that has been proposed by the International Renal Interest Society (IRIS) should be used to guide therapy (Table 121.2).

Antihypertensive therapy should be initiated when the blood pressure exceeds 160 mmHg systolic or 100 mmHg diastolic (i.e., AP2 or above). The goal of therapy is to reduce the blood pressure to less than 150 mmHg systolic or 96 mmHg diastolic (i.e., AP0). Lowering the blood pressure is not an emergency unless there is severe ocular or central nervous system target organ damage. In most cases, blood pressure reduction can be achieved gradually over a period of several weeks. Effective treatment of hypertension should lead to a concomitant reduction in the magnitude of proteinuria in dogs with glomerular disease. Feeding a salt-restricted diet alone will not lower the blood pressure into the target range but it may enhance the antihypertensive effects of the inhibitors of RAAS, generally ACEi. However, ACEi are generally only associated with a 10–15% reduction in blood pressure. This reduction may be all that is needed for dogs that are only moderately hypertensive (i.e., AP2). Dogs that are severely hypertensive (i.e., AP3) should have a calcium channel blocker (i.e., amlodipine) added to their RAAS inhibition therapy. Alternatively, telmisartan can be used as a single agent to manage hypertension and proteinuria.

The consensus recommendation is that dogs with IRIS chronic kidney disease stages 1 or 2 should have blood pressure evaluated 3–14 days after any change in antihypertensive therapy whereas those in stages 3 or 4 should

Table 121.2 International Renal Interest Society substaging by arterial blood pressure

Systolic blood pressure	Substage
<150 mmHg	Normotensive, Minimal Risk
150–159 mmHg	Borderline hypertensive, Mild Risk
160–179 mmHg	Hypertensive, Moderate Risk
>180 mmHg	Severely hypertensive, Severe Risk
No evidence of end-organ damage	nc (no complications)
Evidence of end-organ damage	c (complications)
Blood pressure not measured	RND (risks not determined)

be evaluated 3–5 days after making any change. Dogs that have hypertensive emergencies should be evaluated daily. The purpose of these evaluations is not only to assess effectiveness of the antihypertensive therapy but also to evaluate for exacerbation of azotemia. Dosages should be reduced if the serum creatinine has increased more than 30% from baseline or if the blood pressure is reduced to less than 120–mmHg systolic or 60–mmHg diastolic. Once target blood pressure is achieved, the dogs should be evaluated at 1–4-month intervals, depending upon the stability and severity of the renal disease.

Body Fluid Volume

Dogs with glomerular disease may have fluid excesses, deficits or maldistribution, which may need to be corrected if the dog has decompensated or is being prepared for anesthesia. Correcting body fluid imbalances in dogs that are hypoalbuminemic from glomerular disease is a very difficult therapeutic challenge. Fluid therapy can exacerbate edema and hypertension and diuretics can exacerbate azotemia or uremia. As such, those who have experience and expertise in critical care are the best people to deliver these therapies to dogs with glomerular disease.

Fluid therapy should be given only when needed to help control clinical signs or provide support to those dogs that have inadequate fluid intake. Both colloids and crystalloid can be used. However, the decision to use colloids should not be based on the presence of hypoalbuminemia or decreased colloidal oncotic pressure alone. Colloids should be considered when crystalloids have failed to bring about the desired result. The fluid status of affected dogs should be assessed before and during fluid therapy on the basis of serial body weight and other physical examination findings (e.g., skin turgor, appearance of mucous membranes, capillary refill time, pulse rate and quality, arterial blood pressure). When the serum albumin decreases below 2 g/dL in people, the plasma oncotic pressure is sufficiently reduced to allow for transudation of fluid from the vascular compartment into the interstitial space. Dogs may be more resistant to the formation of edema, which does not generally occur until the serum albumin concentration is below 1.5 g/dL. Plasma volume may be reduced at this point, making the use of diuretics in the management of edema relatively ineffective and also dangerous because of the increased risk of acute kidney injury and vascular stasis leading to thromboembolism.

Diuretics should be avoided unless needed to control respiratory distress. When needed, furosemide is the drug of choice for pulmonary edema but spironolactone may be best for pleural or abdominal effusion. Provision of adequate exercise also may help reduce the formation of edema or ascites.

Immunosuppressive Therapy

Immunosuppressive therapy should be considered in dogs that have severe, persistent or progressive glomerular disease and ICGN documented via appropriate evaluation of a renal biopsy specimen. However, there are many practical and medical reasons why a biopsy might not be performed. In addition, financial limitations may prevent biopsy. The end-result is that sometimes veterinarians must decide about the use of immunosuppressive therapy in dogs with glomerular disease without a pathologic diagnosis. In these situations, immunosuppressive therapy should not be administered if there is any doubt that the proteinuria is of glomerular origin, administration of the specific drug is medically contraindicated, or there is a high index of suspicion that the dog has a non-immune-mediated familial disease or amyloidosis.

Immunosuppressive drugs should be considered without a pathologic diagnosis when standard therapy has been implemented but the azotemia is progressive or the serum creatinine is >3.0 mg/dL or serum albumin is <2.0 g/dL. Because ICGN is the disease process in approximately 50% of dogs with glomerular disease, using immunosuppressive agents in these dogs without a renal pathologic diagnosis has a 50:50 chance of being appropriate. The risks associated with such therapy need to be clearly communicated to the pet owners.

Even with biopsy-proven ICGN, the profession does not have data regarding the expected outcomes of the various possible protocols. Therefore, specific drug recommendations are difficult to formulate. The immunosuppressive protocol should probably vary based on the severity of clinical signs and the rate of progression of the glomerular disease. More aggressive protocols that use rapidly active agents are probably best for dogs with severe and rapidly progressive disease. The rapidity with which the drug becomes active is of less concern in dogs with more slowly progressive disease. Drugs that could be considered are glucocorticoids, mycophenolate, cyclosporine, cyclophosphamide, chlorambucil and azathioprine. Likewise, combined therapy of mycophenolate and prednisolone, cyclophosphamide and prednisolone or chlorambucil and azathioprine could be considered. There is only weak evidence that supports worse outcomes when dogs with glomerulonephritis are managed with glucocorticoids and more evidence is needed before the use of these drugs is discarded. However, it is clear that glucocorticoids will increase proteinuria; UPC monitoring is best performed in samples collected on days when glucocorticoids are not administered in patients receiving alternate-day therapy. Glucocorticoids should also be used with caution in dogs that are receiving concurrent aspirin therapy.

Patients receiving immunosuppressive drugs should be monitored for drug-specific adverse effects as well as

a therapeutic response. Dogs should be thoroughly evaluated 1–2 weeks after starting therapy and every two weeks after for the first 4–6 weeks of treatment, then every four weeks for the next three months and then quarterly until disease resolution.

A therapeutic response is viewed as a reduction in the magnitude of proteinuria with improvement or stabilization of renal function and increases in serum albumin concentration. A reduction in proteinuria is as described earlier (see Inhibition of RAAS). Improvement or stabilization in renal function is defined as a sustained reduction in serum creatinine to less than 1.4 mg/dL (complete response) or by >25% of baseline (partial response). A meaningful increase in serum albumin is defined as a sustained increase to >2.5 mg/dL (complete response) or either to 2.0–2.5 mg/dL or by >50% of baseline (partial response). Secondary goals include improved blood pressure regulation, resolution of edema, and stabilization of body weight. If there are no unacceptable adverse drug effects, treatment should be continued for 8–12 weeks before changing the regimen or discontinuing treatment. Those demonstrating a partial or complete response should have therapy continued for at least 12–16 weeks. If partial or complete responses are not evident by the end of 8–12 weeks, the immunosuppressive protocol should be changed or discontinued. If there is no response by 3–4 months, all immunosuppressive therapy should be discontinued following appropriate drug tapering.

Prognosis

The prognosis for dogs and cats with glomerular disease is variable and probably based on a combination of factors. The prognosis is expected to differ with the various diseases. Although progressive disease can be expected to occur in a large percentage of animals with glomerular disease, spontaneous remission and response to specific therapy can also be expected. Furthermore, disease progression can be slow enough for the animals to lead relatively normal lives, especially when the diagnosis is established early in the disease process. In humans, azotemia, severe proteinuria, systemic hypertension, and marked tubulointerstitial lesions at presentation are the most significant predictors of an unfavorable outcome in most forms of glomerular disease. In dogs, the presence of nephrotic syndrome or azotemia is a negative prognostic indicator. Median survival time for dogs with nephrotic syndrome was only 12.5 days versus 104.5 days for dogs without nephrotic syndrome. When only nonazotemic dogs were considered, (i.e., serum creatinine <1.5 g/dL), the median survival for those with nephrotic syndrome was 51 days versus 605 days for those without nephrotic syndrome.

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122

Obstructive Uropathy

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Urethral Obstruction

Etiology/Pathophysiology

There are a number of potential etiologies for urethral obstruction (UO), with important differences between dogs and cats. For dogs, the most common cause is urolithiasis, with neoplasia, prostatic disease, trauma, and stricture as additional considerations. Calcium oxalate and struvite stones occur most commonly in dogs, followed by ammonium biurate and cystine stones. Urethral strictures develop secondary to chronic urethritis, trauma during prior urethral catheterization, damage to the urethral epithelium from urolith passage, urethral tear or avulsion secondary to trauma, or as a result of exuberant healing following surgical urethral incision. Transitional cell carcinoma of the bladder trigone and prostatic carcinoma are the urothelial neoplasms most commonly associated with urethral obstruction.

For feline UO, urolithiaisis (predominantly calcium oxalate) represents a smaller proportion of cases, with the presence of a urethral plug and/or functional obstruction from urethral spasm/edema recognized more commonly. In any of these circumstances, it is thought that the presence of feline idiopathic cystitis (FIC), and associated inflammation of the lower urinary tract, may set the stage for obstruction. Much less commonly, though for reasons similar to those seen in dogs, cats may have obstruction caused by neoplasia or urethral stricture.

Regardless of underlying cause, complete obstruction of the urethra results in a similar pathologic progression. Urine will accumulate within the urethra and urinary bladder until those tissues can no longer distend. Once this occurs, intraluminal pressure builds, resulting in mucosal injury. The intraluminal pressure is then transmitted up the ureters to the kidney and Bowman's capsule with subsequent reduction of glomerular filtration. As a result, there will be accumulation of normal excretory products such as blood urea nitrogen, creatinine, phosphorus, potassium, and hydrogen ion within approximately 24–48 hours. These then combine to create the expected clinical course associated with UO.

Uremia can have a number of effects including depression, nausea, vomiting, and anorexia. The resulting decreased intake and ongoing losses can cause the patient to become dehydrated. Retention of organic and inorganic acids can result in severe metabolic acidosis with severe implications. Normal protein and enzyme function can be pH dependent, as well as responsiveness to catecholamines and the ability to maintain cardiovascular homoestasis. Finally, the development of severe hyperkalemia contributes significantly to the life-threatening nature of this disease process. Hyperkalemia affects electrical conduction and ultimately leads to bradycardia, atrial standstill, and eventually cardiac arrest (particularly at potassium levels above 9 or 10 mEq/L). As a result of this combination of factors, without intervention complete urethral obstruction will lead to significant illness within 24–48 hours, and mortality within 3–5 days.

Epidemiology and Signalment

Given their long and narrow urethra (compared to females), males are much more likely to develop UO. Among cats, there do not appear to be specific breed predispositions for UO in general, though Himalayan and Persian cats may have an increased risk of urolithiasis. There is some evidence to suggest indoor-only cats, and cats fed an exclusively dry food diet, may have an increased risk of UO.

Dogs that have a predisposition for stone formation have a greater risk for developing UO. This includes older castrated males and small-breed dogs (bichon frise,

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Pomeranian, shih tzu, etc.) at risk for calcium oxalate stones. Because of their strong association with urinary tract infection (UTI), female dogs are much more likely to have struvite urolithiasis. Dalmatians and breeds predisposed to portosystemic shunts (e.g., Yorkshire terriers) should be considered for the potential of urate stones. Lower urinary tract neoplasia is reported to have a higher prevalence in Scottish terriers, Shetland sheepdogs, wire-haired fox terriers, and West Highland white terrier.

History and Clinical Signs

Feline UO typically involves demonstration of lower urinary tract signs: vocalizing and straining unproductively in the litter box. Cats with FIC may present similarly, which could serve to complicate the diagnosis based on these signs alone. Signs of systemic illness (vomiting, lethargy, anorexia, changes in mentation) in conjunction with lower urinary tract signs should point more strongly to UO than FIC. Owners may not be aware of lower urinary tract signs when litter boxes are kept in isolated areas, or the cat is indoor-outdoor. These patients will present for their systemic signs, and so UO might not be considered as quickly. Along those lines, UO should be considered as a differential for any sick male cat that presents.

Dogs may present for signs consistent with lower urinary tract disease leading to obstruction, including frequent trips outside, stranguria/dysuria, and pollakiuria. Once obstruction occurs, owners might report unproductive attempts to urinate, abdominal distension, and abdominal discomfort.

Clinical signs will depend on duration of obstruction and degree of systemic impact by the time of presentation. A firm, distended urinary bladder will be the most prominent feature for patients early in the disease process. In dogs, it may be possible to palpate the presence of a stone in the pelvic urethra, or prostatomegaly, when performing a rectal exam. If the obstruction has been present for greater than 24 hours, the patient may display signs of systemic illness. Systemic signs include dehydration, dull mentation, bradycardia, and hypothermia. Hyperkalemia should be considered for any ill patient that presents with bradycardia as the normal stress response to hospital presentation is tachycardia (though patients with a primary conduction disturbance or cats with septic or cardiogenic shock can also demonstrate bradycardia). For cats with UO, the combination of bradycardia (HR <140) and hypothermia (T <96.6 °F) strongly suggests a serum potassium level greater than 8 mEq/L.

Diagnosis

Diagnosis of UO is largely based on history, clinical signs, and physical exam. However, further diagnostics are helpful to assess the systemic compromise of the patient as well as to determine the underlying cause of obstruction.

Point-of-care diagnostics are especially important in the initial stages of assessing the sick obstructed patient. This should include packed cell volume and total protein, as well as assessment of electrolyte, acid–base status, and/or kidney values (if available). Expected abnormalities include azotemia, hyperkalemia, and metabolic acidosis. An ECG should be placed to evaluate the effects of hyperkalemia on electrical conduction in the heart, even if the patient is not demonstrating bradycardia. Progressive changes that can be seen associated with hyperkalemia include prolonged P-Q interval, diminished to absent P-waves, widened QRS and tall, tented T-waves (Figure 122.1). Eventually, ECG changes can progress to atrial standstill, ventricular fibrillation or asystole. In cats, it is important to note that wide complex tachycardia, rather than the expected bradycardia, has been reported in the setting of severe hyperkalemia.

Once stabilized, more complete systemic bloodwork (complete blood count, biochemical profile) should be performed if clinically indicated. Urinalysis is typically performed in dogs with UO to assess urine pH, presence of crystalluria, and evidence for UTI. As cats are much less likely to have a UTI, and the clinical importance of crystalluria is unclear, the diagnostic value of urinalysis is questionable. Similarly, given evidence that the incidence of UTI at the time of presentation is very low in cats, urine culture should not be performed. However, dogs with UO are much more likely to have concurrent UTI and a culture is more likely indicated.

Diagnostic imaging of some form should be performed in any patient with UO. Typically, abdominal radiographs are a first step to assess for the presence of cystic and/or urethral calculi. Calcium oxalate and struvite stones are radiopaque and should be evident on radiographs. However, ammonium biurate and cystine may be radiolucent and so an apparent absence of stones does not rule out urolithiasis. The entire lower urinary tract should be included (Figure 122.2), and the patient positioned to help minimize superimposition of the pelvis or hindlimbs (Figure 122.3). Common sites where stones lodge include the base of the os penis for dogs and

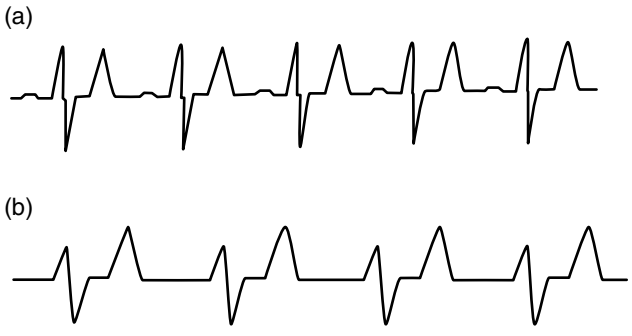


Figure 122.1 Potential ECG changes associated with (a) moderate (approx. 6.0–8.0 mEq/L) and (b) severe hyperkalemia (>8.0 mEq/L).

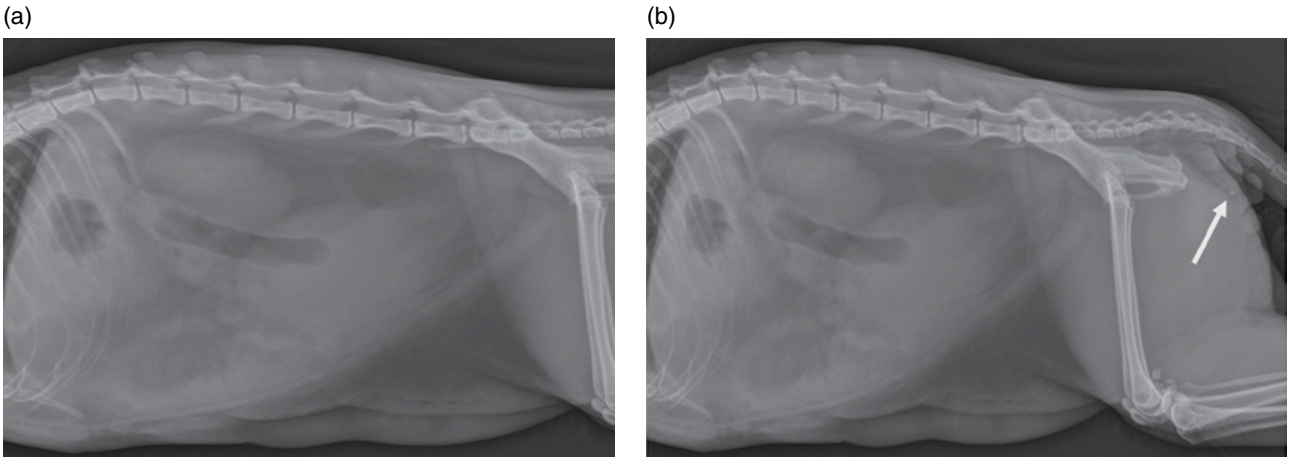


Figure 122.2 Lateral abdominal radiographic projection of a cat depicting (a) normal abdominal positioning technique and (b) positioning to include the entire lower urinary tract. Note the urolith evident in the distal urethra (*arrow*).

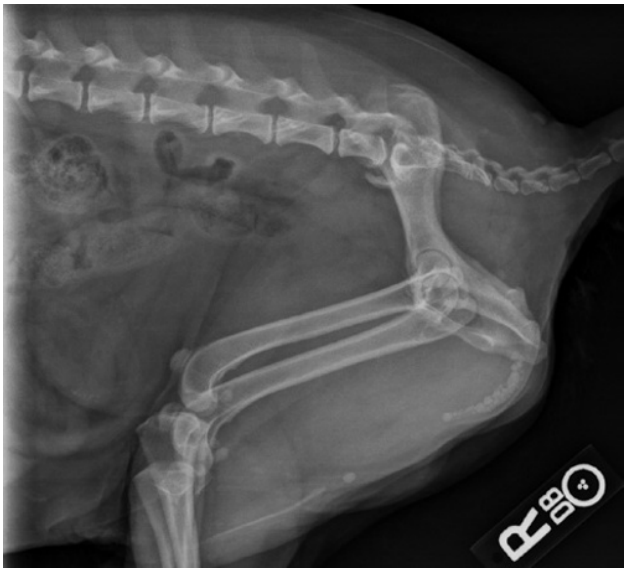


Figure 122.3 Lateral abdominal radiographic projection of a dog depicting proper positioning of the hind legs to avoid superimposition of bony structures. Numerous uroliths are present.

the distal tip of the urethra in cats. Cats may also have mineralized mucous plugs evident on abdominal radiographs (Figure 122.4).

Male dogs should be assessed for prostatomegaly and/or the presence of prostatic mineralization. Loss of abdominal detail may suggest uroabdomen secondary to bladder leakage/rupture. In some cases, it may be useful to perform a positive or negative contrast cystourethrogram, especially if radiolucent stones, stricture or urethral tear are suspected. Abdominal ultrasound may also be of benefit in patients with radiolucent stones, prostatic disease, or lower urinary tract neoplasia.

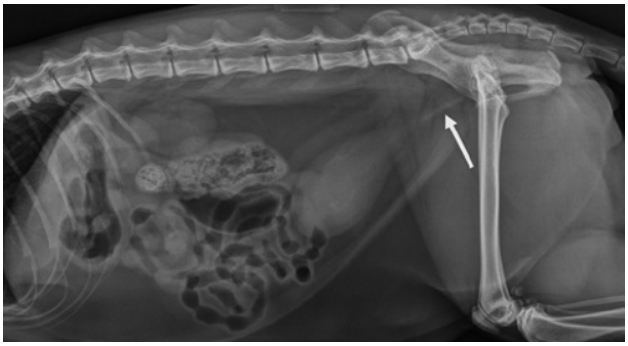


Figure 122.4 Lateral abdominal radiographic projection of a cat depicting the presence of a linear opacity within the proximal urethra, likely representing a mineralized urethral plug (*arrow*).

Therapy

Intravenous catheter placement and fluid therapy should be initiated immediately in the "sick" UO patient. This will serve to begin rehydration/volume repletion, as well as have a dilutional effect on the serum potassium level. There is some debate as to the optimal fluid to use. Traditionally, 0.9% NaCl has been considered the fluid of choice because it has a greater dilutional effect on potassium. However, 0.9% NaCl is an acidifying solution which could exacerbate metabolic acidosis. Conversely, balanced electrolyte solutions are alkalinizing but contain small amounts of potassium (4–5 mEq/L) and therefore may have less of a dilutional effect. It has been demonstrated that between 0.9% NaCl and a balanced electrolyte solution (Normosol R®) there were no differences in outcome (survival, length of stay) or in reduction of serum potassium levels, though acid–base abnormalities corrected more rapidly in the Normosol R group. If cardiovascular collapse is present, it may be necessary to

administer crystalloid "shock doses" (80–90 mL/kg dog, 40–60 mL/kg cat) in bolus fractions (1/4 to 1/3 shock dose over 15–30 minutes, repeated as necessary) to rapidly restore vascular volume. If resuscitation is not necessary, fluid rate should be based on replacement of dehydration added to the maintenance fluid requirement. If time does not allow more accurate determination of fluid rate, it is reasonable to start at a rate of 10 mL/kg in the initial stages and then reassess. Care must also be taken with the amount of fluids given, especially in cats, as a recent study has shown that cats with UO are at risk for volume overload.

While urinary catheter placement and IV fluids will be important in addressing the underlying cause, there is a significant delay for glomerular filtration rate (GFR) to resume and for potassium excretion to occur. Calcium gluconate is the most immediate way to offset the effects of hyperkalemia on electric conduction, though this medication does not decrease the potassium itself. In addition, medications that promote intracellular shift of potassium include regular insulin, dextrose, terbutaline, and/or sodium bicarbonate (see Table 122.1 for dosing recommendations).

Generally, if it was deemed necessary to give calcium gluconate, then one or more of these medications should also be given. It should be noted that dextrose should always be given with insulin to prevent the development of hypoglycemia.

There is also consideration of cystocentesis as part of initial management. On the one hand, it may allow for more immediate relief of bladder pressure compared to urinary catheter placement (particularly for those with limited experience in deobstructing). In addition, relatively less sedation is typically needed to perform cystocentesis. Cystocentesis can allow an uncontaminated urine sample to be obtained for urinalysis and/or urine culture. Finally, it is speculated that decreasing intraluminal pressure may make for easier passage of a urinary catheter. The major counterargument against the use of cystocentesis is related to the concern for bladder tear or rupture. While this is a known potential side-effect whenever cystocentesis is performed, it is believed by some that a distended and friable bladder present with UO is associated with increased risk. There is evidence to suggest that development of clinically significant abdominal effusion, as shown by abdominal ultrasound or radiographs, occurs very uncommonly after cystocentesis in cats with UO and that this procedure can be safely performed. Similar information regarding cystocentesis in dogs with UO is currently unavailable.

Urethral catheterization

Urinary catheter placement is an important step in the management of UO. In this process, every effort should be made to minimize the risk of urethral trauma and optimize the likelihood of successful catheterization. Along these lines, UO patients should receive appropriate sedation and pain medication, with consideration of coccygeal epidural and/or general anesthesia. In addition to impacts on patient comfort and standard of care, inadequate analgesia and sedation may be associated with urethral spasm and urethral injury. If the patient is still reactive to effort (vocalizing, moving), additional medications should be given; alternatively, general anesthesia should be performed.

For cats, the perineal region should be clipped, prepped, and draped in order to minimize risk of contamination. An open-ended semi-rigid catheter (polypropylene or

Table 122.1 Emergency dosing for severe hyperkalemia. All medications given intravenously (IV)

Medication	Dose (IV)	Rate	Indications
Isotonic crystalloid	10–15 mL/kg (c) 20–30 mL/kg (d) 5–10 mL/kg/h	15–30 minutes, repeat if needed Constant rate infusion	Shock Replacement fluid rate
Calcium gluconate	50–150 mg/kg	Over 5 minutes while monitoring ECG	Severe ECG changes Bradycardia
Regular insulin	1 unit (c) 0.1 U/kg (d)	IV bolus	If Ca gluconate given Potassium >8 mEq/L
Dextrose	0.5 g/kg 2.5–5% in fluids	Admin over 3–5 min Constant rate infusion	If Ca gluconate given If insulin given Potassium >8 mEq/L
Terbutaline	0.01 mg/kg	IV bolus	If Ca gluconate given Potassium >8 mEq/L
Sodium bicarb	1 mEq/kg	Admin over 3–5 min	Potassium >10 mEq/L

c, cat; d, dog; ECG, electrocardiogram.

polytetrafluoroethylene) can be used to initially relieve the obstruction. Given the very rigid nature of polypropylene catheters, care should be taken not to use too much force in advancing. For comfort, as well as associated inflammation and irritation, these catheters should also not be left in place. With regard to optimal catheter size, there is some evidence to suggest that use of a 3.5 Fr urinary catheter may be associated with less risk of immediate reobstruction compared to 5 Fr. However, another study failed to show this association.

When passing the catheter, aggressive flushing (rather than force) should be utilized to dilate the urethra and retropulse/break down any physical component of the obstruction. For the flush solution, adding sterile lubricant to sterile saline and mixing across a three-way stopcock (in a ratio of 10:1) may help to decrease urethral injury by allowing lubricant to be deposited throughout catheter placement (rather than just lubricating the end of the catheter). Another helpful technique is to pull the prepuce dorsal and caudally after the catheter is introduced into the penile urethra (Figure 122.5). Elevating the natural downward angle of the urethra as it passes out of the pelvic canal may facilitate catheter placement.

Once the initial catheter is in place, the urinary bladder can be emptied and flushed. A sterile closed collection system should be connected to allow for urine production to be quantified, and decrease risk of ascending infection.

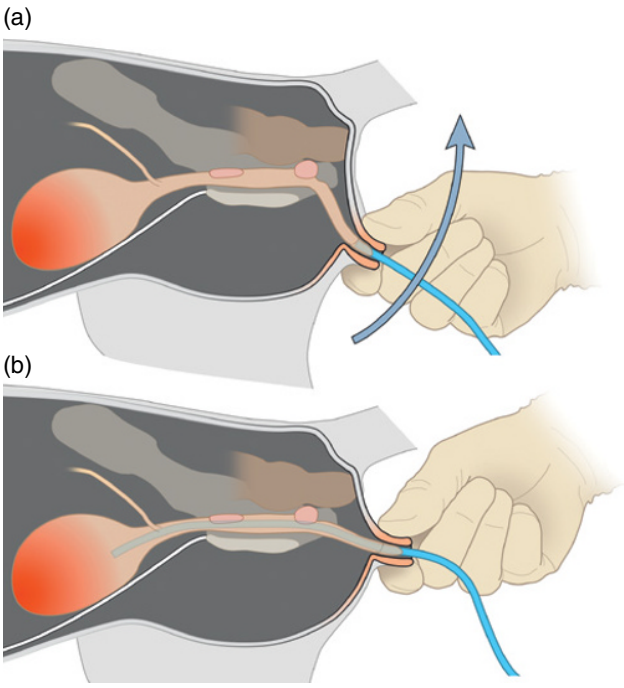


Figure 122.5 Once the catheter is seeded in the distal urethral, the prepuce is pulled dorsal and caudal to straighten the urethra and facilitate passage.

For catheterization and deobstruction in dogs, general anesthesia can be especially important to ensure optimal urethral relaxation. The prepuce or vulva should be cleaned and flushed to decrease risk of contamination. A red rubber or Foley catheter is typically used, though in some circumstances a more rigid catheter may be needed (with potential increased risk of urethral trauma). Similar to the process described for cats, hydropulsion with lubricated saline should be the primary means of retropulsing any physical obstruction. In male dogs, it is helpful to pinch the urethral orifice to prevent antegrade movement of flush solution. An additional useful trick (in either male or female dogs) is to have an assistant rectally apply pressure to the pelvic urethral during hydropulsion. This allows a build-up of pressure which, when released, can help dislodge a luminal obstruction.

If urethral catheterization fails due to urethral trauma, rupture, or persistent partial obstruction, antegrade urethral access can provide a means to deobstruct the patient and facilitate catheterization (Figure 122.6).

Briefly, percutaneous access into the bladder is achieved with an 18 gauge over-the-needle catheter by palpation or ultrasound guidance. Through the catheter, a hydrophilic wire is directed toward the bladder trigone and out the urethra. As the tear or trauma is usually created from a retrograde direction, the wire finds the true urethral lumen easily and often can be directly advanced out the penile urethra. Once wire access is achieved in this manner, the open-ended urinary catheter is advanced over the wire into the bladder lumen. The access catheter and wire are then removed and the urethral catheter sutured in placed and cared for routinely. Ideally, this procedure is performed under fluoroscopic guidance to visualize the path of the wire and appropriate positioning of the catheter.

Postobstructive Care

One major facet of postobstructive care is careful monitoring of urine output and maintaining fluid balance. Some patients may experience a postobstructive diuresis which can lead to significant quantities of urine production. Proposed mechanisms for this diuresis include accumulation of osmotically active substances in the blood, pressure necrosis, medullary washout and/or antidiuretic hormone resistance. Likely owing to these mechanisms, it has been demonstrated that up to 50% of cats may have increased urine production after deobstruction. However, in some circumstances it is unclear whether the initial rates of fluids administered may have also been contributing to increased urine production. Similar data are not available for dogs.

Given the potential to produce significant quantities of urine (>5–10 mL/kg/h), it is very important to keep up with urinary losses to prevent dehydration and hypov-

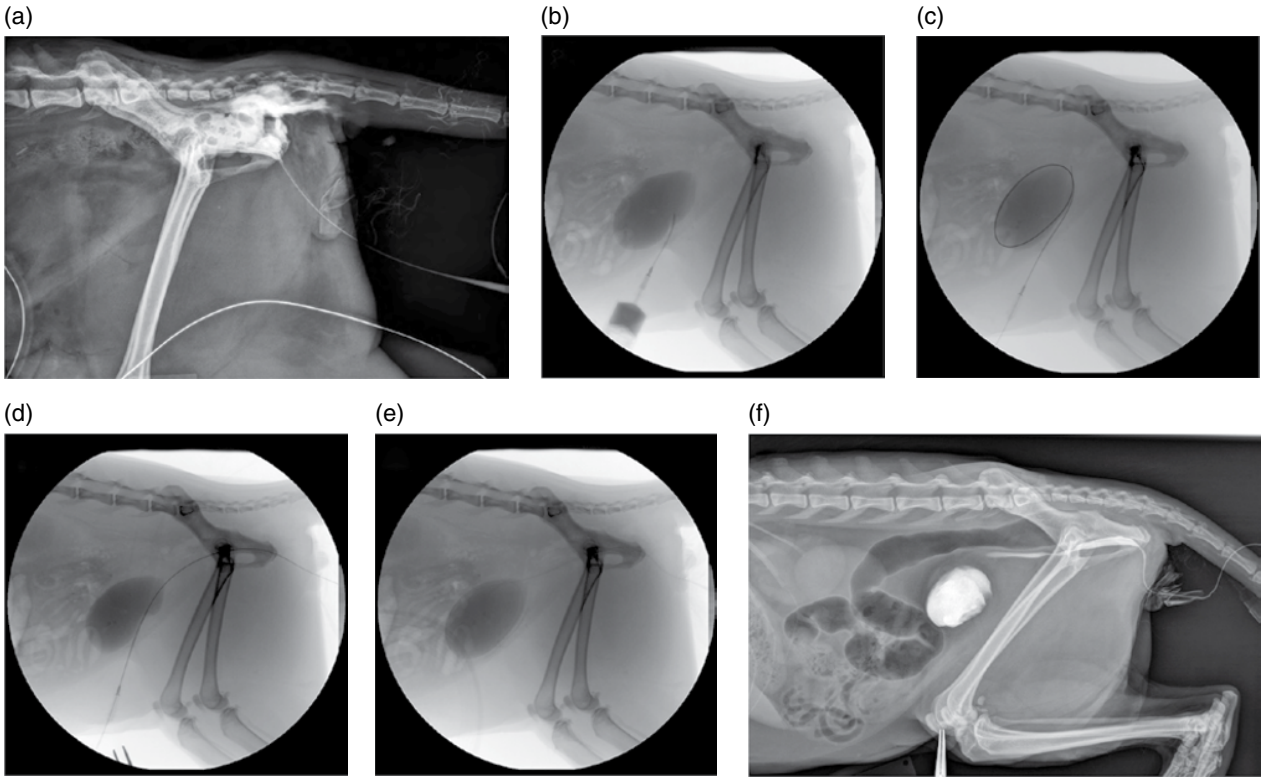


Figure 122.6 Radiographic images of antegrade urethral catheterization for urethral tear in a cat. (a) The initial retrograde urethrogram showing severe contrast extravasation throughout the pelvic canal consistent with urethral rupture during attempted urethral catheterization. (b) Percutaneous access to the bladder has been obtained with an 18-gauge over-the-needle catheter and iodinated contrast has been delivered to highlight the urinary bladder. (c) A hydrophilic guidewire is then advanced through the catheter and into the urinary bladder. (d) The wire is manipulated under fluoroscopic guidance and advanced antegrade out the urethra. As the tear was made during retrograde catheterization, the soft wire will follow the normal urethral lumen and pass out the penile urethra. (e) Once the wire is exteriorized, an open-ended urinary catheter can be advanced over the wire and will follow the true urethral lumen. Once the urinary catheter is within the bladder, the wire and bladder catheter are removed. (f) After seven days of in-dwelling urethral catheterization, a repeat urethrogram shows the urethral tear has healed and the urinary catheter is removed.

olemia. This can be achieved by at least matching the fluid rate to hourly urine production (even though the resultant rate could be very high). In the postobstructive period there is also the potential concern for inadequate urine production (<1 mL/kg/h). Major concerns in this setting would be obstruction of the collection system, dehydration, or oliguria from acute kidney injury.

The obstructive process and urethral catheter placement are painful and stressful, and could add to postobstructive morbidity. As such, provision of adequate analgesia and sedation is also important for managing these patients. For cats, buprenorphine (0.01–0.02 mg/kg q8h) generally provides sufficient pain control. If buprenorphine is not sufficient, a fentanyl continuous rate infusion (CRI) (2–4 µg/kg/h) or intermittent methadone (0.2–0.3 mg/kg q6h) is recommended. Because of the potential to cause excitability and hyperthermia, hydromorphone is typically avoided. For dogs, fentanyl or methadone (similar doses as cats) or hydromorphone (0.05–0.1 mg/kg) typically provide adequate analgesia. Acepromazine (0.05 mg/kg IV/IM/SC or 0.5 mg/kg PO) can provide adequate sedation to decrease stress and agitation, so long as the patient is stable. Given the potential functional nature of feline UO, the alpha-antagonist effects of acepromazine might promote urethral relaxation and decrease risk of reobstruction once the urinary catheter is removed.

Another important consideration is whether UO patients should be placed on antibiotics after catheter placement. This may be done with concern for existing UTI, or for introducing a UTI secondary to catheter placement. For cats, it has traditionally been accepted that the incidence of bacterial infection in lower urinary tract disease is very low. There is also evidence that prophylactic antibiotics do not prevent development of catheter-associated UTI. Therefore, antibiotic therapy is not recommended for UO in cats while the urinary catheter is in place unless bacteriuria and pyuria are documented. Dogs with evidence of UTI (based on urine cytology or positive culture) should be placed onto appropriate antibiotics.

Electrolytes and renal values should be monitored every 12–24 hours (or more frequently depending on patient severity at presentation) and should rapidly correct to normal. If there has not been a significant reduction in renal values within 24 hours, complications (such as uroabdomen) may have occurred. Given the potential for potassium wasting secondary to diuresis in the postobstructive period, supplementation may be needed, even for patients that initially presented with life-threatening hyperkalemia.

Further Therapeutic Considerations

For cats with UO not secondary to urolithiasis, medical management is typically sufficient. The urinary catheter should remain in place until bloodwork abnormalities, gross urine changes (major debris, clots or plugs), and postobstructive diuresis have resolved in order to help minimize the risk of immediate reobstruction. Performing a urine culture and susceptibility after catheter removal (sample obtained by cystocentesis) is recommended to determine if a UTI has been introduced. Observation for 12–24 hours after catheter removal will help to ensure effective spontaneous urination prior to discharge. In order to improve comfort and potentially decrease risk of reobstruction, continued analgesia and sedation after discharge may be helpful. While buprenorphine was previously recommended for oral administration in cats, its bioavailability has been called into question and it may not be effective. Instead, gabapentin (10 mg/kg) has potential as an oral analgesic, and could be given in conjunction with continued administration of acepromazine (0.5 mg/kg) for 5–7 days. As an alpha-1 antagonist and urethral relaxant, prazosin (0.25–0.5 mg per cat q12h) has also been suggested to decrease urethral spasm. However, a recent study failed to show an impact of prazosin administration on the overall risk of reobstruction. Antibiotics should only be dispensed based on results of urine culture taken after catheter removal.

Other recommendations which may help to decrease the risk of reobstruction include increasing water intake by switching to wet food, flavoring the water, or using a running-water bowl. In order to decrease stress, and thereby potentially reduce risk of reobstruction, environmental enrichment may be of benefit.

Urethral obstruction caused by urolithiasis often requires surgical intervention for stone removal. In most circumstances, successful catheterization is associated with retrohydropulsion of stones into the urinary bladder, which can be removed by subsequent cystotomy. If catheterization and deobstruction was not successful, it may be necessary to perform a urethrotomy, but this can be associated with significant risk of urethral stricture. For more distally lodged stones, penile amputation and perineal or scrotal urethrostomy may be preferred. Minimally invasive techniques for stone removal, including laser lithotripsy, percutaneous cystolithotomy, and cystoscopic-guided stone basket retrieval, are available in some centers. Stones should always be submitted for analysis to determine composition, with subsequent dietary management to decrease risk of recurrence.

Historically, dogs that presented with complete UO secondary to neoplasia were euthanized, managed by indwelling urinary catheters until NSAIDs (piroxicam), chemotherapy or radiation therapy alleviated the obstruction, or underwent urinary diversion procedures that are invasive and associated with moderate to severe rates of morbidity. In the last decade, intraluminal stenting for malignant urethral obstruction has been employed with increasing frequency as a mechanism to palliate the disease and restore urethral patency (Figure 122.7).

In the largest series to date on urethral stent implantation, involving 42 dogs, the obstruction was relieved in 41 dogs and median survival was reported as 78 days, with some dogs living for over a year after stent implantation. The most common complication associated with the procedure was urinary incontinence, graded as severe in approximately 25% of the dogs. While placement of a urethral stent for urothelial malignancy provides a minimally invasive option for animals with complete urethral obstruction, it is solely a palliative procedure and further tumor growth and/or spread should be expected unless additional chemotherapy or radiation therapy is pursued.

Surgical therapy is often advised for patients with urethral stricture if the animal is stranguric or oliguric and can result in an excellent outcome if the stricture is in the penile urethra and either a perineal urethrostomy (feline) or scrotal urethrostomy (canine) can be performed. Treatment of urethral strictures is complicated when they occur within the pelvic urethra as this will require surgical exposure to the pelvic canal and resection of the stricture. Additionally, surgical resection and anastomosis to remove a urethral stricture may induce development of a stricture at the anastomotic site as the tissues heal. Options in these cases include urinary diversion procedures such as a cystostomy tube, which are associated with a high rate of complications, balloon dilation of the stricture, or placement of an intraluminal stent. Urethral stenting for the palliation of urethral strictures has been reported with good to excellent results in both the dog and cat (Figure 122.8).

While effective in many cases, there is a risk of urinary incontinence with stent implantation that is higher in female dogs and in animals with greater amounts of urethral coverage (e.g., longer stents). Anecdotally, strictures have been observed to grow through the interstices of bare-metal stents. Consequently, covered stents may

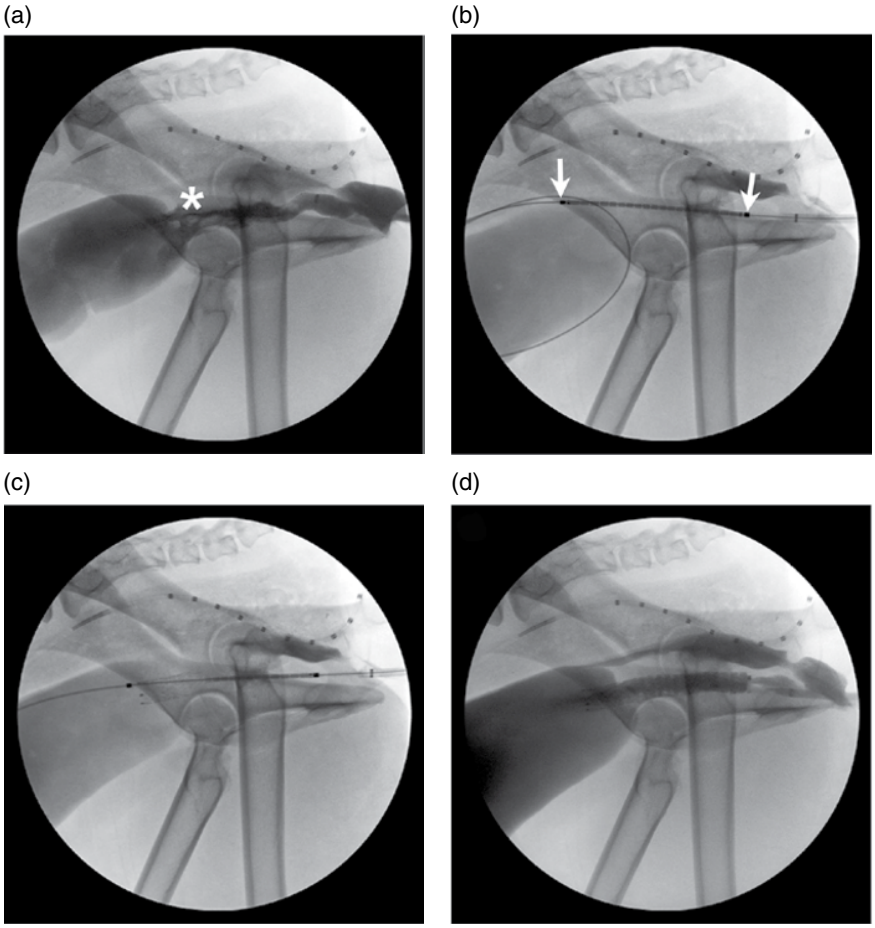


Figure 122.7 Fluoroscopic images during urethral stent placement from a 9-year-old female mixed-breed dog with transitional cell carcinoma of the bladder trigone and severe stranguria. (a) The initial urethrogram shows multiple filling defects in the area of the bladder trigone and proximal urethra (*asterisk*). (b) A wire has been advanced past the obstruction and into the bladder, over which the self-expanding stent is advanced. The length of the stent can be seen between the two arrows. (c) The stent is partially expanded under fluoroscopic guidance. (d) A repeat urethrogram post stent implantation shows improved urethral patency with mild urethral spasm at the distal aspect of the stent. A marker catheter is present in the colon in all images to correct for radiographic magnification.

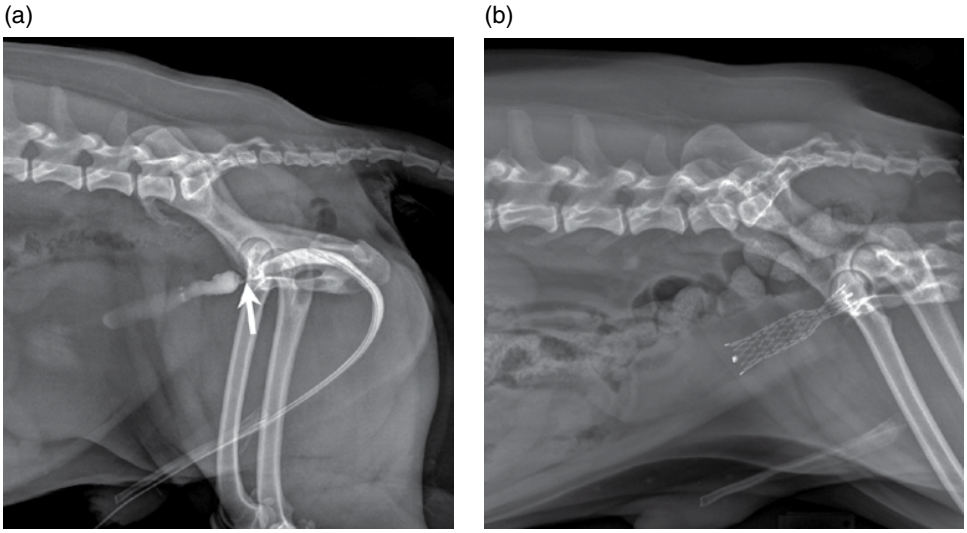


Figure 122.8 Radiographic images from a male mixed-breed dog with a urethral stricture and severe stranguria. (a) The contrast urethrogram prior to stent implantation with a focal stricture in the urethra (*arrow*). (b) One day post stent implantation with improved urethral lumen diameter; the dog was continent and urinating normally upon stenting.

be considered to avoid this potential development, albeit with a possible increased stent infection rate, in the authors' experience.

Alternative Management Protocols for Feline UO

Unfortunately, the ability to provide the optimal treatment course (close monitoring, IV and urinary catheterization) may be limited by owner financial constraints. Predicated on the notion that there is a component of functional obstruction (urethral edema and spasm), it has been demonstrated that pharmacologic manipulation (buprenorphine and acepromazine +/- dexmedetomidine), a low-stress environment, and intermittent cystocentesis can result in spontaneous urination without the need for catheterization. This approach was successful in achieving spontaneous urination in approximately 75% of cats in one study. However, while a reasonable alternative to euthanasia, this protocol cannot be recommended in lieu of traditional management (which carries a reported success rate of 91–94%) as no direct comparison between the two has been made. Further, severely debilitated cats in need of emergency stabilization, based on significant physical exam/metabolic derangements, should be excluded from this protocol.

In some cases, financial limitations might preclude the ability to hospitalize for treatment. Under those circumstances, it may be necessary to offer euthanasia, especially for severely affected patients (hypothermia, bradycardia, lateral recumbency, etc.). For those patients presenting in the earlier stages of obstruction that are not yet significantly ill, it may be possible to provide care on an outpatient basis, though this should be reserved as a last resort. One option would be to provide sedation and analgesia (acepromazine and buprenorphine) and bladder decompression through either passage of a urinary catheter or cystocentesis. Catheterization would offer the benefit of removing any physical obstruction within the urethra but could also result in damage or irritation to the urethral and an increased risk of reobstruction. Cystocentesis would likely be less expensive to perform and less injurious to the urethra, but might only provide temporary relief if a significant physical obstruction is present.

In either approach, the patient would be discharged in the hopes that continued analgesia and sedation will allow for spontaneous urination to occur. Aside from anecdotal reports and clinical experience, there is no evidence to support the merits of either of these approaches, nor is there information regarding the likelihood of success or recurrence. The client would have to be well informed of the potential for treatment failure, and follow-up phone calls to determine response would be strongly recommended.

Prognosis

Depending on the underlying cause, there is an approximately 15–40% incidence of recurrence with feline UO. With repeated obstructive episodes, it may be necessary to consider perineal urethrostomy (PU). This procedure will decrease risk of UO, though will not impact underlying FIC if present. In addition, patients with a PU may be at increased risk for UTI.

Prognosis for UO in dogs is even more dependent on the underlying cause. Obstruction secondary to urolithiasis is generally very good with successful catheterization and stone removal, though there is potential for recurrence. Proper dietary management to decrease stone formation may help decrease this risk. Prognosis for bladder/urethral/prostatic neoplasia is guarded, with palliative efforts (chemotherapy, radiation, urethral stenting) only providing temporary relief. Reported median survival for dogs with urothelial malignancy varies from days to nearly one year after diagnosis, depending on the severity of disease and the treatment pursued.

Ureteral Obstruction

Etiology/Pathophysiology

Ureteral obstruction in small animals results from urolithiasis, stricture, blood clots, congenital anomalies (ureteropelvic junction stenosis), neoplasia, external compression, severe ureteritis, or as a functional consequence of urethral obstruction. In nearly all cats and most dogs, urolithiasis is identified as the underlying cause. A rare cause of ureteral stricture is the presence of a circumcaval ureter, reported in four of 10 cats with strictures in one series and also reported in case reports of dogs. The consequences of ureteral obstruction vary depending on several factors: whether one or both kidneys are affected, the acuity versus chronicity of the disease, whether the obstruction is partial or complete, and the presence of any complicating co-morbidities, such as infection.

Ureteral obstruction may be complete or partial, depending on whether any urine is able to flow beyond the site of obstruction. The degree of obstruction dictates the severity of any rise in hydrostatic pressure exerted upstream of the obstruction – to the proximal ureter, renal pelvis, and renal parenchyma. The effect of this increased pressure on the proximal ureter and renal pelvis is passive dilation of these structures, which can become profound (Figure 122.9).

Similar to UO, the increased pressure upstream of a ureteral obstruction is transmitted from the renal pelvis to the renal parenchyma, specifically to the nephron and

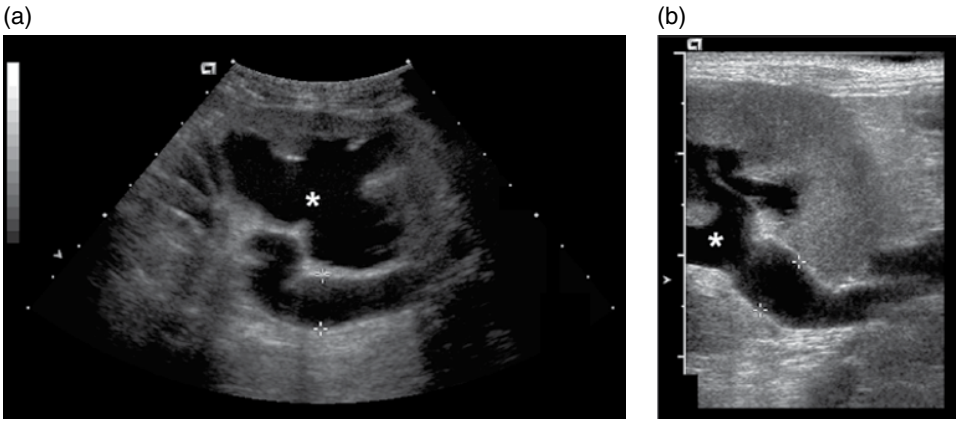


Figure 122.9 Ultrasound images of ureteral obstruction in a dog (a) and cat (b). In both images, moderate to severe dilation of the renal pelvis (*) and proximal ureter (between the +) can be appreciated. The dog suffered from transitional cell carcinoma of the bladder and the cat from ureterolithiasis.

Bowman's space, resulting in impairment or even cessation of glomerular filtration. With experimental acute ureteral obstruction, renal blood flow initially increases, but gradually declines as ureteral hydrostatic pressure rises and the obstruction is not alleviated. Permanent damage to the kidney occurs within days to weeks after ureteral obstruction though if the obstruction can be alleviated rapidly, there may be no permanent effect on renal function. Experimental studies in dogs suggest the obstructed kidney will recover only a fraction of its initial, normal GFR after weeks of complete obstruction even if the obstruction is completely alleviated at that time. In the setting of bilateral ureteral obstruction, the effect on GFR is even more dramatic. This implies that diagnosis of ureteral obstruction is an urgent problem that requires rapid deobstruction to preserve renal function, particularly as animals with ureteral obstruction often are older and likely have a degree of renal compromise prior to the development of the obstruction.

Epidemiology and Signalment

Large-scale epidemiologic studies of ureteral obstruction in veterinary medicine are lacking. As described above, the cause in most feline cases appears related to ureterolithiasis while the cause in dogs is often related to ureterolithiasis or urothelial malignancy. The epidemiology of urolithiasis (both upper and lower urinary tract) in small animals suggests that from the 1980s to the early 2000s, there was an increasing frequency of this condition in both dogs and cats, concurrent with an increased proportion of calcium oxalate calculi compared to struvite. This trend for increasing calcium oxalate calculi in cats appears even more dramatic when only upper urinary tract stones are considered. In dogs with ureterolithiasis, struvite and calcium oxalate calculi seem to be found in a comparable proportion.

Breed predilections are observed in dogs with upper urinary tract calculi, with miniature schnauzers, Lhasa apsos, shih tzus, and Yorkshire terriers affected with greater frequency than other breeds. No consistent breed differences have been reported in cats specific to ureterolithiasis. There are breeds of dog that are recognized to have a greater incidence of urothelial malignancy than others. Specifically, the Scottish terrier, Shetland sheepdog, beagle, wire-haired fox terrier, and West Highland white terrier are reported to have an increased risk.

The effect of gender on prevalence of ureterolithiasis is unclear. It has been suggested that male cats are more frequently affected by urolithiasis in general than females, though reports evaluating solely ureteral stones suggest a higher proportion of female cats. In dogs with ureterolithiasis, there are fewer cases reported, but a female majority was also observed. Female dogs have been recognized as having a higher prevalence of urothelial neoplasia compared to males; additionally, castrated dogs of both sexes are at higher risk for transitional cell carcinoma compared to sexually intact dogs.

History and Clinical Signs

The signs of ureteral obstruction are often nonspecific, with vomiting, lethargy, and inappetence commonly reported. Abnormalities in urination, such as pollakiuria, hematuria, or stranguria, can also be seen, which may be related to concurrent lower urinary tract uroliths, lower urinary tract infection, or ureteral irritation. Weight loss may be reported if the animal has a chronic course of disease with compromised renal function. Increased urination and thirst may also be observed, associated with renal dysfunction if present.

Diagnosis

Abdominal pain may be the only finding associated with unilateral ureteral obstruction, as the animal's renal function from the contralateral kidney should be sufficient to maintain renal values in a normal range. Abdominal discomfort appears to be a more easily recognized sign in the dog than the cat. On physical examination, a poor body condition may be observed if the obstruction has been chronic and renal dysfunction is long-standing. It is relatively common to observe cats with marked discrepancy in renal size on abdominal palpation, the so-called "big kidney, little kidney" syndrome. This is theorized to occur secondary to prior chronic obstruction of the little kidney, which led to a reduction in glomerular filtration and renal blood flow, progressive nephron loss, renal fibrosis, and compensatory hypertrophy of the unobstructed big kidney.

Diagnostic testing involves arterial blood pressure measurement, serum biochemical analyses to investigate the degree of renal dysfunction and concurrent disease, a complete blood count to screen for anemia or leukocytosis, urinalysis and urine culture, and imaging. Abdominal radiographs are advised to look for evidence of urolithiasis as most, at least in the cat, are calcium oxalate and therefore radiopaque. However, radiography is imperfect as small stones may be missed or findings interpreted as stones may not be within the urinary tract. The presence of calculi in the kidneys, bladder, or urethra as well as the relative size of each kidney can also be investigated with survey radiographs. For dogs with urothelial neoplasia, an increased soft tissue opacity may be observed at the bladder trigone or prostate. Confirmation of ureteral obstruction, however, typically requires ultrasound (see Figure 122.9). Ultrasound should be utilized to quantify the magnitude of renal pelvic and ureteral dilation, the presence, number, and location of uroliths throughout the urinary tract, the existence of a stricture or area of ureteral thickening, the location of a trigonal or other extramural lesion compressing the ureter, an assessment of renal blood flow, and the presence of any free abdominal fluid.

Therapy

Treatment is directed at providing the animal comfort and alleviating the obstruction. Analgesia should be given due to the pain associated with ureteral obstruction, related to stretch of the ureteral wall and renal capsule resulting in activation of mechanoreceptors. Medical therapy should be initiated as soon as a diagnosis of ureteral obstruction is made as it will be necessary to help stabilize the animal and may aid in alleviating the obstruction in a small proportion of cases. However, medical therapy is typically insufficient to cure most ureteral obstructions, as the physical barrier (stone, tumor, stricture) must be addressed.

Upper urinary tract calculi are typically calcium oxalate, particularly in the cat, and dietary dissolution will therefore not be effective in most cases. Furthermore, there is insufficient time to allow dissolution to take place in the setting of a complete ureteral obstruction in which rapid nephron loss is occurring. In the patient with ureterolithiasis, intravenous fluid therapy should be initiated as the animal is often dehydrated and an increase in urine flow may help to move the calculus into the bladder.

Ureteral relaxation and reduced ureterospasm can be achieved by administration of an alpha-receptor antagonist such as prazosin (0.25–0.5 mg per cat q12h) or the smooth muscle relaxant amitriptyline (1 mg/kg PO q24h). There are additional medications with greater urinary selectivity now available on the human market, such as tamsulosin, though there is only anecdotal evidence of their use in animals. An additional strategy to facilitate movement of ureteroliths is a mannitol infusion (0.25-0.5 g/kg over 20 min, followed by CRI at 1 mg/kg/min) to promote an osmotic diuresis. Mannitol should be given with caution in these animals, however, as hypervolemia can develop – particularly in cats or dogs with bilateral ureteral obstruction. In the dog, broad-spectrum antibiotics should be initiated as canine upper urinary tract calculi are more likely to be infected than in cats, which are typically sterile.

While medical therapy should be initiated once a diagnosis of ureteral obstruction is made, it must be recognized that medical therapy is effective in only a small portion (reported as less than 15%) of cats with obstructive ureteroliths. Medical therapy should be attempted for no more than 12–48 hours in animals with ureteral obstruction secondary to urolithiasis, depending on the stability of the patient, with serial monitoring to evaluate for progressive renal decline or movement of the stone. If medical therapy is unsuccessful, or in the setting of ureteral obstruction secondary to urothelial malignancy that will not respond rapidly to medical therapy, intervention by surgery or minimally invasive therapy is advised.

Currently, noninvasive therapy for ureteral obstruction secondary to urolithiasis involves the use of extracorporeal shock wave lithotripsy. This treatment modality employs high-energy shock waves directed through the body and focused at the site to pulverize the urolith into sufficiently small particles that can be safely passed out of the body. This is the standard of care in the treatment of human upper urinary tract calculi, but has not gained wide use in veterinary medicine. Few veterinarians employ this therapy in cats as the small size of the feline

ureter makes even small stone fragments problematic and even in dogs there is risk of ureteral obstruction after shock wave therapy of nephroliths. The likelihood of ureteral obstruction following shock wave therapy can be limited if a ureteral stent is implanted at the time of the shock wave treatment. Extracorporeal shock wave lithotripsy is a consideration for dogs and appears well tolerated, though transient hematuria or shock wave-induced pancreatitis may occur.

In dogs, surgical ureterotomy for an obstructive urolith is typically associated with a favorable outcome in the hands of an experienced surgeon. In cats, however, major complications were reported in a significant number of the cases, with a mortality rate of 18% in the largest series from a highly experienced center. In light of these figures, alternatives to surgical ureterolith removal have been developed in recent years, including ureteral stenting (Figure 122.10) and subcutaneous ureteral bypass (Figure 122.11).

An indwelling ureteral stent is composed of a flexible polymeric compound that has a loop at each end, which help maintain the stent's position throughout the ureter, with one loop in the renal pelvis and the other in the bladder. Ureteral stents may be placed endoscopically, though this is most feasible in female dogs where a rigid cystoscope and a comparatively larger urethra facilitate the procedure. For cats, the stents are typically placed via an open abdominal procedure with fluoroscopic guidance. The stent may be placed antegrade through the renal parenchyma after needle access into the renal pelvis, or retrograde through a cystotomy incision and visualization of the ureterovesicular orifices. Reports of ureteral stents in both dogs and cats suggest successful implantation in greater than 95% of cases with low complication or reintervention rates. The cat shown in Figure 122.10 presented with a BUN of 280 mg/dL (reference interval, 13–30 mg/dL) and a creatinine of 20.5 mg/gL (reference interval, 0.9–2.1 mg/dL) and complete

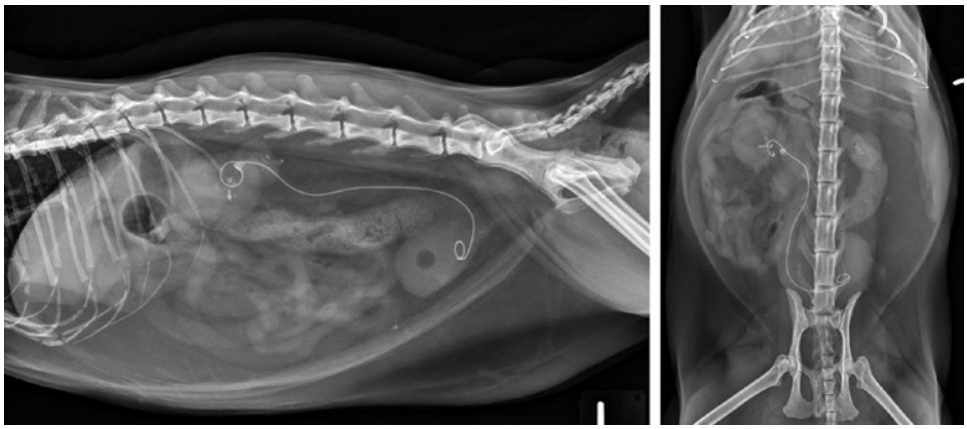


Figure 122.10 Radiographic images from a cat with complete right ureteral obstruction secondary to a circumcaval ureter and ureterolithiasis. A double-pigtail ureteral stent has been implanted in the obstructed right ureter to restore urine flow. Note that the left kidney is severely shrunken and small.



Figure 122.11 Radiographic images from a cat with a subcutaneous ureteral bypass system. The system includes a nephrostomy tube and a cystostomy tube connected to a dual-lumen vascular port that is sutured to the body wall under the ventral skin.

right ureteral obstruction. In addition, it had a severely shrunken left kidney, which was likely nonfunctional. After placement of the right ureteral stent, the cat was discharged four days later with a BUN of 16 mg/dL and a creatinine of 1.4 mg/dL.

In the authors' experience, ureteral stents in cats provide acute resolution of the obstruction but have a moderate risk for ureteral irritation and pollakiuria that can be challenging to manage. Studies suggest one-third of cats with a ureteral stent will have dysuria either transiently or permanently and that 19% of feline ureteral stents will become obstructed. There is also an increased risk of ascending urinary infection with a stent in place. In human medicine, ureteral stents are left in place for only 3–4 months in most cases to avoid stent encrustation and calcification. However, stents have been left indwelling in cats for greater than five years that were seemingly well tolerated (see Figure 122.10). In dogs, ureteral stents for benign ureteral obstructions are well tolerated, can be placed cystoscopically, and are often removed once the obstructive stone has passed, avoiding long-term risk for stent dysfunction. The presence of a ureteral stent induces passive ureteral dilation which may allow a previously obstructive urolith to pass, after which the stent can be removed via an outpatient cystoscopic procedure. Currently, the authors monitor animals with ureteral stents every 3–4 months by imaging and urine culture. If stent malfunction develops, evidenced by recurrent infection, pollakiuria, obstruction, abdominal pain, or stent migration/fracture, then the stent is removed via cystoscopy or cystotomy.

To avoid eventual dysuria and potential complications of a ureteral stent in cats, or for those animals in which a stent cannot be placed, subcutaneous ureteral bypass devices are commercially available. Subcutaneous ureteral bypass employs a nephrostomy tube and a cystostomy tube, which are connected to a dual-lumen vascular port that is attached under the skin to the ventral body wall. This port allows the system to be flushed at regular intervals to avoid obstruction and facilitates urine sampling (see Figure 122.11). At many centers, subcutaneous ureteral bypass devices are now the treatment of choice for obstructive urolithiasis in cats but are rarely implanted in dogs where conventional surgery or temporary ureteral stenting are often effective. Long-term complications of ureteral bypass devices include infection and biofilm formation, encrustation and obstruction, and rarely signs of dysuria. The rate of complications appears lower in cats with a subcutaneous ureteral bypass device than was observed with ureteral stents but routine surveillance (imaging, system flushing, urine culture) is still required.

For animals with ureteral obstruction secondary to urothelial malignancy, ureteral stenting is advised to deobstruct the kidney and restore urine flow. In the dog, this is done via percutaneous transabdominal access to the dilated renal pelvis with a small needle, through which a wire is advanced under fluoroscopic guidance to the site of obstruction (Figure 122.12).

The wire is manipulated through the obstruction, into the bladder, and out the urethra. The stent is then advanced over this wire and into place within the renal pelvis proximally and the bladder distally and urine now flows through the stent lumen, bypassing the neoplastic obstruction. A small series of 12 cases found that percutaneous stent implantation for trigonal urothelial carcinoma was feasible in all dogs and the stents remained patent for the remainder of the animals' lives, which ranged from 0.25 to 11 months.

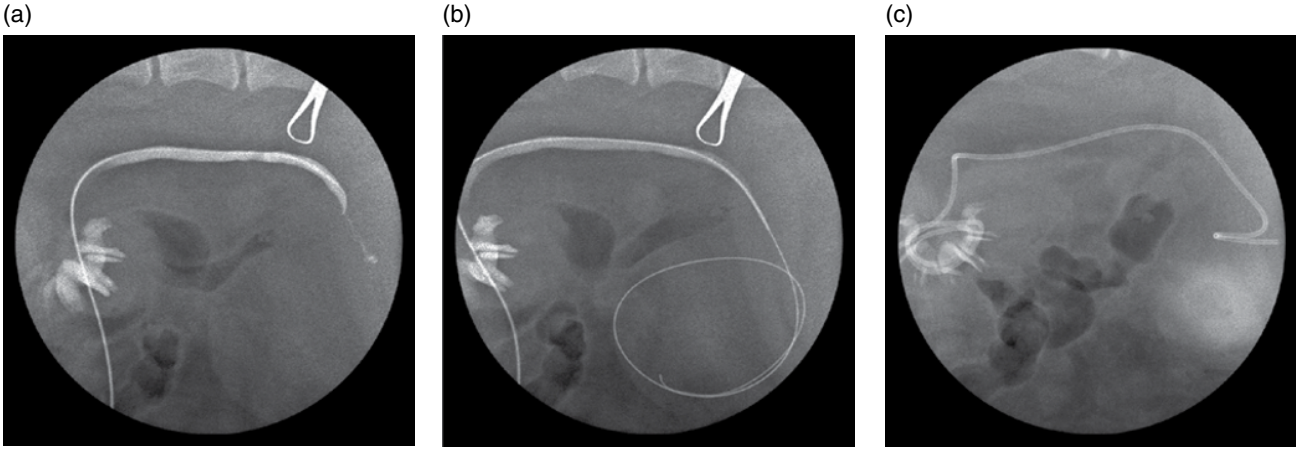


Figure 122.12 Fluoroscopic images from an 8-year-old Labrador retriever with urothelial neoplasia causing ureteral obstruction. (a) Direct puncture of the renal pelvis was obtained and a wire was advanced down the dilated ureter to the site of obstruction at the ureterovesicular junction. (b) With manipulation, the wire is advanced across the obstruction and into the bladder. (c) The stent has been positioned throughout the length of the ureter with one pigtail in the renal pelvis and one in the bladder, allowing restoration of urine flow past the malignant obstruction.

Prognosis

The prognosis for ureteral obstruction is fair, dependent on the chronicity of the obstruction, the ability of the veterinarian to alleviate the obstruction, and the underlying disease process. If the obstruction has been in place for some time, a return to normal renal function after ureteral patency is restored is unlikely. In the setting of urolithiasis, recurrence of stones and progression of intrinsic renal dysfunction are common, but typically manageable. In dogs with urothelial malignancy, the prognosis by the time they have developed ureteral obstruction is typically poor. However, ureteral decompression in this disease can allow an improved quality of life and give the patient additional time until conventional therapy (e.g., chemotherapy) has an impact.

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123

Urolithiasis in Small Animals

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Overview

Definition

Urine is a complex solution that contains multiple crystal components. The ionic elements of crystals in urine are referred to as crystalloids, which can be organic or inorganic. Uroliths are organized assemblages of crystalloids, combined with a small amount of organic matrix, located within the urinary tract.

Urolith Formation

Formation of urinary calculi (uroliths) has been hypothesized to occur through multiple mechanisms or processes. Three of the more common of these theories are:

- *the precipitation-crystallization theory*: supersaturation of urine with crystalloids is followed by growth of calculi
- *the matrix-nucleation theory*: an abnormal substance in the urine is responsible for calculi development
- *the crystallization-inhibition theory*: the absence of a critical inhibitor (or the presence of a promoter) of crystal formation is the primary factor in calculi development.

All three of the above theories (individually or in combination) likely contribute to development of individual uroliths.

Urine is commonly supersaturated with crystalloids, and this is a prerequisite for urolith formation (Figure 123.1). Supersaturation of urine with crystalloids depends on urine crystal volume, renal crystal excretion, urine concentration, urine pH, and the presence of urolith promoters or lack of inhibitors. Following establishment of these supersaturation criteria, and dependent on numerous patient-related factors, urine crystals may begin to aggregate into a nucleus. The crystal nucleus, commonly referred to as the nidus, can then develop into a urolith, aka the "stone."

Additional theories regarding urolith development have been postulated. One of these, homogenous nucleation, refers to the spontaneous precipitation of crystals from a pure solution. This process is considered uncommon in urine, and urine crystal formation is believed to occur through heterogenous nucleation. This theory is similar to the matrix-nucleation theory, whereby another substance (e.g., bacteria, inflammatory cells or debris) acts as a nidus for crystal precipitation. Once again, after the crystal nidus has formed, it may develop into a urolith dependent on the following: degree and duration of urine supersaturation, and sufficient time for the nidus to remain in the urinary tract without being flushed out.

Factors that predispose to urine stasis also play an important role in urolithiasis formation. Consequently, factors that induce frequent and regular voiding of urine may be protective and aid in prevention of urolith development and progression.

History and Physical Examination

History

Dogs and cats with uroliths may present for a variety of animal owner concerns. Most commonly, dogs and cats present with lower urinary tract signs (i.e., pollakiuria, hematuria, stranguria) related to the irritating presence of uroliths in the bladder or urethra. In patients with upper urinary tract uroliths (i.e., nephroliths, ureteroliths), signs

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Figure 123.1 One canine oxalate urolith from a 12-year-old female spayed miniature schnauzer. *Source:* Courtesy of Andrew Moore, Canadian Veterinary Urolith Centre.

of systemic disease may be noted (e.g., vomiting, lethargy, anorexia, polyuria-polydipsia secondary to uremia, etc.), which can range in severity, as related to secondary infection or complete urethral obstruction. Other patients may have subclinical disease, that is, no signs, and either upper or lower urinary tract uroliths are discovered incidentally, for example via radiographs, ultrasound, etc.

Physical Examination Findings

Physical examination is frequently normal but dependent on stone type and, more importantly, location, abnormalities associated with either the lower or upper urinary tract can occur and are detailed below. Systemic signs (i.e., fever, dehydration, etc.) can be found in patients with secondary infections or obstructive disease.

Lower Urinary Tract Urolith Physical Exam Findings

Palpation of urinary calculi can be challenging, particularly in overweight or tense patients. If the bladder is empty and there are multiple stones, a crepitant sensation may be noted on bladder palpation. Urethral stones can sometimes be palpated rectally or via palpation of the perineum or penile urethra. A large firm bladder may be suggestive of urethral obstruction. However, in the case of uroabdomen, the bladder may be empty (not palpable), and the patient may have a tense and painful abdomen.

Upper Urinary Tract Urolith Physical Exam Findings

The patient may be subclinical. An enlarged kidney may be palpated with hydronephrosis associated with ureteral obstruction in dogs and cats; however, most cats have chronically small kidneys, even with obstruction. Unilateral renal or ureteral obstruction should not result in clinical signs related to uremia, unless there is contralateral kidney disease.

Systemic disease signs, such as fever, weight loss or dehydration, associated with uremia may be present dependent on functionality of the renal parenchyma and the presence of infection. Flank pain may be present with ureteral obstruction or infection.

Patient Signalment Related to Specific Stone Types

In dogs and cats, signalment (breed, sex, age) and geographic region can provide clues to urolith composition (Tables 123.1, 123.2).

Oxalate Urolithiasis

Calcium oxalate uroliths are usually composed of 100% calcium oxalate, although some also contain varying amounts of calcium phosphate. Additionally, concurrent infection can change the composition of the stone, for example calcium oxalate nidus encased in struvite shell. Two crystalline forms of calcium oxalate uroliths can occur: calcium oxalate monohydrate (whewellite) and calcium oxalate dihydrate (weddellite). Calcium oxalate monohydrate is more frequent in canine uroliths than calcium oxalate dihydrate.

The surface characteristics of oxalate uroliths can vary widely; uroliths may be smooth, mulberry shaped or have sharp projections (Figure 123.2; see also Figure 123.1).

Epidemiology and Risk Factors

Calcium oxalate uroliths represented 48.1% (49.5% including mixed stones) of all canine and feline uroliths submitted to the Canadian Veterinary Urolith Centre (CVUC) from 2009 to 2014 (see Table 123.2). Most upper urinary tract uroliths in cats (98%) and half of those found in dogs are composed of calcium oxalate.

Although calcium oxalate stones are not considered infection induced, they may be associated with secondary urinary tract infections (UTI). This is because the presence of the uroliths is believed to affect the patient's local immune defenses. In one study, 52% of female dogs and 31% of male dogs with calcium oxalate urolithiasis were found to have concurrent bacteria present, that is, positive urine or urolith cultures. However, other studies have not supported an association between calcium uroliths and UTI.

Risk factors for calcium oxalate uroliths in dogs include sex, and they occur more commonly in male than female dogs. Additionally, neutered male dogs have an increased risk of calcium oxalate uroliths compared with intact males. Obese dogs are more likely to form calcium oxalate uroliths, which is similar to cats and humans.

Table 123.1 Summary of the signalment of cats and dogs with each type of stone

	Dogs			Cats		
	Breed	**Sex**	**Age**	**Breed**	**Sex**	**Age**
Cystine	English bulldog, Newfoundland, dachshund, Irish terrier, basset hound, bullmastiff, Rottweiler,mastiff, Australian cattle dog, Australian shepherd, Chihuahua, Basenji, Scottish deerhound, Staffordshire terrier, pitbull terrier, Welsh corgi, miniature pinscher, silky terrier, bichon frise, Yorkshire terrier, Dalmatian, borzoi, Shetland sheepdog, Doberman, border collie	Male dogs much more commonly than females (except in Newfoundlands)	Young to middle-aged dogs (3–8 years), exception in Newfoundlands	Very rare in cats	Males equal to female	Any age, average 3–5 years or older
Oxalate	Any breed but increased risk in miniature schnauzer, bichon frise, Lhasa apso, Yorkshire terrier, miniature poodle, shih tzu, and other small breed dogs. The predisposition for smaller breeds may be related to their lower urine volume, fewer numbers of micturitions, and likely increased mineral concentrations compared with larger breeds	Male dogs more commonly than females; exception miniature schnauzer	No age predilection (generally older than those with struvite calculi)	Persian and Himalayan cats	Male neutered cats more commonly than females	>7 but <10 years
Purine	Black Russian terriers, shih tzus, miniature schnauzers, Yorkshire terriers, Dalmatians, English bulldogs	Pure urates are more common in males than females	Variable (in Dalmatians, any age but often 1–4 years; other breeds 3–6 years)	Siamese, Birman, Egyptian Mau (male)	No sex predisposition in cats	Mean age 6.3 ± 0.17 years; portosystemic vascular shunts (PSS) are more common in cats <1–5 years
Silicate	German shepherds, Old English sheepdog, miniature schnauzer, shih tzu, Lhasa apso, Yorkshire terrier, Pekingese, Labrador retriever, golden retriever, cocker spaniel, English bulldog, bichon frise, Rottweiler, and mixed breeds	Male dogs much more commonly than females	Middle-aged dogs	Does not appear to be a breed predisposition	Does not appear to be a gender predisposition	Does not appear to be an age predisposition
Struvite	Any breed Increased risk in miniature schnauzer, bichon frise, shih tzu, Lhasa apso, Yorkshire terrier, miniature poodle (and other small-breed dogs). The predisposition for smaller breeds may be related to their lower urine volume, fewer numbers of micturitions, and likely increased urine mineral concentrations compared with larger breeds	Female dogs more commonly than males	No age predilection (middle-aged but generally younger than those with oxalate calculi). Calculi that occur in dogs younger than 1 year are frequently composed of struvite	Any breed Himalayan Persian, domestic cats	No sex predilection, may be slightly more common in females >2 years	No age predisposition but typically >6 years

Table 123.2 Urolith composition for feline and canine samples submitted to the Canadian Veterinary Urolith Centre (Guelph, Ontario, Canada; 2009–2012)

Major composition	Canine n (%)	Feline n (%)	Total n (%)
Ammonium urate	619 (2.9)	257 (4.7)	876 (3.3)
Brushite	60 (0.3)	2 (0.04)	62 (0.2)
Calcium oxalate	10 043 (47.4)	2778 (50.7)	12 821 (48.1)
Calcium phos apatite	221 (1.0)	69 (1.3)	290 (1.1)
Calcium phos carbonate	240 (1.1)	11 (0.2)	251 (0.9)
Cystine	134 (0.6)	6 (0.1)	140 (0.5)
Silica	181 (0.9)	7 (0.1)	188 (0.7)
Sodium urate	21 (0.1)	1 (0.01)	22 (0.08)
Struvite	7226 (34.1)	2238 (40.9)	9464 (35.5)
Uric acid	5 (0.02)	0	5 (0.02)
Xanthine	5 (0.02)	5 (0.09)	10 (0.04)
X-oxalate/Ca phosphate	237 (1.1)	28 (0.5)	265 (1.0)
X-oxalate/silica	63 (0.3)	1 (0.02)	64 (0.2)
X-oxalate/struvite	39 (0.2)	13 (0.2)	52 (0.2)
X-struvite/Ca phosphate	1878 (8.9)	21 (0.4)	1899 (7.1)
X-struvite/urate	215 (1.0)	41 (0.7)	256 (1.0)
Total	21 187	5478	26 665

Source: Courtesy of Andrew Moore, Canadian Veterinary Urolith Centre.



Figure 123.2 Feline oxalate stones from a 16-year-old female spayed domestic short-hair. *Source:* Courtesy of Andrew Moore, Canadian Veterinary Urolith Centre.

Etiopathogenesis

Hypercalciuria and Hyperoxaluria

Excessive urinary excretion of calcium (hypercalciuria) or oxalate (hyperoxaluria) results in increased risk of calcium oxalate urolith formation. Lulich *et al*. reported that 6/6 miniature schnauzers with calcium oxalate urolithiasis had hypercalciuria. Similarly, urinary concentration of oxalate is an important factor in calcium oxalate crystallization and urolithiasis. This is because increases in urine oxalate concentration have a greater effect on urinary saturation of calcium oxalate than equivalent increases in urinary calcium concentration on a molar basis.

Urinary oxalate is derived mainly from endogenous production in the liver (metabolism of ascorbic acid, glyoxylate, and glycine) with lesser amounts from dietary intake of oxalate. Enteric (large intestine) colonization of *Oxalobacter formigenes*, an anaerobe which exclusively relies on oxalate metabolism for energy, is correlated with absence of hyperoxaluria or calcium oxalate (CaOx) urolithiasis in humans and laboratory animals. It has recently been demonstrated that the absence of enteric colonization of *O. formigenes* is a risk factor for CaOx urolithiasis in dogs.

Water Type

In humans, the mineral content of water may play a role in calcium oxalate urolith formation. It is also thought that increased sodium content can increase water intake and offset its calciuretic effect. Increased water sodium, calcium, or the absence of trace minerals such as zinc, which chelates calcium, may increase the risk of calcium oxalate urolithiasis. However, in cats, the source of water (bottle, municipal, etc.) did not appear to affect the risk of calcium oxalate urolithiasis. A similar study has not been conducted in dogs.

Modifiers of Calcium Oxalate Crystal Formation

In humans, urine normally contains several natural inhibitors of urolith formation and growth. Inhibitors can be either organic or inorganic substances in urine that reduce crystal formation, aggregation, or growth. A defect or deficiency in these inhibitors may contribute to urolith formation. Inhibitors of calcium oxalate include citrate, magnesium, pyrophosphate, glycosaminoglycans, nephrocalcin, and Tamm–Horsfall mucoprotein. Although little is known about these inhibitors in dogs, it is suspected they may play a similar role as in humans.

Concurrent Medical Conditions

Hyperadrenocorticism is associated with calcium oxalate urolithiasis in humans and dogs. In humans, glucocorticoid excess leads to hypercalciuria secondary to increased mobilization of calcium from bone. Glucocorticoid-

induced decreases in tubular resorption of calcium, chronic metabolic acidosis, and decrease in urinary excretion of citrate may also occur. Similar glucocorticoid-associated mechanisms are believed to occur in dogs.

A recent study in humans demonstrated an association between calcium oxalate stones and hypertriglyceridemia. The predisposition of miniature schnauzers for idiopathic hyperlipidemia may one day be found to explain why this breed is at high risk of calcium oxalate stones.

Struvite Urolithiasis

Epidemiology

Struvite uroliths are typically composed of 100% magnesium ammonium phosphate hexahydrate. Struvite stones may also contain varying amounts of calcium phosphate (termed *calcium apatite*) or calcium carbonate phosphate (termed *carbonate apatite)*. These uroliths are commonly referred to as "infection stones" or "urease stones" because, in dogs, they are primarily due to the presence of urease-producing bacteria. Struvite stones are often multifaceted or pyramidal in appearance, especially when multiple urocystoliths are present, because the adjacent surfaces are smooth and flattened. If solitary, struvite may have sharp spiculated projections (Figure 123.3). Struvite uroliths represented 35.5% (43.6% including mixed stones) of all canine and feline uroliths submitted to CVUC from 2009 to 2012 (see Table 123.2). More recently, struvite urolith submissions have increased and have exceeded the calcium oxalate urolith submissions for small animals (2018 Minnesota Urolith Center [MUC] Global Data generated by Minnesota Urolith Center, February 2019).



Figure 123.3 Bladder struvite uroliths retrieved from a 10-year-old female spayed golden retriever. *Source:* Courtesy of Andrew Moore, Canadian Veterinary Urolith Centre.

Struvites are most commonly located in the lower urinary tract (LUT) (95%). Risk factors appear related to sex and associated higher bacterial infection risk, as they are more frequent in female dogs (71–85% of struvite submitted to urolith centers) than male dogs (15–29%). Certain breeds are predisposed to struvite uroliths (see Table 123.1).

Etiopathogenesis

The majority of canine struvite uroliths are due to urinary tract infection, most commonly related to bacterial infection with urease-producing organisms. However, sterile struvite urolithiasis has been reported in related cocker spaniels. In dogs, *Staphylococcus pseudintermedius* is cited as the most common urease-producing bacterium associated with struvite uroliths. Other less common urease-producing organisms include *Pseudomonas* spp., *Klebsiella* spp., *Proteus*, and *Corynebacterium urealyticum*. Urease-producing mycoplasmas (termed ureaplasma) such as *Ureaplasma urealyticium* may also cause struvite urolithiasis.

Infection-based struvite uroliths form when urease cleaves urea to form ammonia and bicarbonate. The available ammonium then combines with magnesium and phosphate, normally present in urine, to form magnesium ammonium phosphate hexahydrate (struvite) crystals. Bicarbonate increases the urine pH (i.e., urine becomes more basic), which then decreases the solubility of struvite crystals. Ammonium also damages the urothelial glycosaminoglycan layer by acting as an irritant. This allows struvite crystals and bacteria to adhere to the urothelium and may promote production of an organic matrix for the crystal–matrix interaction, leading to stone formation. Unlike in cats, where sterile struvite urolithiasis may occur solely because of excess mineral intake in the diet, infection with a urease-producing bacterium is associated with struvite urolithiasis in most dogs.

Infection-induced struvite uroliths may contain viable bacteria trapped in the interstices of the stone layers. Bacteria have been cultured from the core of struvite uroliths that have been stored in formalin for years. Dissolution or fragmentation of struvite uroliths may release viable bacteria into the urinary tract and this may cause reinfection unless appropriate antimicrobials and duration of therapy are provided. If the bacteria isolated from the urine and the urolith differ, a change in antimicrobial is only necessary if poor clinical response is observed. If a nonurease-producing bacterium is isolated and subclinical bacteriuria is suspected, an antimicrobial

is rarely indicated. If a urease-producing bacterium is isolated, antibiotic therapy should be continued as long as struvite uroliths are present. If therapy duration is insufficient, UTIs will not resolve or a relapse of infection will likely occur.

Purine Urolithiasis

Epidemiology

Naturally occurring purine uroliths consist of uric acid (and its various salts) and xanthine. Xanthine and uric acid are successive biodegradation products in the metabolism of purines (Figure 123.4). Purine uroliths may be pure (100%) in composition, or less commonly, may contain varying amounts of other minerals. The term "urate" includes uric acid, ammonium urate, and the other salts of uric acid, mostly sodium acid urate, sodium calcium urate, and ammonium calcium urate. Ammonium urate accounts for 86% of urate uroliths.

Urate uroliths are typically small, round, smooth stones that are greenish-brown in color (Figure 123.5). There are often multiple urate uroliths present. Cross-sections of urate uroliths reveal a concentric appearance. Xanthine uroliths are typically similar in size and shape to urate uroliths but are usually yellow to brown (Figure 123.6).

Purine uroliths accounted for 6.4% of canine uroliths analyzed at the MUC between 1981 and 2007, making it the third most common type of canine urolith in this region. In Canada, purine uroliths represented 3.44% of canine and feline uroliths submitted to the CVUC between 2009 and 2012 (see Table 123.2). The majority of urate (97%) and xanthine (94%) uroliths that are submitted for analysis have been removed from the LUT. However, considering the difficulty in removing uroliths from the upper urinary tract (UUT), nephroliths and ureteroliths may be underrepresented in submission frequency.

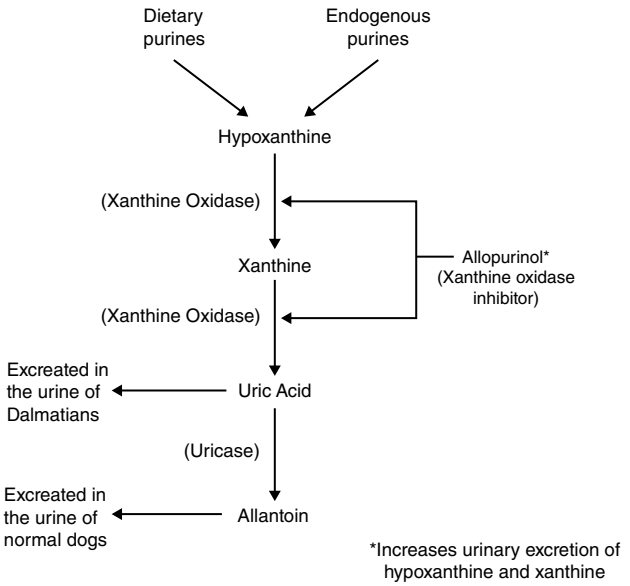


Figure 123.4 Normal canine purine degradation pathway.

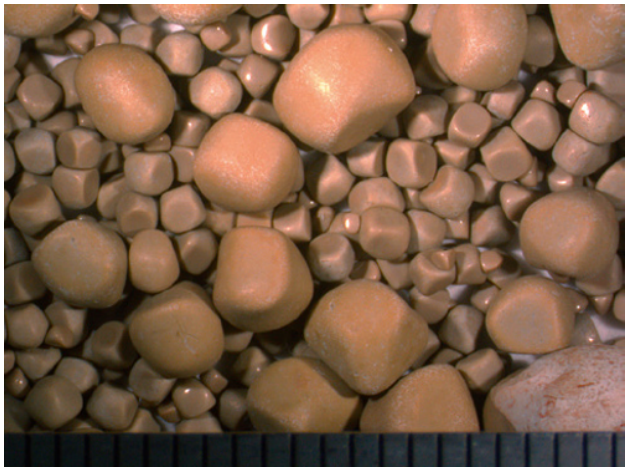


Figure 123.5 Urate stones retrieved from a 12-year-old male neutered Dalmatian dog. *Source:* Courtesy of Andrew Moore, Canadian Veterinary Urolith Centre.

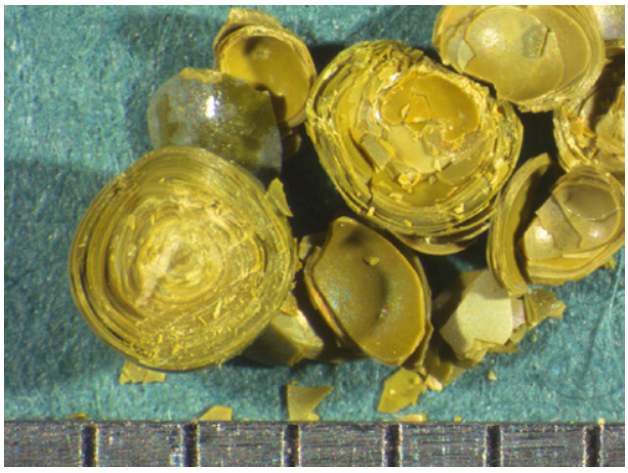


Figure 123.6 Xanthine stone retrieved from a 2-year-old male neutered Dalmatian. *Source:* Courtesy of Andrew Moore, Canadian Veterinary Urolith Centre.

Risk factors for purine uroliths (and types of these) include species, breed, age, and sex. Ammonium urate is the most common (approx. 95%) naturally occurring purine urolith in cats. Xanthine uroliths are uncommon specimens submitted to the CVUC, having been diagnosed in only five cats and five dogs (0.02% of uroliths in cats and 0.09% of uroliths submitted in dogs) from 2009 to 2012 (see Table 123.2). Uroliths composed of hypoxanthine have not been recognized in cats.

Urate stones may be found in dogs of any age but are most frequently retrieved from young to middle-aged dogs (see Table 123.1). Pure urate uroliths occur more

often in males than in females. Female dogs may spontaneously void urate uroliths without being detected. In dogs, urate uroliths are most commonly retrieved from Dalmatians (61% of ammonium urate and 91% of sodium and calcium urate uroliths). In cats, the typical patient with urate uroliths is a pure-bred neutered cat, 4–7 years old, with uroliths in the bladder or urethra. The Siamese breed seems to be overrepresented, along with the Egyptian Mau and Birman breeds. Cat breeds that had lower odds for urate urolith submission than mixed breeds included Abyssinian, American shorthair, Himalayan, Manx, and Persian. There is no sex predisposition in cats.

Naturally occurring xanthine uroliths are rare and are frequently retrieved from dogs that have been treated with allopurinol.

Etiopathogenesis in Dogs

The purine metabolites, uric acid and xanthine, have much lower solubility than that of allantoin. Consequently, if urine is oversaturated with these substances, uroliths can form. A high dietary intake of purines and purine precursors, along with acidic urine, aids in urolith formation. Infection with urease-producing bacteria may also promote formation of urate uroliths by increasing ammonium ion concentration from the breakdown of urea (see Figure 123.6).

Dalmatian Dogs

Dalmatian dogs are predisposed to the development of urate uroliths because of their reduced transport of uric acid into hepatocytes. This results in decreased conversion of uric acid to allantoin, a subsequent moderate increase in serum uric acid concentration (hyperuricemia), and then hyperuricosuria. The inheritance of hyperuricosuria in Dalmatians is via a simple autosomal recessive gene. The missense mutation in the SLC2A9 gene that encodes for a urate transporter is responsible for this defect, and all Dalmatians are homozygous. Despite excretion of relatively large quantities of uric acid, not all Dalmatians form urate uroliths. It is estimated that 25% of male Dalmatians will have urolithiasis and it is suspected that other risk factors play a role in dogs who become urate stone formers.

Non-Dalmatian Dogs

Dogs other than Dalmatians accounted for approximately 30–60% of urate uroliths submitted for analysis. Similar to Dalmatians, urolith-forming bulldogs and black Russian terriers have been shown to be homozygous for a mutation in SLC2A9. However, the reasons for development of urate uroliths in these non-Dalmatian breeds is unknown and does not appear associated with hepatic dysfunction.

Hepatic Dysfunction

Hepatic dysfunction is associated with a reduced ability to convert ammonia to urea and uric acid to allantoin. Therefore, dogs suffering from hepatic dysfunction may develop hyperammonuria and hyperuricuria, which may result in urate urolith formation. The incidence of urate urolithiasis appears to be higher in dogs with portal vascular anomalies than with other causes of hepatic dysfunction.

Xanthine

Xanthine is an important mediator in purine metabolism; the drug allopurinol binds rapidly to (and inhibits the action of) xanthine oxidase, thereby decreasing conversion of hypoxanthine to xanthine and xanthine to uric acid. The result is a reduction of serum and urine concentrations of uric acid, with an increase in serum and urine concentrations of xanthine. As such, most xanthine uroliths in dogs form secondary to therapy with allopurinol via this mechanism. This is particularly true when a diet high in purines (meat based) is fed to these at-risk dogs.

Naturally occurring xanthinuria has been reported in Cavalier King Charles spaniels and dachshunds, and is thought to reflect an inborn error of xanthine oxidase activity.

Etiopathogenesis of Urate Urolithiasis in Cats

The pathophysiology of urate urolith formation in cats is unknown. Ammonium urate uroliths have been recovered from cats with portovascular anomalies. Such congenital anomalies can be found in male and female cats and are typically are detected when cats are <12 months of age. As Siamese cats are overrepresented among those with portosystemic shunts, it is recommended to evaluate them for underlying liver pathology when this breed is presented with calculi. However, most cats with urate stones do not have portovascular anomalies, and risk factors for urate lithogenesis in cats are thought to include an increase in renal excretion and urine concentration of uric acid, the potential presence of promoters, or the absence of inhibitors of urate urolith formation.

Xanthine urolithiasis is considered rare in cats, and only five cats have been reported with spontaneous xanthine urolithiasis and hyperxanthinuria in the last 20 years.

Calcium Phosphate Urolithiasis

Calcium phosphate uroliths are commonly called apatite uroliths. Most pure calcium phosphate uroliths in dogs are composed of hydroxyapatite. Brushite (calcium hydrogen phosphate dehydrate) stones are less common and whitlockite (calcium orthophosphate) uroliths are rare.

Epidemiology and Risk Factors

Pure calcium phosphate uroliths are rare in dogs, comprising only 0.3–0.6% of uroliths submitted to the MUC per year and 2% of uroliths submitted to the CVUC (see Table 123.2). Most calcium phosphate uroliths are mixed in composition and are predominantly (≥70%) struvite or calcium oxalate. Mixed stones are very common in cats and dogs.

Risk factors for these uroliths vary based on stone content and sex, as pure hydroxyapatite uroliths occur slightly more in male dogs (52%) than female dogs (48%) whereas with brushite uroliths, male dogs (75%) are more commonly affected than female dogs (24%).

Etiopathogenesis

Several factors may influence urine calcium phosphate saturation including urine concentration of calcium and phosphate, urine pH, and the presence or absence of inhibitors of calcium phosphate crystal formation. Alkaline urine pH decreases the solubility of hydroxyapatite and likely contributes to calcium phosphate uroliths. Excessive urinary excretion of calcium (hypercalciuria) and phosphate (hyperphosphaturia) may also induce calcium phosphate urolith formation.

Co-morbidities such as primary hyperparathyroidism and hypercalcemia may influence stone formation, and up to 30–40% of dogs with primary hyperparathyroidism present with calcium-containing uroliths. However, hypercalcemic cats are more likely to have calcium oxalate rather than calcium phosphate uroliths.

It has been reported that some dogs with urinary tract hemorrhage can develop blood clots mineralized with calcium phosphate. These stones are not considered true calcium phosphate uroliths as they do not contain the same matrix proteins or ultrastructure as typical calcium phosphate uroliths.

Cystine Urolithiasis

Dogs that develop cystine uroliths excrete an increased amount of cystine (and to a variable extent other amino acids) in their urine, a condition called cystinuria. Cystine is composed of two cysteine amino acid molecules linked by a disulfide bond. Urine solubility of cystine is low, and dogs with cystinuria are predisposed to urolith formation.

Canine cystine uroliths are typically pure, but a few contain struvite, urate, silicate, oxalate or calcium apatite. Typically, urolith appearance is smooth, oval and light yellow to reddish-brown. The size of cystine uroliths varies, but small and multiple stones are common. The cystine uroliths submitted to urolith centers have usually been retrieved from the LUT.

Epidemiology

Geographic location of the dog or cat plays a large role in the prevalence of cystine urolithiasis. In the USA, urolith prevalence has been reported as 1–2%. This is in contrast to parts of Europe where cystine urolithiasis has been reported as 8% in Sweden and 26% in central Spain. In Canada, cystine uroliths submitted to the CVUC represented 0.6% and 0.1% of all canine and feline stones, respectively, between 2009 and 2012 (see Table 123.2).

Risk factors for cystine urolithiasis in dogs include age, breed, and sex. Most affected dogs are males (98%), although the disease is not genetically sex linked, and young to middle-aged (3–8 years). The exception to these risk factors is the Newfoundland breed, where these stones occur in both genders and often at a younger age. Newfoundland dogs also appear to have an increased incidence of cystine nephroliths.

Breed predisposition has varied widely over the last 15 years and urolith risk may depend on the dog's geographic location. Unfortunately, most studies do not compare breed distribution to the national registry for dog breeds, nor are dog health insurance numbers, which have provided the information for these studies, common everywhere. Bull mastiff, Scottish deerhound, English bulldog, Newfoundland, Chihuahua and dachshund are the most common breeds affected in North America, while terrier breeds (Yorkshire, Jack Russell, and West Highland white) are the most affected in the UK.

Etiopathogenesis

In normal dogs, cystine is freely filtered at the glomerulus and then actively reabsorbed in the proximal tubules. Cystinuria is a limited hereditary renal transport disorder involving cystine and the dibasic amino acids ornithine, lysine, and arginine, collectively known as COLA. Instead of the normal >99% reabsorption in the proximal renal tubules, these amino acids are lost in the urine; however, only cystine causes a problem. In cystinuric patients, the carrier proteins responsible for reabsorption are defective. The type of amino acids lost and their quantity vary depending on the case. The low solubility of cystine in acidic urine predisposes to the formation of cystine crystals and uroliths in the urinary tract.

Cystinuria in humans and dogs is classified into several distinct types depending on age of onset, severity, sex, inheritance, and mutant gene. In dogs, type I-a cystinuria is an autosomal recessive disease caused by a SLC3A1 gene mutation common in the Newfoundland, Landseer, and Labrador retriever breeds.

A nonsense mutation in exon 2 of the SLC3A1 (amino acid – aa-transport) gene has been identified as a molecular basis of the defect but the underlying genetic

defect(s) in most cystinuric breeds of dogs have yet to be identified. More recently, Labrador retrievers were found to have a different mutation in the same gene, encoding for a renal basic amino acid transporter. DNA-based genetic tests are available to detect abnormal cystine excretion for some breeds of dogs.

Type II cystinuria is an autosomal dominant disease that has been reported in Australian cattle dogs, border collies (type II-a) and miniature pinscher (type II-b). In the latter, the mutation affects the SLC7A9 gene and encodes for intramembrane transporter protein.

The molecular basis for androgen-dependent type (type III) cystinuria is unknown. Type III cystinuria regroups several breeds of dogs such as the English bulldog, English mastiff, French bulldog. Type III cystinuria is typically detected later in life, is less severe clinically, and appears to involve only males. Castration seems to lower cystine excretion, therefore the mode of inheritance is unclear. No gene mutation has been identified as the cause of type III cystinuria.

Etiopathogenesis of cystine in cats is not well characterized, but one study recently reported an SLC3A1 mutation causing cystinuria in a cat as well as three different SLC7A9 gene variants in four cats.

Resources for cystinuria testing (urine nitroprusside/genetic testing) can be found at PennGen Laboratories: http://research.vet.upenn.edu/penngen

Silicate Urolithiasis

Epidemiology

Silica (silicon dioxide) uroliths are infrequently diagnosed. They account for 0.9% of specimens submitted to the MUC and 0.7% of specimens submitted to the CVUC between 2009 and 2012 (see Table 123.2). Silica-containing nephroliths are rarely submitted to urolith centers, but have been reported in native Kenyan dogs.

Some silica uroliths are pure, while others are composed of different layers, with oxalate and struvite being the most commonly associated minerals. Most silica uroliths have a "jackstone" appearance; however, an outer layer (coating) of another mineral type may mask this configuration. Typically, multiple silica uroliths present and cross-section of the urolith usually reveals laminations.

The majority of dogs with silica uroliths are male, with a mean age of 7.2 +/- 3.1 years (range 1–17 years).

Etiopathogenesis

Silica uroliths are thought to form due to individual animal increase in consumption of this mineral. Animal protein contains very low concentrations of silica and consumed dietary sources are likely plant origin, such as direct ingestion of soil or ingestion of contaminated crops. Plant sources implicated in silicate urolithiasis include rice and soybean hulls and corn gluten feed. Silicates may be high in certain home-made diets and in some groundwater from aquifers. In certain regions, soil may contain high concentrations of silicate so consumption of dirt and grass (pica) should be discouraged.

Experimentally, beagle dogs consuming large quantities of antacids containing magnesium trisilicate were predisposed to silica uroliths. Homeopathic, other medications and vitamin-mineral supplements may contain silica, for example silica is used in anticaking materials added to tablets.

Other Types of Urolithiasis

In dogs, mixed composition uroliths comprised 2.3% of uroliths submitted to the MUC, with an additional 8.8% of uroliths being described as compound. Compound uroliths are likely to form when factors initially promoting precipitation of one type of mineral are replaced by factors promoting precipitation of a different mineral. This can make compound uroliths poorly responsive to medical management due to the need to treat each mineral type separately for dissolution or prevention.

The list below includes uncommon types of uroliths submitted to major urolith centers.

- *Suture induced*: some stones can be induced by residual or retained suture material. Uroliths typically have a piece of suture contained within the stone, or have a hole where the suture was located (Figures 123.7 and 123.8).
- *Dried solidified blood calculi*: calculi composed solely of dried solidified blood have been removed from the urinary tract of cats.



Figure 123.7 Suture-induced stone removed from the bladder of a 7-year-old male neutered Yorkshire terrier. *Source:* Courtesy of Andrew Moore, Canadian Veterinary Urolith Centre.

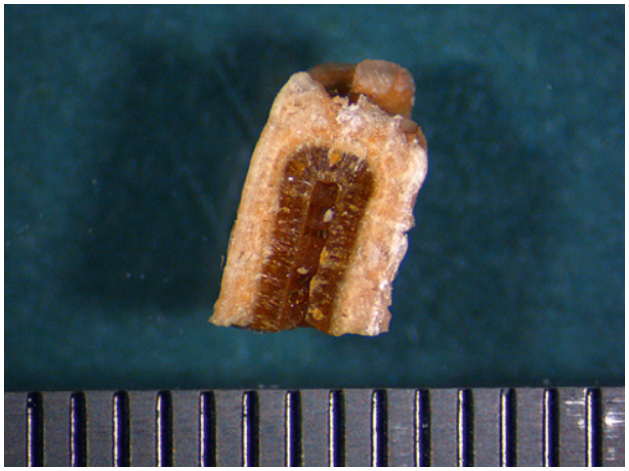


Figure 123.8 Suture-induced stone (60% struvite, 40% calcium phosphate) removed from a 4-year-old female spayed miniature schnauzer. *Source:* Courtesy of Andrew Moore, Canadian Veterinary Urolith Centre.

- *Potassium magnesium pyrophosphate*: the etiology of these uroliths is not definitively known, and it is theorized that formation is related to a type of temporary or permanent enzymatic dysfunction causing pyrophosphate supersaturation of the urine.
- *Melamine and/or cyanuric acid-induced uroliths*: after a devastating occurrence of diet-related renal failure in dogs and cats, melamine urolithiasis or crystalluria was noted in affected patients (Figure 123.9).
- *Drug and drug metabolite uroliths*: these are most commonly related to the use of the sulfonamides or allopurinol and there are reports of fluoroquinolone (ciprofloxacin), primadone, and tetracycline uroliths. Factors predisposing to precipitation of drugs in urine include reduced volume of highly concentrated urine, urine stasis, high rate of urinary excretion of drugs that are poorly soluble in urine, and/or prolonged treatment with high doses of potentially lithogenic drugs.



Figure 123.9 Melamine cyanuric acid removed from the bladder of a Burmese cat. *Source:* Courtesy of Andrew Moore, Canadian Veterinary Urolith Centre.

Urolith Diagnosis

Urinalysis

Urine Sediment

Urolithiasis typically induces inflammatory urine sediment, such as pyuria (presence of white blood cells), hematuria (red blood cells), and proteinuria. Bacteria may also be present if there is a primary or secondary UTI, (i.e., infection induced by urolith-associated trauma).

Urine pH

The urine pH of dogs and cats depends on many factors and can be affected by method of measurement. A study in dogs found that urine dipstick tended to overestimate pH, in some cases yielding an alkaline result for a sample that had a mildly acidic urine as determined by the reference method. As such, if accurate measurement of urine pH is important, a pH meter should be used. Relatively inexpensive hand-held instruments are commercially available.

Certain minerals are more soluble in acidic or alkaline pH. For these reasons, some minerals tend to precipitate and form stones in acidic (e.g., cystine, purine, calcium oxalate) or in alkaline pH (e.g., struvite, calcium carbonate, and calcium phosphate stones). At present, research indicates conflicting results regarding the role urine pH plays in the formation of calcium oxalate stones.

Crystals

Crystals may indicate the presence of uroliths or be normal, that is, no urolith. As such, specific therapy for crystalluria is not indicated unless a urolith is documented through imaging, the patient has a history of urolithiasis or urethral plugs (cats), and/or specific crystal types are noted.

In order to correctly identify crystalluria, urine should be analyzed within one hour of collection. This is advised because both calcium oxalate and struvite crystals can form *in vitro* if there is a delay prior to analysis or due to refrigeration. Crystal types that are not normally present in the urine, and demand attention regardless of urolith presence, include cystine, xanthine, and urate (excluding Dalmatians).

Urine Culture

Urine culture and susceptibility should be performed in all patients with urolithiasis in order to detect infections and start appropriate antibiotic treatment if necessary,

that is, there are concurrent clinical signs of infection. Urinary tract infections can be the primary cause of urolith formation (e.g., struvite uroliths in dogs), or they can be secondary to urolith-induced irritation of the urinary tract. If the urine culture is negative despite a high suspicion of UTI in a patient (i.e., a dog with struvite stones), culture of the bladder wall and stone nidus, at the time of stone removal, is strongly advised in order to accurately direct any needed antimicrobial therapy.

Bloodwork

Complete blood count (CBC) is usually normal in patients with urolithiasis. A left shift may (or may not) be present with pyelonephritis or pyonephrosis. A serum biochemistry may show evidence of liver dysfunction in a dog with hepatic vascular abnormalities (portosystemic shunt [PSS]), microvascular dysplasia (portal hypoplasia), or severe hepatic disease. The lab changes can include increased alanine aminotransferase (ALT) and alkaline phosphatase (ALP), and with hepatic dysfunction there can be low albumin, urea, and glucose.

Bile acid (pre- and postprandial) measurement is strongly recommended if a young dog or cat presents with bladder stones and clinical signs compatible with PSS (i.e., signs of hepatoencephalopathy, polyuria/polydipsia [PU/PD], poor growth) or increased liver enzymes. Dogs with portovascular abnormalities are more likely to have urate uroliths than those with other types of hepatic dysfunction. Middle-aged, small-breed dogs with a portovascular anomaly and good portal perfusion can have normal chemistry panels with urate stones, making bile acid testing indicated.

In cases of ureteral calculi resulting in urinary tract obstruction, blood urea nitrogen (BUN) and creatinine may or may not be increased. This will depend on the laterality (unilateral or bilateral obstruction) and underlying intrinsic renal damage due to the calculi. Azotemia will not be present if the contralateral (nonobstructed) kidney is normal. Most cats (88%) with unilateral ureteral calculi are azotemic (>90%), indicating the presence of intrinsic renal disease in the contralateral kidney.

Stone Analysis

A common pitfall for clinicians dealing with urolithiasis in small animals is attempting to guess the type of stone(s) noted on imaging based on signalment of the patient, diet, urine pH, urine culture results, and radiographic density of the stone. For this reason (and if possible), it is always recommended to submit uroliths for mineral analysis. It is important to note that even if there is recurrence of urolithiasis in the same patient, the urolith type may be different from the prior episode. An example of this is a calcium oxalate stone forming in an at-risk breed of dog after an incidence of struvite urolithiasis due to bacterial infection.

Stone Layers

When a urolith is analyzed, it is named according to the constituents making up the majority of the "stone" (Figure 123.10). These layers consist of the following.

- *Nidus* (center of the urolith): this may or may not be composed of crystalline material and/or a foreign body, such as suture material.
- *Stone*: the stone may or may not be composed of the same minerals as the nidus.
- *Shell*: the layer(s) that surround the stone. The shell is the outermost complete layer on the urolith.
- *Surface crystals*: these may or may not be present on the outermost surface of the urolith. They do not completely encase the urolith (incomplete layer).

Ideally, all four layers of the urolith should be analyzed separately and their respective mineral amounts listed. Only quantitative analysis ensures that all urolith layers are examined and provides an estimate of the mineral content of each visible layer. This is important since confusion over urolith content and therapy and prevention can occur when only the outer layer is analyzed. This type of confusion can also occur when using the qualitative

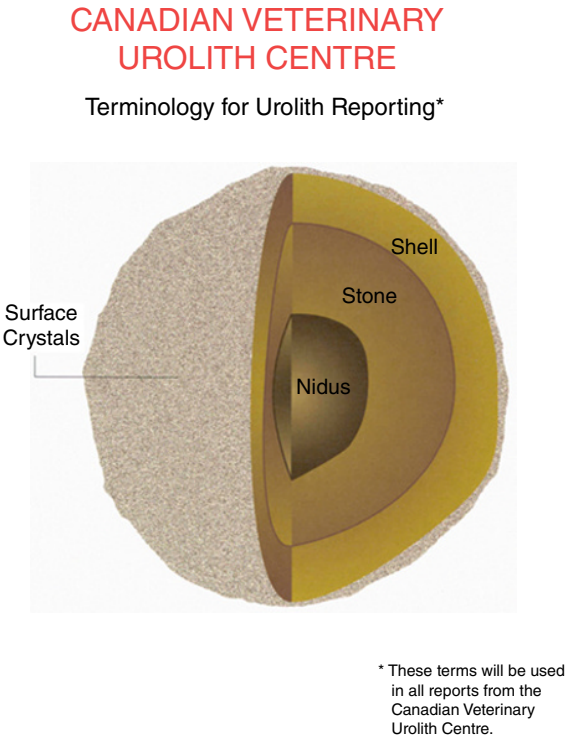


Figure 123.10 Stone layers description. *Source:* Courtesy of Andrew Moore, Canadian Veterinary Urolith Centre.

test for urolith analyses, where the entire urolith is crushed and then analyzed. An example of why this is important would be with a primary metabolic stones (i.e., urate) which may have a large (or several) outer covering (s) of struvite. If only the outer layer was assessed or if the urolith was crushed and then analyzed, then ongoing diagnostics and therapy would be misdirected, at the struvite rather than the urate portion.

Stone Characterization

Uroliths are defined based on their mineral composition as noted earlier. The following terms are used to identify type.

- *Pure urolith*: when 70% or more of the urolith is composed of one type of crystalloid, it is named for that crystal type. In dogs and cats, most stones have one major crystal component.
- *Mixed urolith*: when less than 70% of the urolith is composed of one mineral, it is called a mixed urolith. This means that the urolith does not contain one predominant mineral type but is a combination of two or more types.
- *Compound urolith*: this is a urolith in which each layer is composed of a different mineral. Uroliths that have formed around foreign material in the urinary tract are often classified as compound. Suture material, urinary catheter, metal pellets, plant material, hair strands, and other foreign objects (ex. porcupine quill) have all been reported to be a part of uroliths of various mineral types.

Specific Tests to Detect Cystinuric Dogs

On average, dogs with type I cystinuria have a several-fold higher urinary COLA excretion than non-type I cystinuric male dogs. A simple urinary screening test to determine if a dog is cystinuric is available through the Metabolic Screening Laboratory, Section of Medical Genetics, at the University of Pennsylvania (http://research.vet.upenn.edu/penngen). This test can detect any type I cystinuric animal, but not necessarily all dogs with non-type I cystinuria. High-performance liquid chromatography can be further used to determine the amount of cystine and other amino acids in urine. However, this form of quantitative amino acid analysis is currently restricted to a few laboratories (PennGen and LaboKlin) and is relatively expensive. Based on studies, dogs with either cystine levels of >200 µmol/g creatinine or COLA values of >700 µmol/g creatinine are considered cystinuric. Moreover, for Newfoundlands and Labrador retrievers, a breed-specific mutation test is available that detects not only cystinuric dogs but also asymptomatic carriers. Finally, in mastiffs, a preliminary linked marker test to identify dogs at risk for early stone formation is being evaluated.

Imaging of the Urinary Tract

Radiography

Most uroliths are radiopaque on survey abdominal radiographs. Radiopaque uroliths include calcium phosphate, calcium oxalate, struvite and silicate (Figures 123.11 and 123.12). Survey radiography is suitable for identification of these radiopaque uroliths, provided they are greater than approximately 2–3 mm in diameter. However, urate, cystine, and xanthine uroliths are generally characterized as radiolucent or only slightly radiopaque on survey radiographs. The failure rate for detection of uroliths by survey radiography was 2–27% dependent on urolith size and composition.

Clinicians may try to guess the chemical composition of a urolith based on the density, shape, and number of uroliths on radiographs. One aid for this type of "guesstimate" is the pneumonic POCUS, which is used by clinicians to remember the order of the stones that are most radiodense to radiolucent: calcium phosphate, calcium oxalate, struvite, silicate, cystine, and urate calculi.

Contrast-enhanced radiographic procedures or ultrasound are needed to identify uroliths composed of compounds similar to the radiographic density of soft tissue. Double-contrast cystography has been associated with high sensitivity and low false-negative detection rates (Figure 123.13). Small uroliths are detected more reliably by double-contrast cystography or ultrasonography. However, ultrasound is superior to double-contrast cystogram in experienced hands and for very small stones and sand.

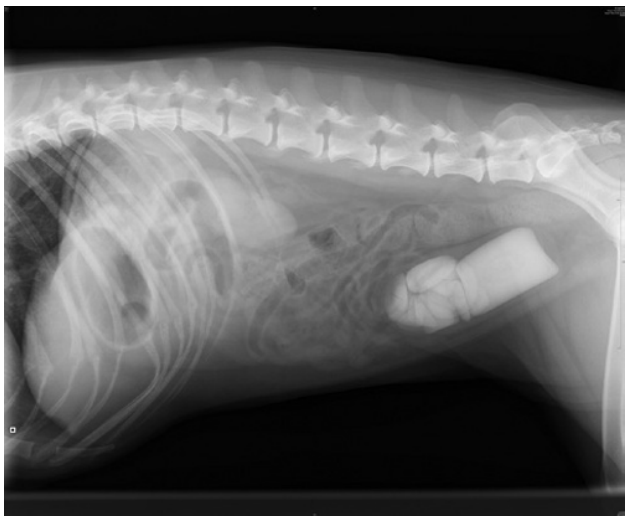


Figure 123.11 Abdominal radiographs (lateral view) showing bladder stones in a dog. *Source:* Courtesy of Stephanie Nykamp, Radiologist, Ontario Veterinary College.

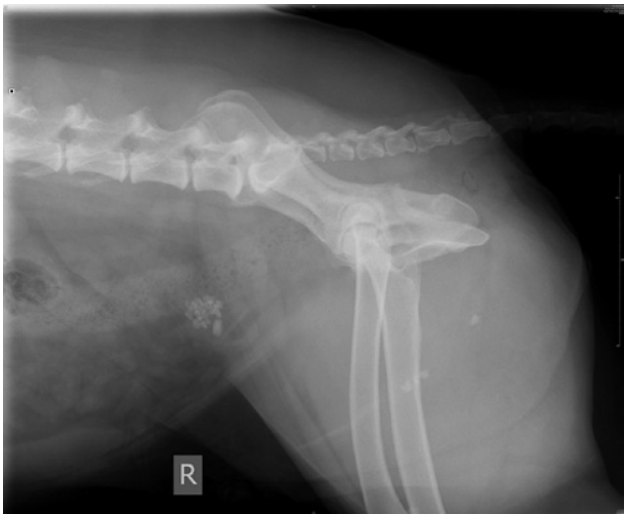


Figure 123.12 Abdominal radiographs (lateral view) showing bladder and urethral stones in a dog. *Source:* Courtesy of Stephanie Nykamp, Radiologist, Ontario Veterinary College.

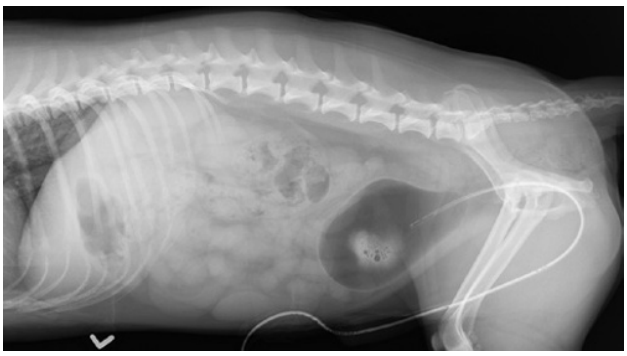


Figure 123.13 Double-contrast cystography (lateral view) in a dog showing multiple, various sized filling defects centrally in the contrast pool indicative of bladder stones. *Source:* Courtesy of Dr Stephanie Nykamp, Radiologist, Ontario Veterinary College.

Ultrasonography

Ultrasonography is a cost-effective tool in the diagnosis of urolithiasis but it may overlook some important aspects of the stones that can help the clinician predict the nature of the uroliths, such as surface contour and shape. One limitation of ultrasound is that it often overestimates urolith size, so radiographs should be used for determining size when possible. Ultrasound is also less reliable than radiography for predicting the number of stones and their location. Finally, ultrasound only provides evaluation of the most proximal portion of the urethra and therefore cannot replace radiography.

Ultrasonographic examination can detect radiopaque and radiolucent uroliths. One study compared survey and contrast radiographs, pneumocystography, double-contrast cystography, and ultrasound using a 7.5 MHz transducer, and found that ultrasonography may be more sensitive than survey and contrast cystography for detection of urocystoliths, with false-negative rates of 6%.

Ultrasonography allows simultaneous evaluation of the upper urinary tract for nephroliths and ureteroliths. Therefore, radiography combined with ultrasonography are preferred over contrast radiography alone. Ultrasound can detect upper urinary tract obstruction that is characterized by renal pelvis dilation >13 mm. However, pelvis dilation can be iatrogenic (diuresis) or secondary to different diseases such as chronic kidney disease or pyelonephritis. Although a renal pelvis >13 mm may indicate ureteral obstruction, the absence of dilated renal pelvis does not rule out an upper urinary tract obstruction. The combination of proximal ureteral dilation and normal kidney pelvis diameter can be associated with ureteral obstruction in cats. In a recent study, 25% of cats with confirmed ureteral obstruction had a renal pelvis <13 mm but a proximal ureteral dilation. In 25% of cats with ureteral obstruction, ureteropyelography is necessary to determine the cause of the obstruction.

Computed Tomography

Determination of urolith composition using computed tomographic (CT) peak attenuation measurement has been described *in vitro*. In humans, this technique is preferentially used in order to detect uroliths and also to predict their composition. CT may be more specific for ureteral calculi than either radiography and/or ultrasonography in cats.

Educated Guess

Determining the type of urolith based on imaging studies alone is very risky. This type of "guesstimate" of urolith composition based on the radiolucency of a stone and its shape can lead the clinician to misdiagnosis (Figure 123.14). In certain scenarios the chemical composition of uroliths may be predicted based on patient signalment, in combination with the results of urinalysis, urine culture, and radiographs. However, it must be understood that this technique can lead to error and is not advised as the best method of urolith identification. In situations where uroliths are not available for analysis or are pending analysis, the guesstimate may need to be used; however, communication to clients that errors may be made with this technique and verification of stone type (when practical and possible) are ideal. Unfortunately, this verification cannot be made until stone analysis occurs. For example, the clinician can make an educated guess as to the likelihood that a given stone is composed of struvite based on finding a urease-positive

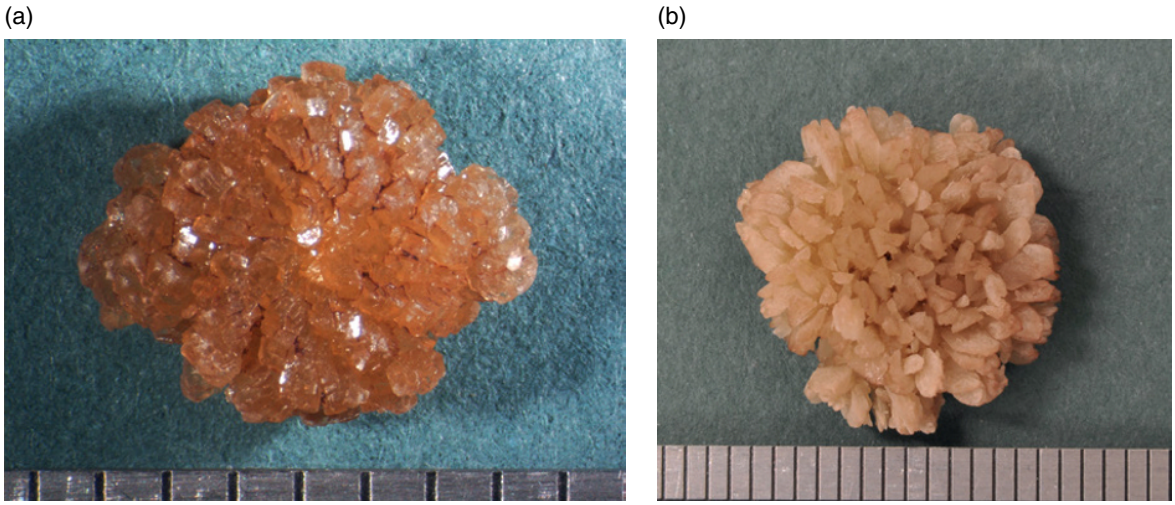


Figure 123.14 (a) Cystine stone in a 3-year-old male pug. (b) Struvite urolith in a 4-year-old female Chihuahua mixed dog. These two look the same, but they are not the same type. *Source:* Courtesy of Andrew Moore, Canadian Veterinary Urolith Centre.

UTI (usually *Staphylococcus* spp.), alkaline urine, struvite crystalluria, and radiodense calculus in a high-risk breed (ex. female bichon frise). Certain breeds are also predisposed to a specific type of urolith which makes guesstimating a bit less risky, for example Dalmatians (see Table 123.1).

As mentioned, there are multiple "traps" or pitfalls to avoid when guesstimating the chemical composition of a urolith. Areas where errors can occur include urine pH, urinalysis and crystalluria, urine culture results, and radiographic density of the stone. Urine pH can be influenced by meals and time of day. First morning preprandial urine is typically the most acidic and concentrated sample of the day. After eating, the pH will become more alkaline, often referred to as the "alkaline tide." Urine pH is also affected by stress and hyperventilation, leading to respiratory alkalosis and consequent urine alkalinization, for example a stressed dog panting in clinic. Additionally, an acidic pH does not rule out the presence of struvite stones. One example of this would be a compound urolith made of a struvite core surrounded by an oxalate shell. The pH may also be alkaline if there is concurrent infection with urease-producing bacteria, while the predominant urolith type may be unrelated to infection, for example a calcium oxalate stone and concurrent *Staphylococcus* spp. infection.

Similarly to urine pH pitfalls, crystalluria is not a consistent feature of the urinalysis in dogs and cats with uroliths. For example, in one study of 30 cats with struvite urocystoliths, struvite crystals were only detected in 17 patients. Additionally, dogs and cats may have a small number of struvite or calcium oxalate crystals, but other types of crystals do not typically form *in vitro*.

Medical Management of Lower Urinary Tract Stones

It is ideal to identify urolith type prior to initiation of dissolution protocols, and if uroliths are small enough, voiding or catheter retrieval may be possible and allow for this. Unfortunately, stone composition identification is rarely possible prior to the need to make therapy decisions, and best "guesstimate" strategies are warranted in most cases. As such, it is imperative to perform diagnostic studies (urinalysis, urine culture, radiography) to evaluate urolith size and location and to provide the most information to guide therapy as available.

Attempts to medically dissolve uroliths are not always the least expensive method of management, nor is medical dissolution an option for all stone types, such as calcium oxalate. For other urolith types (e.g., struvite), the cost of diet and antimicrobial therapy along with the cost of the recheck appointments and imaging should be discussed thoroughly when considering medical dissolution. Similarly, animal owner communication to ensure compliance is essential in order for medical dissolution strategies to be successful.

Rationale for Medical Dissolution

Medical dissolution of amenable urolith types consists of reducing the concentration of the calculogenic material in the urine and increasing its solubility.

Regardless of urolith type, increasing water intake through diet and via increased water consumption will assist in dilution of urine crystalloids and help prevent ongoing crystal formation. This may also aid in flushing existing stones from the bladder in female dogs. The aim

of water increase strategies is to obtain a urine specific gravity of <1.020.

Indications for (and Limitations of) Medical Urolith Dissolution

Urolith Type

Struvite, urate, and cystine stones in dogs may be amenable to medical dissolution; however, the uroliths must be located in undersaturated urine for this to occur. This requires intervention with diet and urine dilution strategies, along with appropriate therapy of concurrent bacterial infections. Dissolution success is much lower for urate and cystine stones than struvite, and in cats, only struvite uroliths are responsive to medical dissolution. In cats, low-protein diet and allopurinol has been reported as effective in urate stone dissolution; however, until further studies looking into safety and efficacy of this treatment are performed, mechanical removal of bladder or urethral urate uroliths is advised. Mechanical urolith removal is recommended for bladder or urethral cystine stones in cats, in part because 2-MPG (Thiola®, tiopronin) is toxic in cats, and is only effective about 60% of the time in dogs.

Urolith Location

Medical dissolution for specific stone types can be successful, but is more efficient when uroliths are located in an area where they are in constant contact with urine, such as the bladder. Suspected struvite nephroliths or ureteroliths should be medically dissolved unless they are too large to be effectively bathed in urine.

If uroliths are obstructive, relief of obstruction with a minimally invasive approach and rapid control of infection should preserve kidney function.

Obstructive ureteroliths cannot be dissolved by medical or dietary protocols unless a ureteral stent is placed concurrently. Urethroliths are typically not amenable to dissolution, although they may be flushed into the bladder by retrograde hydropulsion and then dissolution can be attempted.

Calcium oxalate uroliths are not amenable to medical dissolution regardless of location, and must be removed from the urinary tract mechanically. In cats, because more than 90% of feline upper urinary tract stones are composed of calcium oxalate, dissolution should not be attempted with obstructive nephroliths or ureteroliths. Silica uroliths are also thought to be unresponsive to medical dissolution.

Size and Number of Uroliths

The size and number of the stones will influence rapidity of dissolution but do not dictate the likelihood of therapy success in stones that are amenable to dissolution. Since the rapidity of dissolution is related to the size and surface area of the urolith being exposed to urine, one large urolith will take longer to dissolve than multiple small uroliths. An analogy for this is that one large ice cube will dissolve more slowly than an equal volume of crushed ice. The rate of dissolution is influenced by the surface area of the urolith exposed ("bathed") in undersaturated urine.

Presence of Obstruction

Medical dissolution is contraindicated in patients with obstruction of the urinary tract. Relieving urinary tract obstruction in those cases is mandatory in order to avoid consequences such as postrenal azotemia, irreversible renal damage, bladder rupture, and death.

Risk of Obstruction in Males

Medical dissolution of urocystoliths in male dogs is associated with a risk of urethral obstruction once the urocystoliths are small enough to pass into the urethra. The risks and clinical signs of urethral obstruction should be explained to the owner if medical dissolution is elected in male dogs, and regular monitoring of urination is recommended. Medical dissolution should only be tried in male dogs after clear owner communication and assurance of owner compliance and ability to observe and act on clinical evidence of obstruction.

Infection-Induced Urolith

If the urease-producing bacterium is isolated from urolith culture, appropriate antibiotic therapy based on urine culture and susceptibility must be administered during the entire urolith dissolution period. Otherwise, the persistence of infection with a urease-producing organism will confound dissolution of the stones. Despite diet change, concurrent urinary tract infection will maintain alkaline urine and promote urolith formation and growth.

Dietary Factors

Limitations of medical dissolution are inherent to the diet and medical therapy needed for the given urolith; for example, an acidifying diet with low protein and caloric content should not be fed to a pregnant or lactating bitch. Similarly, thoughtful consideration of nutritional growth requirements in young dogs and kittens needs to occur when a diet lower in purines (protein) is indicated for medical urolith dissolution (e.g., urate uroliths). Similarly, a diet with a high salt or fat content should be avoided in a patient with congestive heart failure or pancreatitis, respectively, as these patients may require varying levels of sodium or fat restriction for their concurrent medical condition.

Protocol for Medical Management and Prevention of Individual Urolith Types

Calcium Oxalate Uroliths

Dissolution of Calcium Oxalate Uroliths

At present, calcium oxalate stones cannot be dissolved through medical (nutritional) means in dogs and cats. As such, removal or bypass of these uroliths by different interventional methods is recommended. As upper urinary tract stones in cats are predominantly composed of calcium oxalate (>98%), medical dissolution is also not recommended in these patients.

Follow-Up and Prevention of Calcium Oxalate Uroliths

Dietary therapy has been recommended to help prevent recurrence of calcium oxalate stones. Nutritional strategies to aid prevention of calcium oxalate stones in cats or dogs primarily focus on increasing water intake via feeding canned or wet food or by adding water to dry food. These techniques help to increase dilution of urine and flush crystals from the urinary tract, and one study showed that feeding canned food to a group of dogs decreased their risk of calcium oxalate compared to feeding a dry diet.

Medical management that is believed to prevent recurrence of calcium oxalate urolithiasis includes the following factors.

- Increased water content of food (>75% water: high moisture).
- Avoidance of dietary urinary acidification (pH <6.25 cats and <6.6. dogs).
- Correction of underlying hypercalcemia. In cats with recurrent CaOx stones and idiopathic hypercalcemia, there may be a benefit to feeding a high-fiber diet in association with potassium citrate therapy.
- Dietary sodium increase. Controversial at this time. Feeding high-sodium diets (3.5 g/1000 kcal) is not a substitute for increased dietary moisture, as had been previously thought, and any benefit of dietary increase in salt is believed to be short-lived.
- Management with potassium citrate in cats and dogs with persistence of acidic urine, and consideration of thiazide diuretics if recurrence despite other interventions.
- Dietary protein restriction. At present, the recommendation to restrict dietary protein in these patients is controversial and it is very difficult to reduce dietary protein without concurrent dietary phosphorus reduction. Unfortunately, lower phosphorus has been associated with a higher risk of calcium oxalate uroliths. This is due to low diet phosphorus leading to increased intestinal absorption of calcium and increased calcitriol production, which then leads to further calcium gastrointestinal absorption and calciuresis.
- Avoidance of calcium-containing supplements in at-risk patients.
- Reduction in foods rich in oxalate precursors. Examples of these include chocolate, nuts, beans, sweet potatoes, wheatgerm, spinach, rhubarb. For a complete list of the oxalate content in foods, please visit the Oxalosis and Hyperoxaluria Foundation website: www.ohf.org.

In dogs, the diets recommended to achieve the above goals are those that have undergone specific urinary testing (i.e., CORI, RSS, Activity Product Ratio) to reduce risk of calcium oxalate formation. Examples of these diets include Hill's c/d, Purina St/Ox, and Royal Canin S/O. Unfortunately, the ideal diet to prevent calcium oxalate urolith recurrence remains unknown.

Despite diet modification, recurrence in animals with CaOx is high: 33% at two years in cats and up to 57% at three years in dogs. If calcium oxalate uroliths recur despite dietary therapy, the use of medications such as thiazide diuretics or potassium citrate may benefit specific patients.

Potassium citrate supplementation has been shown to reduce recurrence of calcium oxalate uroliths in humans. In veterinary patients, there are conflicting opinions on the utility of potassium citrate for prevention of calcium oxalate urolithiasis. In normal dogs, potassium citrate supplementation did not significantly increase the mean citrate excretion, although in three miniature schnauzers supplementation did increase urinary citrate excretion and lower relative calcium oxalate supersaturation. In another study, potassium citrate did not increase mean urinary citrate concentration but did cause a dose-dependent increase in urine pH. If calcium oxalate crystalluria is persistent or calcium oxalate uroliths recur, potassium citrate is commonly recommended to achieve a urine pH of 6.5–7.0 using a dose of 150 mg/kg PO q24h. The serum potassium should be initially monitored monthly during potassium citrate supplementation and the dose reduced if hyperkalemia occurs.

Thiazide diuretics are proven to reduce the recurrence of calcium oxalate urolithiasis in humans by reducing urinary calcium excretion. However, there are conflicting results for dogs, and in normal dogs, administration of chlorothiazide did not reduce urinary calcium excretion. In contrast, administration of hydrochlorothiazide decreased urinary calcium excretion and urine calcium concentration in dogs with calcium oxalate urolithiasis. Reduction in urinary calcium was greatest in dogs with the highest pretreatment urine calcium concentrations when combined with using Hill's Prescription Diet u/d. As thiazide diuretics contribute to urine acidification, concomitant administration of potassium citrate may be recommended. Hydrochlorothiazide (2 mg/kg PO q12h)

should be considered in dogs that have persistent calcium oxalate crystalluria or recurrence of calcium oxalate urolithiasis despite dietary therapy. This drug can cause severe gastrointestinal (GI) side-effects.

Decreased serum vitamin B6 concentrations were detected in a small number of oxalate stone-forming dogs compared to nonstone formers. Based on this study, supplementation of vitamin B6 (2–4 mg/kg PO q24–48h) could be considered in repeat stone formers. Vitamin C is converted to oxalate, so vitamin C supplementation may contribute to hyperoxaluria and increased risk of calcium oxalate urolithiasis. Vitamin D supplementation increases intestinal absorption of calcium, thereby promoting hypercalciuria and increased risk of calcium oxalate urolithiasis.

Dietary recommendations for prevention of calcium oxalate uroliths in cats are thought to be similar to those in dogs, although higher salt levels are sometimes used to aid increased urination. In addition, one two-year study in cats showed no significant difference between two diets that differed in calcium and magnesium contents and in urinary pH potential. Primary hyperoxaluria can occur in cats. Examples of diets that have undergone urinary testing for reduction of calcium oxalate include Hill's c/d Multicare (canned and dry), Purina UR St/Ox (canned and dry), and Royal Canin S/O (canned, chunks and gravy, and dry).

Struvite Uroliths

Dissolution of Struvite Uroliths in Dogs

Struvite uroliths in dogs are almost always due to infection with a urease-producing organism, and as such medical dissolution of struvite depends on the careful elimination of infection together with specific dietary therapy.

The calculolytic diets most commonly advised for struvite stone dissolution in dogs are the Prescription Diet Canine s/d (Hill's Pet Products, Topeka, Kansas) and Royal Canin S/O. Of these two, the Prescription Diet Canine s/d has been used successfully to induce dissolution of struvite calculi in dogs. The Royal Canin diet was effective for struvite dissolution in an *ex vivo* setting.

When using the Hill's s/d diet, laboratory changes in the patient will occur that can also be used to monitor owner compliance. The diet is low in phosphorus and protein which reduces urea, phosphorus, and serum albumin. Mild increases in serum alkaline phosphatase may also be present. These changes are not expected with Royal Canin S/O. Both diets promote undersaturation of the urine with ions necessary for the formation of struvite uroliths and, thus, promote dissolution of existing struvite calculi. Both diets also contain a high NaCl content in order to induce diuresis and dilution of urine. Concurrent antibiotic therapy is recommended to eradicate UTI throughout the diet treatment and is likely the most important facet of medical dissolution of struvite uroliths. The average time of dissolution of canine infection-induced struvite urocystoliths on the Hill's s/d diet was approximately 2–3 months in dogs. This diet should not be continued beyond this time as it is not meant to be a long-term diet.

Feeding small meals throughout the day rather than one or two large meals may prevent postprandial alkaline tide and is associated with more acidic urine production and less struvite crystalluria.

The use of urinary acidifiers has been suggested in dogs because struvite and hydroxyapatite are most soluble in acidic urine (pH 6.0–6.5). In most dogs with infection-induced struvite uroliths, eradication of the UTI with dietary modification will return urine pH to the acidic range. Use of urine acidifiers in these cases is not indicated.

Most clinical symptoms of lower urinary tract inflammation resolve after the first 10 days of antibiotic and diet therapy. However, antibiotic and diet therapy should be continued for one month beyond radiographic evidence of urolith dissolution or one month beyond stone removal. Although feeding a dissolution diet is advised, struvite uroliths have been managed with effective control of the underlying UTI alone.

Prevention and Follow-Up of Struvite Uroliths in Dogs

Examination of urine pH, specific gravity, sediment, and culture is recommended at 5–7 days after starting therapy, and then every four weeks until the stones are dissolved (Table 123.3). Once dissolution (based on radiographic evidence) or removal is accomplished, a urine culture should be obtained at four and eight weeks later, with cessation of antibiotic and dietary therapy four weeks after resolution. Urine culture and radiographs should then be repeated every three months for one year and then every six months thereafter. The goal is to maintain the average urine pH 6–6.5, the average urine specific gravity <1.020, the sediment free of significant crystalluria, and the dog free of bacterial infection.

In dogs with a history of urinary tract infections, proactive and routine urine culture and susceptibility is recommended. This is particularly important if co-morbid situations arise (e.g., hyperadrenocorticism, renal disease) that may predispose to the development of a urinary tract infection.

The need for specific ongoing dietary therapy for prevention of struvite uroliths in dogs is unknown. Since the majority of dogs have infection-induced struvite uroliths, it is likely that effective control and prevention of infection alone would be sufficient to prevent recurrence. However, dietary therapy to lower urine concentration (canned food or addition of water) or minimize

Table 123.3 Compound urolith recurrence prevention strategies. The strategy for prevention of compound uroliths is typically directed at the nidus of the urolith; however, dependent on the proportion of the concurrent mineral layers/types, preventive measures may need to be instituted for more than one mineral type. Further consultation is advised for these complex stones. As with all uroliths, increased water intake should be promoted to decrease the resulting concentration of calculogenic material in urine

Type of compound urolith		
Inner layer –nidus	**Outer layer**	**Prevention strategies**
Calcium oxalate	Magnesium ammonium phosphate (struvite)	Infection is very common with urolith-induced trauma of the LUT, so treat the infection with appropriate antibiotics and direct nutritional therapy at the calcium oxalate
Calcium oxalate	Calcium phosphate	Calcium phosphate is commonly found – patient-related and nutritional control strategies are directed at the calcium oxalate
Calcium oxalate	Silica	Control strategies are directed at the calcium oxalate
Magnesium ammonium phosphate (struvite)	Calcium phosphate	Calcium phosphate is commonly found – patient-related and nutritional control strategies are directed at the struvite
Magnesium ammonium phosphate (struvite)	Ammonium urate	Patient-related and nutritional control strategies are directed at control of urease-producing micro organisms, and/or assessment of liver function. Control is typically directed at the struvite portion of the stone and/or concurrent liver disease if present
Purine/urate salts	Magnesium ammonium phosphate (struvite)	Infection is very common with urolith-induced trauma of the LUT, so treat the infection with appropriate antibiotics and direct nutritional therapy at the purine/urate. Liver assessment may be indicated in these patients
Purine/urate salts	Calcium oxalate	Control strategies are directed at the purine/urate. Liver assessment may be indicated in these patients
Purine/urate salts	Calcium phosphate	Calcium phosphate is commonly found – control strategies are directed at the purine/urate. Liver assessment may be indicated in these patients
Hollow cylindrical central area	Calcium oxalate	Selection and use of appropriate suture material for the urinary tract. Attempt to minimize suture material in the lumen of the urinary tract, thus eliminating a potential nidus for crystal formation

LUT, lower urinary tract.

urolith burden may aid in prevention of urine stasis and crystal aggregation (to "help flush" the urinary tract). Diets proposed for prevention in dogs include Hill's c/d, Royal Canin S/O, and Purina St/Ox UR. If the struvite stones are sterile, which is very rare in dogs, acidifying the urine pH is necessary. This can be achieved with calculolytic dietary therapy or urine acidifiers alone. Antibiotic therapy is not required.

Medical Management of Struvite Uroliths in Cats

Struvite uroliths in cats are typically sterile. Since struvite is more soluble in acidic urine, any factors that may contribute to urine alkalinization should be assessed (e.g., vegetable protein diet, familial history, obesity/inactivity leading to urine stasis). Although struvite stones in cats are generally sterile, lower urinary tract infection can occur and predispose to alkaline urine. Urinary tract infections are more common in cats <1 year and >10 years, as well as in those with compromised host defenses (e.g., diabetes mellitus, perineal urethrostomy, renal disease, urinary tract neoplasia, upper urinary tract stone disease, etc.). A thorough urine assessment and culture should not be omitted in at-risk patients. Upper urinary tract stones in cats are almost never struvite.

The calculolytic diets most commonly advised for struvite stone dissolution in cats are Hill's s/d and Royal Canin S/O. Hill's Feline s/d diet has been used successfully to dissolve stones in cats with struvite urolithiasis. The average time for dissolution of sterile struvite cystoliths in cats fed this diet was about 30 days. Dissolution of feline infection-induced struvite stones, which are uncommon, took 60–90 days. Urinary acidifiers are not useful or advised in cats fed Hill's c/d, s/d, or soft-moist diets because these foods are already acidifying. Dissolution of feline struvite stones in cats eating Royal Canin Urinary SO (canned and dry) occurred in a median of 18 days (range, 10–55 days) in 31 of 39 cats.

Prevention and Follow-Up of Struvite Uroliths in Cats

Radiographs are recommended after stone removal or dissolution to ensure all uroliths have been eradicated.

After this time, examination of urine pH, specific gravity, and sediment is recommended at two weeks, four weeks and then every three months for one year. The aim is to maintain the average urine pH <6.5, the urine specific gravity <1.030 and the sediment free of significant crystalluria. If the cat remains free of clinical signs and free of significant crystalluria and uroliths, rechecks may be decreased to twice yearly.

For cats with infection-induced struvite uroliths, follow-up urine culture and sensitivity is recommended one week after the end of the antibiotics. Further assessment is recommended in cats that have repeat urinary tract infections and struvite crystalluria.

Examples of diets recommended for use in struvite prevention due to their known efficacy in reducing magnesium and phosphorus levels and urinary acidification properties include Hill's c/d Multicare (canned and dry), Purina UR St/Ox (canned and dry), and Royal Canin S/O (canned, chunks and gravy, and dry). Many of the lifestage diets from Hill's, Purina, and Royal Canin are also aimed at concurrent struvite urolith prevention. It is particularly important in cats that therapy is directed at reduction of urine concentration, and thus a high-moisture diet is advised.

Ammonium Urate Uroliths

Dissolution of Ammonium Urate Uroliths in Dogs

Medical dissolution of urate can be achieved, although it may not always be in the patient's best interest, such as urinary tract obstruction.

Dissolution of urate is only indicated in patients with an underlying defect in purine metabolism and not in cases of liver dysfunction. Nutritional therapy for urate dissolution is achieved with a combination of the following.

- *Urine alkalinization*: alkaline urine contains low amounts of ammonia, which subsequently reduces ammonium urate. Feeding a low-protein (purine) diet and/or with potassium citrate supplementation produces alkaline urine.
- *Increase in urine volume*: a canned diet (or addition of water to the diet) is preferred for this reason. A low-protein diet also decreases the concentration of urine by "wash-out" of the medullary concentration gradient (via low urea). The goal is a urine specific gravity of <1.020.
- *Decreasing the excretion of ammonium ions*: feeding a diet low in protein-purines decreases urea production and consequently ammonium and its ions.
- *Decreasing the excretion of uric acid*: feeding a diet low in purines and their precursors will aid in this. The purine content of proteins varies (e.g., it is high in organ meats and fish), and by using selected protein sources (plant, egg white), severe protein restriction is not mandatory to achieve a low urinary urate level.
- The desired urine pH for urate dissolution is approximately 7.0. Targeting a higher urine pH (>7.5) could be detrimental because it could favor the formation of calcium phosphate urolith. Potassium citrate (50–150 mg/kg q12h) may be needed to alkalinize the urine if diet alone is not enough to sustain an average urine pH of approximately 6.8–7.0. Obtaining both a fasting and postprandial (2–6 hours after a meal) urinary pH will allow for consistent and accurate medical titration of potassium citrate. The patient should be monitored for hyperkalemia when higher doses of potassium citrate are used.

Hill's Prescription Diet canine canned u/d (the most purine-restricted diet currently commercially available) and allopurinol (30 mg/kg/day, divided q8–24h) has been recommended for medical dissolution of urate stones. This diet is very low in protein-purine and contains potassium citrate and calcium carbonate for urinary alkalinization. In a clinical study of 25 dogs with ammonium urate uroliths fed this diet and treated with allopurinol, complete urolith dissolution occurred in nine dogs (36%), partial dissolution in eight (32%), and no dissolution in eight (32%). The mean time for urate urolith dissolution was 3.5 months. Similar results were reported when this diet was used for dissolution of sodium urate uroliths. Owners must be fully compliant (i.e., no other food or treats should be given) if this option is selected. Careful patient monitoring is necessary as these uroliths are prone to migrating into the urethra where lower urinary tract obstruction can occur. However, Hill's u/d is contraindicated in dogs prone to pancreatitis or hyperlipidemia due to its high fat content.

Allopurinol is a specific enzyme inhibitor that causes partial blockage of the purine degradation pathway above the level of uric acid (see Figure 123.6). Allopurinol inhibits the enzyme xanthine oxidase. As a result, hypoxanthine, xanthine, and urate are all excreted in the urine. Each of these purine metabolites has a different urinary solubility; hypoxanthine is very soluble, whereas xanthine and urate are only poorly soluble. Allopurinol will reduce the oxidation of xanthine to urate. Consequently, xanthine concentration in the urine increases.

The dose of allopurinol recommended is variable (5–30 mg/kg/day, divided q8–24h). It has a dose-dependent half-life of 2.5–3 hours in dogs. For dissolution of ammonium urate stones, the higher dose is recommended (15 mg/kg q12h). Allopurinol and its metabolites are excreted via the kidney, therefore the dose should be reduced in patients with renal failure. In addition, any medications the dog is receiving need to be carefully assessed. For example, allopurinol can inhibit

metabolism of azathioprine, and can reduce metabolism of anticoagulants, theophylline or aminophylline. Ciclosporin (Atopica®) increases uric acid levels in urine and should not be used in dogs with urate urolithasis.

There is a risk of xanthine stone formation with allopurinol use. Careful monitoring for the presence of xanthine is strongly advised in all patients on allopurinol, as it is likely to occur in patients treated with allopurinol while fed a nonpurine-restricted diet. This may also occur in patients treated for leishmaniosis with allopurinol. Clinicians may be able to dissolve xanthine uroliths by discontinuing allopurinol and starting a low-purine diet. Alternatively, a preliminary study evaluating a low-purine, moderate-protein diet evaluated the reduction of xanthine calculi in dogs on allopurinol for long-term support of leishmaniasis therapy and appears to be promising. Control of concurrent urinary tract infection with appropriate antibiotics based on culture and sensitivity is also essential for both dissolution and prevention of urate uroliths.

Follow-Up and Prevention of Ammonium Urate Uroliths in Dogs

A low-purine diet is advised (Hill's Prescription Diet u/d or Royal Canin UC Low Purine). Diets that contain lean meat and glandular organs are high in purines, thus avoidance of meat-based protein (diet or treats) is recommended. Acceptable treats include carrots, apple slices, and air-popped popcorn. Urine alkalinization to decrease the production of ammonia and ammonium ions by the kidneys is also recommended. The goal of urinary alkalinization is to keep the urine pH around 6.8–7.0.

Allopurinol is only recommended for urate prevention if urate crystals persist despite dilute and alkaline urine. If urate crystals persist despite these interventions, the lowest dose of allopurinol that prevents crystals is advised, to avoid risk of xanthine stones.

For all urolith types, increasing water consumption decreases supersaturation of urine with crystals through dilution. Ideally, a urine specific gravity <1.020 in the morning is desired. Dry food may be soaked with water (aka "swim the kibbles") or canned food may be fed to help increase water consumption. Multiple water bowls, small feedings, and ice cubes are all potential ways to encourage drinking. Control of urinary tract infections with appropriate antibiotics (based on culture and sensitivity results) is essential in prevention.

The risk of recurrence is high for metabolic uroliths. Owner compliance is essential to reduce risk, and awareness of the genetic (breed) predisposition must be encouraged.

The recommended follow-up for these patients is examination of urine pH, specific gravity and sediment at two weeks, four weeks, and then every three months (see Table 123.3). Double-contrast cystography or ultrasonography should be performed every two months. If the dog remains urolith free, free of clinical signs, and significant crystalluria, rechecks may be decreased to every 2–4 months for the first postoperative year, and then twice yearly.

If the urate uroliths are secondary to a PSS, correction of the portal vascular anomaly is expected to resolve hyperuricuria and hyperammonuria followed by dissolution of ammonium urate uroliths. The frequency of successful dissolution post attenuation of the shunt has not been reported. Similarly, there is no study evaluating the success rate of a low-protein diet alone to dissolve urate stones in dogs with a PSS. Stones can and should be removed during correction of the PSS. Nephroliths typically dissolve after PSS attenuation, so they do not need to be removed unless problematic (obstruction).

Prevention of Ammonium Urate Uroliths in Cats

Similar to dogs, the features of a balanced diet designed to prevent recurrence of ammonium urate and uric acid urolithiasis in cats are high moisture, low purine (low-protein or vegetable-based protein), and the ability to produce a urine pH of 6.8–7.0. For example, Hill's Prescription Diet k/d (wet) would be recommended. Anecdotally, a commercially available hydrolyzed soy protein diet has been fed to cats to provide an adequate protein intake in a low purine form.

Calcium Phosphate Uroliths

Calcium phosphate uroliths are frequently multiple small uroliths, and their removal by surgical or nonsurgical methods is recommended to avoid urethral obstruction. Dissolution of calcium phosphate has been reported following parathyroidectomy for treatment of hyperparathyroidism in dogs.

Prevention of stone recurrence includes identification and therapy of any underlying disorder that causes an elevated calcium or phosphorus level or alkaline urine pH. Examples of these include primary hyperparathyroidism, disorders that predispose to hypercalciuria (hypercalcemia, excess vitamin D, systemic acidosis, excess dietary calcium), disorders that predispose to hyperphosphaturia (excess dietary phosphorus), and decreased urine volume.

Dietary manipulation that increases moisture and subsequent polyuria (e.g., canned formula or moderate sodium supplementation), and also provides the targeted calcium and calcium:phosphorus ratio is also recommended to prevent recurrence. A diet that avoids excessive acidification (to prevent calcium oxalate risk) or excessive alkalinization of urine is desired. The features of a diet designed to prevent recurrence of calcium

phosphate urolithiasis in cats are thought to be similar to those in dogs.

Cystine Uroliths

Cystine Uroliths in Dogs

Medical dissolution of cystine in dogs consists of reducing cystine concentration in the urine and increasing its solubility. As with all uroliths, increasing urine volume is beneficial for dilution of crystalloids. The solubility of cystine can be increased by making the urine pH alkaline (approximately 7.0–7.5), either by feeding a specific diet or by treatment with potassium citrate.

Features of a diet thought to help recurrence of cystine are:

- urine dilution
- low protein/purine levels (low protein or vegetable protein)
- alkalinize urine – target pH of 6.8–7.0
- limit sodium intake
- taurine and carnitine supplementation.

Hill's Prescription Diet Canine u/d and Royal Canin UC Low Purine have been recommended because they alkalinize the urine and reduce urine concentration. They are also markedly protein restricted (low in sulfur-containing amino acids), which decreases cystine excretion by 20–25% via reduction of cystine precursors.

Some dogs with cystinuria have increased renal excretion of carnitine, and low-protein diets increase the risk of carnitine deficiency and associated dilated cardiomyopathy in cystinuric dogs. As such, carnitine supplementation may be indicated. In addition, cystine is a precursor for taurine synthesis, and taurine supplementation may be warranted in these patients.

Dissolution of cystine urolithiasis has been reported by treating patients with a thiol-containing drug without feeding a protein-restricted diet. Thiol-containing drugs react with cystine, resulting in its conversion to a more soluble compound by a disulfide exchange reaction. Thiol-containing drugs include D-penicillamine and 2-mercaptopropionylglycine (2-MPG) (tiopronin, Thiola®, Mission Pharmaceuticals). Although both drugs are effective, metal chelation and gastrointestinal side-effects of D-penicillamine make it a less desirable choice. 2-MPG, at a dosage of 15–20 mg/kg of body weight divided and given orally twice daily, is the treatment of choice, in combination with dietary modifications for dissolution and prevention of cystine calculi. Use of this protocol resulted in dissolution of 60% of uroliths in one study within 1–3 months and was effective in 18/18 dogs in another. This drug has been reported to be associated with side-effects in dogs such as aggression, myopathy, anemia, proteinuria, thrombocytopenia, elevations of liver enzymes, and dermatologic changes.

Prevention of Cystine Uroliths

Diets used for dissolution of cystine uroliths are appropriate for cystine urolith prevention. Thiol-containing drugs have been used to prevent recurrence of cystine uroliths in dogs, at doses similar to those used for dissolution. Older dogs are less likely to form cystine uroliths and it may be possible to stop or taper therapies as patients mature. The risk of recurrence of these uroliths is high because cystinuria is an inherited defect in some affected dogs. Giger *et al*. observed that castration of mastiffs, Kromfohrlanders, and Irish terriers with non-type I cystinuria drastically diminished the excretion of cystine and dibasic amino acids. Maintaining a negative cyanide-nitroprusside test may be used to monitor and adjust therapy. In the subset of dogs with androgen-dependent cystinuria, castration can resolve cystinuria. If cystinuria decreases two months after castration compared to baseline measurement (before castration), the patient is less likely to have recurrence of cystine uroliths. If cystinuria persists four months after castration, it was probably not androgen dependent. Nitroprusside test and cystine crystalluria are less reliable tests than urine cystine measurement to detect persistent risk of cystine uroliths formation.

For information on screening for cystinuria please contact:

Dr Giger/PennGen Laboratories
School of Veterinary Medicine
University of Pennsylvania
3900 Delancey Street, Room 4013
Philadelphia, PA 19104
Website: http://research.vet.upenn.edu/penngen
Email: PennGen@vet.upenn.edu
Tel: (215) 573-7545 (Metabolic Lab)

Silica Uroliths in Cats and Dogs

Effective dissolution protocols have not been reported for silicate stones in small animals. The risk of silica urolith recurrence is not well documented. In one study of silica uroliths, 12% of dogs had a previous episode of urolithiasis, but in most cases it was not known whether the previous urolith was also composed of silica.

To reduce the risk of silica stone recurrence, it is recommended to change the diet to one in which the vegetable content is limited. The recommendation is to avoid diets containing soybean hulls and corn gluten feed, and to avoid the ingestion of soil. As with all uroliths, increased water intake should be promoted to decrease the resulting concentration of calculogenic material in urine.

Mixed and Compound Uroliths

The management of compound uroliths is challenging because they consist of layers containing different mineral

compositions. Theoretically, the objective of compound urolith dissolution is to design a protocol to dissolve the outer layer of the urolith first, and then change the protocol to address each successive outer layer. Serial reevaluation of the size of the compound urolith by an appropriate imaging technique is recommended. Once the urolith does not decrease in size, medical therapy may be adjusted to attempt dissolution of suspected minerals in the inner layers. An alternative to the above consists of dissolving the outer layer of the urolith to reduce its size, followed by removing the remaining smaller portion by voiding urohydropropulsion. Neither of these techniques is usually possible in practice given the inability to predict each layer of the compound urolith and then adjust medical therapy as each layer dissolves. As such, mechanical removal is recommended for the majority of compound stones.

Compound uroliths may also contain layers that are not amenable to dissolution (i.e., calcium oxalate). For example, dissolution of an outer layer (i.e., struvite) may lead to a smaller size of urolith, which will then not dissolve any further as the underlying layer is calcium oxalate. This may increase the risk of urinary tract obstruction in male dogs. For this reason, most compound uroliths are removed either surgically or using a minimally invasive method (see later). Following removal of the compound urolith, the specific management strategy is aimed at prevention of the inner layer (nidus) of the compound urolith (i.e., the first layer to form).

Suture-associated stones have become more common. In one study they accounted for 0.6% of all canine uroliths and 9.4% of recurrent uroliths from 1999 to 2006. Suture-induced stones were more likely to be compound uroliths and often had a calcium phosphate nidus. Suture material that dissolves rapidly (like poliglecaprone versus polydioxonone) is recommended, in case bladder mucosal penetration occurs during closure.

Removal of Lower Urinary Tract Uroliths

Lower urinary tract calculi should be removed if they are not amenable to medical dissolution and if they are causing, or may cause, clinical signs, urinary tract obstruction, inflammation, or recurrent infection.

Surgical Removal

In small animals, surgical removal of uroliths by cystotomy or urethrotomy was the traditional standard of care for many years. However, urethral surgeries may result in permanent alterations of the anatomy and function of the urethra. For this reason, urethral surgeries are now discouraged and minimally invasive management of urethral stones has become the standard of care (see later).

Calculi remained in the bladder after cystotomy in up to 20% of dogs and cats. When removing cystic calculi, the urethra should be catheterized and flushed to ensure that it is free of calculi. Postoperative radiographs of the entire urethra are indicated as well to ensure that all calculi have been removed. A 2008 study reported that 9.4% of recurrent stones in dogs were suture induced. Luminal penetration is common in thin-walled bladders, but this is not believed to be associated with formation of calculus if absorbable monofilament suture is used.

Complications of cystotomy include a high recurrence rate of calculi, the need for serial surgeries that can lead to suture-induced stones, strictures, adhesions, bleeding, uroabdomen, pain, and other life-threatening complications.

Nonsurgical Treatment Options

In humans, minimally invasive treatment options have mostly replaced traditional surgical stone removal. In 2002, open surgical removal of uroliths was described in only 0.3–4% of human patients. In small animals, minimally invasive treatment options are now considered the standard of care to manage lower urinary tract stones. They consist of voiding urohydropropulsion (VUH), intracorporeal lithotripsy, extracorporeal shock wave lithotripsy (ESWL), cystoscopic stone basket retrieval, percutaneous cystolithotomy (PCCL), and laparoscopic-assisted cystotomy.

All minimally invasive stone retrieval procedures should ideally be performed after a negative urine culture has been documented, or the patient has been placed on an appropriate antibiotic for at least 24 hours.

Voiding Urohydropulsion

Voiding Urohydropulsion consists of removing small bladder calculi by inducing voiding while the dog or cat is positioned vertically or laterally (Figure 123.15). This procedure was first described by Lulich *et al.* and can be successfully performed in dogs and female cats but not in male cats as their narrow urethra may become obstructed by the stones.

Stone size is the most important criterion in deciding if VUH is an appropriate treatment option. Stones smaller than 3–4 mm can typically be voided respectively by small and small-medium female dogs. In female ultra-small breeds (such as Pomeranian, Chihuahua), careful evaluation of the size of the urethra in relation to stone is indicated. We recommend passing an 8 Fr urinary catheter before doing a VUH while the dog is under anesthesia and choosing an alternative stone removal method if

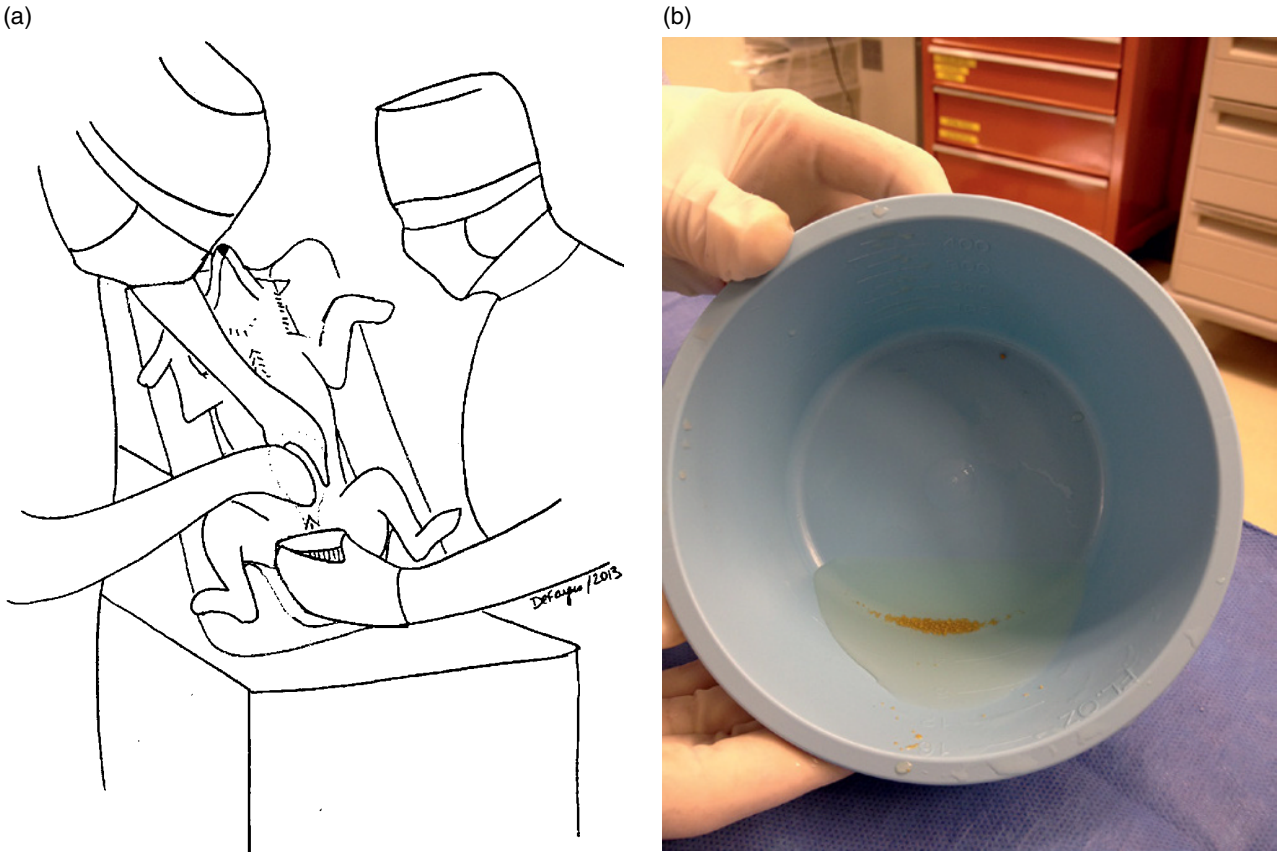


Figure 123.15 (a) Vertical positioning of a female dog to perform voiding urohydropulsion. (b) Container with cystic calculi removed by voiding urohydropulsion.

the urethra is smaller than 8 Fr. Stones smaller than 3 mm can be voided by male dogs weighing 10–25 kg. In male dogs weighing 5–10 kg, stones smaller than 2–3 mm may be voided. The clinician needs to try to catheterize the urethra first to evaluate its size. A catheter that is 3 Fr is equivalent to 1 mm, so that if an 8 Fr urinary catheter can be passed through the urethra, a 3 mm stone can be voided.

For VUH, the patient is placed under general anesthesia. The urethra is catheterized and the bladder is distended with warm sterile saline. The capacity of the bladder is typically 10–15 mL/kg. Once the bladder is fully distended, the patient is positioned vertically and then the urinary catheter is removed (see Figure 123.15a). The bladder is agitated so that gravity causes the stones to fall into the trigone. With strong, steady bladder expression while pulling the bladder cranially to straighten the urethra, the intravesicular pressure will maintain a strong urine stream as small fragments of stone material are voided into a container (see Figure 123.15b). General anesthesia is mandatory for this procedure, as the bladder can rupture if the patient does not have a relaxed, unobstructed urethra. The procedure is repeated until no calculi or stone fragments are passed for two expressions. Radiography, with or without positive or negative contrast (depending on the lucency of the stones), or cystoscopy, can be performed after the procedure to confirm complete urolith removal. VUH can also be used to obtain a few small stones for analysis to determine whether medical dissolution is an option for the remaining stones. Empiric antibiotics should be given during the procedure and for 3–5 days afterward. Broad-spectrum antibiotics such as amoxicillin or cephalexin are usually prescribed. To minimize discomfort during urination, NSAIDs or opioids are administered for 1–4 days as needed and based on clinical signs.

Extracorporeal Shock Wave Lithotripsy (Box 123.1)

Extracorporeal shock wave lithotripsy uses an external unit guided by fluoroscopic visualization to create shock waves that pass through the soft tissue of the patient. It is typically used for the fragmentation of upper urinary tract calculi from a renal pelvis or ureter, which are then left to pass spontaneously through the ureter, bladder, and urethra. It has also been used to fragment bladder stones in some dogs. However, the movement of stones within the bladder during treatment limits the repeated

Box 123.1 Candidates for extracorporeal shock wave lithotripsy

Nephroliths (dogs)

Indications
- Hydronephrosis
- Recurrent infection
- Pain
- Worsening chronic renal failure

Stone size
- <10 mm: ESWL alone
- >10–25 mm: ESWL with ureteral stent or PCNL
- >25 mm: consider PCNL

Ureteroliths (dogs and cats)

Indications
- Ureteral obstruction
- Pain
- Recurrent infection

Patient characteristics
- Dogs with ureteroliths; cats with distal ureteroliths
- Normal coagulation status
- Not pregnant
- No evidence of concurrent pancreatitis
- Appropriate antibiotic therapy for >48 hours before ESWL

Source: Reproduced with permission from Defarges A, Berent AC, Dunn M. New alternatives for minimally invasive management of uroliths: nephroliths. *Compend Contin Educ Vet* 2013; **35**(2): E3.
ESWL, extracorporeal shockwave lithotripsy; PCNL, percutaneous nephrolithotomy.

shock wave effect and may result in larger than desired fragments. After ESWL for bladder stones, VUH or cystoscopic stone basket retrieval is required for stone fragment removal. Typically, intracorporeal methods are preferred for optimal fragmentation and immediate removal of cystoliths.

Intracorporeal Lithotripsy

Electrohydraulic lithotripsy (EHL) and laser (Ho:YAG: holmium:yttrium, aluminum, garnet) lithotripsy were developed in the 1970s to fragment bladder uroliths in humans, with success rates reported to exceed 90%. Both types of intracorporeal lithotripsy have been described in veterinary patients. To date, the Ho:YAG laser is the most commonly used device for intracorporeal lithotripsy in veterinary and human medicine.

During laser lithotripsy, the patient is placed under general anesthesia as for routine cystoscopy. Once the urolith is visualized with the cystoscope, a small-diameter flexible quartz laser fiber (200, 365, or 550 µm) is guided through the working channel. The tip of the fiber is placed in direct contact with the surface of the urolith at a 90° angle, and pulsed laser energy is transmitted from the energized crystal to the urolith via the fiber (Figure 123.16). The stone is fragmented by a thermal drilling process, in which the pulse of energy traveling through the fiber creates a microscopic vapor bubble on the surface of the calculus. The closer the fiber tip is to the target, the larger the effect, having its greatest effect in contact mode. The energy is absorbed in <0.5 mm of fluid, making it safe to fragment uroliths in tight locations, such as within the urethra, ureter, renal pelvis, or urinary bladder, with limited risk of adjacent urothelial damage.

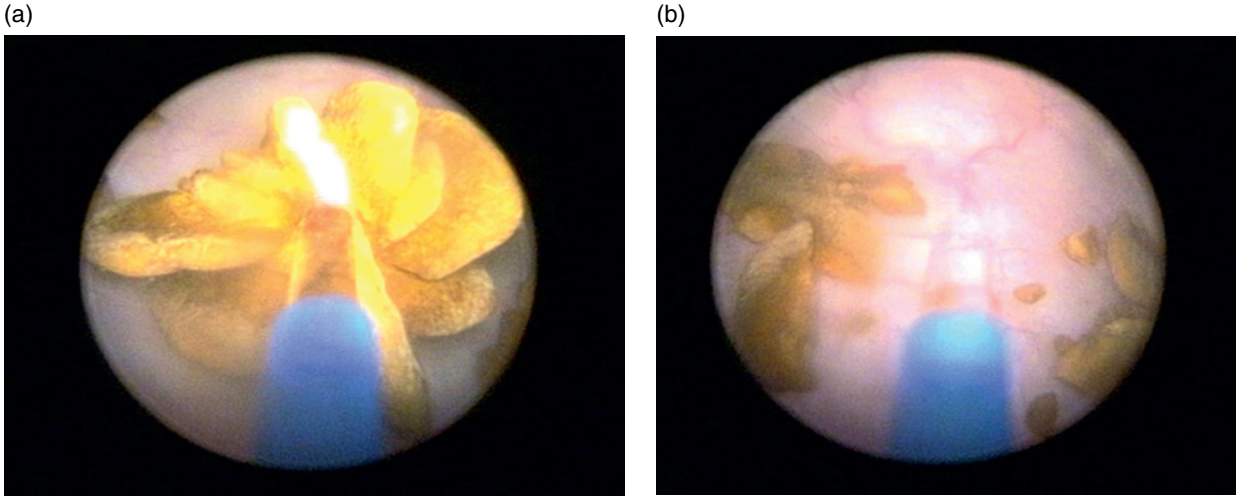


Figure 123.16 Visualization of bladder stones (oxalate) before (a) and after (b) fragmentation with the Ho:YAG laser in a female dog.

Stones are typically fragmented until the pieces are small enough to be voided using VUH or manually extracted from the bladder using a stone retrieval basket. This technology is considered the standard of care in human medicine and is currently being utilized for lower urinary tract stones in many veterinary hospitals in North America.

The Ho:YAG laser has been reported to be effective on all stone types. Adams *et al*. reported that laser lithotripsy resulted in complete fragmentation of all uroliths in 100% of females (28/28 dogs) and 86.7% of males (39/45 dogs). In the literature, complete urolith removal is typically achieved in 100% of dogs with urethroliths, 83–96% of female dogs with cystoliths, and 68–81% of male dogs with cystoliths. In the Adams *et al*. study, the complication rate reported with laser lithotripsy was 17.9% in female dogs and 13.3% in male dogs. Complications were typically minor and shortterm, including urethral swelling, edema, and mild hematuria, which were medically managed. Shortterm complications were most commonly related to urethral mucosal swelling from serial passage of the cystoscope in female dogs and resolved with the placement of an indwelling urinary catheter for 12–24 hours. Short-term complications were reported in 5/28 (17.9%) of female dogs and 6/45 (13.3%) male dogs in this study. In comparison, Thierman-Mankin *et al*. reported short-term complications in 37–50% of 144 dogs using traditional surgical cystotomy.

In another canine study in which laser lithotripsy was retrospectively compared with traditional cystotomy, both methods were considered equally effective. Complete urolith removal rate was not significantly different between dogs in the cystotomy group (86%) and those in the lithotripsy group (89%). There were no significant differences in complications evaluated between the groups and patients undergoing lithotripsy were discharged from the hospital 12 hours earlier than those having a cystotomy. Adams *et al*. reported that of 73 dogs with uroliths treated by laser lithotripsy, only 19% (14/73) had stone recurrence after approximately 12–24 months of follow-up, which is less than that previously reported with cystotomy (42%).

The greatest challenge of both laser and EHL lithotripsy is the removal of small stone fragments from the bladder following fragmentation, which can take extended periods of time and result in urethral trauma/edema during repetitive endoscope passage. Grant *et al*. identified female sex as a positive predictor of success (complete stone removal). They reported that smaller body weight, large urolith burden, and increasing urolith size significantly increased the time required to perform laser lithotripsy. This has made the use of other procedures, like PCCL, appealing for smaller dogs and cats with a large bladder stone burden, regardless of size or sex.

Cystoscopic-Guided Basket Removal

Another option for stones that are too large for VUH but small enough to fit through the urethra with gentle traction is stone basket retrieval. A variety of stone baskets are available from several manufacturers. Basket retrieval is usually performed under cystoscopic guidance, although fluoroscopy can also be used. Typically, the size of the stone is the limiting factor. Basket retrieval can be considered in female dogs with stones <4–5 mm, male dogs with stones <3 mm, and female cats with stones <3 mm.

Percutaneous Cystolithotomy (PCCL)

This minimally invasive approach has been reported in 27 dogs and cats with excellent complete stone removal rates (96%), short procedure times (40–75 min), and similar hospitalization times as those seen with transurethral lithotripsy, regardless of patient sex, size, stone number, or species. This procedure can be an alternative in animals in which transurethral lithotripsy is a challenge (small male dogs, male dogs with a large stone burden, male and female cats, rabbits, guinea pigs, etc.) or if lithotripsy is unavailable.

For this procedure, a single small incision (approximately 1–1.5 cm) is made into the abdominal cavity just over the apex of the urinary bladder. Once the bladder is palpated digitally, stay sutures are used to hold the bladder up to the incision while a laparoscopic screw-tip cannula or port is inserted into the bladder at the apex. Surgical aspiration is usually used while fluid is flushed into the bladder with a urethral catheter, as the best visualization is achieved with a saline-filled bladder. The bladder is typically not fully exteriorized (Figure 123.17a,b). A small, rigid cystoscope is inserted through this port into the bladder, and stones are identified and removed with a stone retrieval basket through the working channel of the cystoscope (Figure 123.17c–e). If the stones are very small, they can be flushed out of the port in a retrograde manner with a urinary catheter in the urethra flushing fluid into the bladder while a suction device is placed into the port suctioning out the fluid and small fragments. If the stones are larger than the port, they can either be fragmented by lithotripsy or manipulated through the small incision with the stone basket. It is very rare that lithotripsy is needed concurrently. After all calculi are removed from the bladder, the entire urethra is examined with a rigid cystoscope (female dogs) or a flexible ureteroscope (male dogs) to ensure that all fragments have been removed and the small incision is sutured closed. A basket

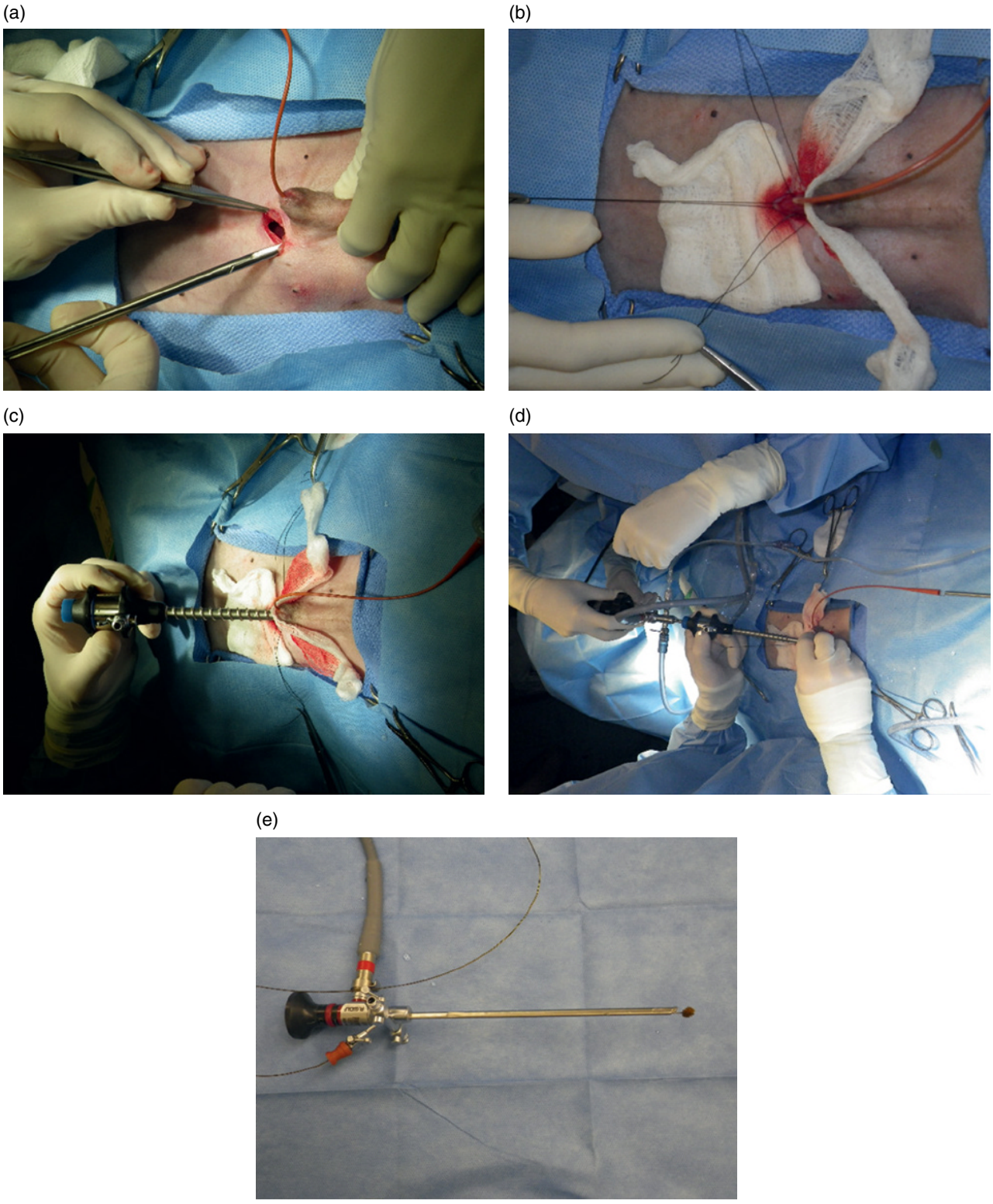


Figure 123.17 Percutaneous cystolithotomy performed in a male dog. (a) A single small incision is made into the abdominal cavity just over the apex of the urinary bladder. (b) Once the bladder is palpated digitally, stay sutures are used to hold the bladder up to the incision. (c) A laparoscopic screw-tip cannula is inserted into the bladder at the apex. (d) A small rigid cystoscope is inserted through this port into the bladder. (e) Stones are identified and removed.

retrieval device can be used to remove any remaining urethral calculi through the working channel of the endoscope.

In patients with embedded urethral stones, laser lithotripsy can be performed. Percutaneous cystotomy can also be used to aid in gaining access to the ureters for diagnostic or therapeutic purposes and for resection of bladder polyps or diagnostic evaluation of the bladder and proximal urethra in dogs that are too small for retrograde cystoscopy.

Laparoscopic-Assisted Cystoscopy

Laparoscopic-assisted cystoscopy is performed via a mini laparotomy. In this technique, the abdomen is insufflated with carbon dioxide and the bladder is isolated. Another trocar is inserted into the abdomen at the level of the bladder apex, and the bladder is exteriorized at this access point using a laparoscopic Babcock forceps. The incision is enlarged, creating a mini laparotomy, to pull the urinary bladder. A small cystotomy is performed and the bladder wall is sutured to the skin of this small abdominal incision. A rigid cystoscope is then inserted into the bladder for calculus retrieval. The use of a basket passed through the working channel or a grasping forceps next to the cystoscope aids in removal of the stones. The cystotomy incision is closed routinely. This procedure makes it difficult to maintain bladder distension for the best visibility.

Laparoscopic-assisted cystoscopy can circumvent some of the limitations associated with laser lithotripsy, but it does require creating a pneumoperitoneum, making the alternative PCCL very appealing.

Removal of Upper Urinary Tract Uroliths

The incidence of nephroliths and ureteroliths in cats has increased as much as 50-fold since the early 1980s. Calcium oxalate is the most common (>98%) type of stone found in the upper tract of cats, followed by calcium phosphate, in the form of apatite, or urate. Approximately 30–60% of ureteroliths in dogs are composed of calcium oxalate.

Indications for Upper Urinary Tract Urolith Removal

Nephroliths

Many canine and feline nephroliths remain static in size and clinically silent for years. Some controversy exists as to whether nonobstructive kidney stones worsen underlying kidney disease. Most recent studies in human and cats show that the presence of nephroliths (vs no nephroliths) seems to worsen renal disease and outcome. For this reason, removal of nephroliths in people is encouraged. In small animals, because of the challenges associated with removal of nephroliths and the lack of evidence that nephroliths are a cause of renal disease progression rather than a marker for more aggressive renal disease, it is not yet recommended to remove nephroliths that are not complicated. Nephrolith removal is not indicated unless uroliths are increasing in size and compressing the renal parenchyma, causing recurrent infections despite appropriate duration of medical management, or if the patient has a partial or complete ureteropelvic junction (UPJ) obstruction resulting in hydronephrosis, renal parenchymal loss, worsening renal function, chronic hematuria, or pain.

Ureteroliths

If one or more ureteroliths are obstructing urine flow, causing hydroureter and/or hydronephrosis, or are associated with discomfort, hemorrhage, or concurrent pyelonephritis, management for medical stone passage or interventional urinary diversion is indicated immediately, regardless of stone composition, as time is critical. The presence of a hydroureter without renal pelvic dilation greater than 5 mm is sufficient to suspect ureteral obstruction. If the ureteral obstruction is complete, decompression of the renal pelvis becomes urgent to preserve the function of the ipsilateral kidney. The longer the ureter remains obstructed, the more significant and irreversible the damage. In one study, after seven days of obstruction, the GFR was permanently diminished by 35% after relief of the obstruction, and recovery took five weeks to occur. When the obstruction lasted for 14 days, the GFR was permanently diminished by 54%, with recovery taking four months to occur. These studies were performed in dogs without preexisting renal or ureteral disease, so a worse outcome might be expected in feline and canine patients with chronic obstructions, previous and/or exhausted renal hypertrophy compensation, and preexisting renal insufficiency. These data suggest that aggressive and timely intervention is necessary when a ureteral obstruction is diagnosed and that the "watch and wait method" should be avoided whenever possible.

Medical Management

Medical management of upper urinary tract stones includes dissolution (nephroliths), aggressive diuresis, or intermittent hemodialysis (IHD).

More than 50% of dogs with ureteral obstructions have been reported to have urinary tract infection. For that reason, any patient with ureteral obstruction should have a urine culture performed and should be given the

appropriate antimicrobials. For dissolution to occur, the uroliths must be surrounded by undersaturated urine to allow them to go back into solution. For these reasons, urocystoliths and nephroliths are amenable to dissolution but ureteroliths and urethroliths are not. Dissolution of struvite nephroliths has been reported in six dogs that had bacterial pyelonephritis and impaired urine-concentrating ability. An average of 184 days of treatment (range, 67–300 days) with a calculolytic diet (Hill's Prescription Diet Canine s/d) and antibiotic therapy was required for radiographic dissolution of the stones in these dogs. In the author's experience (AB), ureteroliths should be dissolved within 2–6 weeks and nephroliths should be decreased in size (<75 % initial size) by three months. It can take up to nine months to dissolve large nephroliths. Increasing the number of walks per day should be encouraged to improve stone elimination.

Aggressive diuresis has been effective at helping move ureteroliths down into the bladder and in resolving azotemia in 8–14% of cats with ureteroliths. This limited success rate of diuresis may be explained by the high percentage of ureteral obstruction secondary to stricture in cats.

Surgical management was effective in 101 cases, but has a high postoperative complication rate (31% in cats and ~35% in dogs) and perioperative mortality rate (18% in cats and 25% in dogs). Medical management should be considered prior to surgical intervention; however, more aggressive management should be considered if the patient fails to improve with medical management alone for 48 hours, or if the patient is anuric/oliguria, hyperkalemic, overhydrated or if there is progressive renal pelvic dilation.

In the authors' experience, aggressive diuresis in cats appears to be more effective for small stones (<1–2 mm) in the distal third of the ureter compared to larger stones, or those in the proximal ureter. Aggressive diuresis consists of aggressive IV fluid therapy while monitoring central venous pressure, body weight, electrolyte concentrations, and hydration status. One recommended fluid therapy protocol includes administering 0.45% saline mixed with 2.5% dextrose at a maintenance rate (e.g., 50–60 mL/kg/d). Additionally, a replacement fluid such as Plasma-Lyte® (Abbott Animal Health) or lactated Ringer's solution (avoiding saline, if possible, to reduce sodium load) is administered to correct dehydration and promote diuresis (e.g., 45–75 mL/kg/d). The maximum combined fluid rate should not exceed 120 mL/kg/day. In patients without cardiac compromise, mannitol is administered as a bolus at 0.25–0.5 g/kg over 20–30 minutes followed by a constant rate infusion of 1 mg/kg/min for 24 hours. If, after 24 hours, there is no evidence of improvement based on imaging and serial bloodwork, the mannitol infusion is discontinued. Other medical alternatives include amitriptyline, alpha-adrenergic antagonist therapy (prazosin or tamsulosin), or glucagon therapy.

Intermittent hemodialysis has been reported to resolve acute kidney injury secondary to obstructive ureteroliths. Thirteen cats did not have any surgical intervention and eight of these 13 survived 365 days or longer past discharge; all of these cats had a degree of renal recovery sufficient for discontinuation of IHD prior to hospital discharge.

If medical management fails or the patient is unstable (e.g., hyperkalemic, overhydrated, oligo-/anuric, developing progressive hydronephrosis), or if IHD is not available at the institution, immediate renal decompression should be considered. If minimally invasive urolith extraction or bypass is not possible, then the two best options are to (1) place a nephrostomy tube or (2) initiate IHD or continuous renal replacement therapy (CRRT), for stabilization. Immediate renal pelvis decompression is recommended over hemodialysis or CRRT if the patient is stable enough to undergo anesthesia and the operator is comfortable with the procedure. Renal pelvis decompression halts the damage being done by the increased hydrostatic backpressure, whereas hemodialysis stabilizes a patient while the ureteral obstruction persists, resulting in ongoing renal injury. A short delay in treatment in a stable patient is preferred over immediate treatment by an inexperienced operator, as the complication rates with any of the decompression procedures are high if experience is limited. Partial obstructions allow a longer window of opportunity for treatment without such dramatic renal damage as seen with complete obstructions, allowing time to arrange referral to a facility with experience in these procedures. Over 75% of obstructed feline patients have a partial ureteral obstruction based on ureteropyelography.

Many patients with ureteral obstruction have concurrent urinary tract infections (75% of dogs and 10–30% of cats) so broad-spectrum antimicrobial therapy is recommended for all patients, and a urine culture and sensitivity should be part of the work-up.

Surgical Removal of Upper Urinary Tract Uroliths

Nephroliths

In small animals, traditional intervention for treatment of nephrolithiasis involves a nephrotomy, pyelotomy, or salvage ureteronephrectomy. Complications can be severe and life-threatening after a nephrotomy, including hemorrhage, decreased renal function, ureteral obstruction by remaining nephrolith fragment passage, and urinary leakage into the abdomen from the renal incision.

In a study of normal cats, the GFR of the ipsilateral kidney decreased by 10%–20% after a nephrotomy. This was clinically insignificant in normal cats but in a clinical patient with maximally hypertrophied nephrons due to prior nephrolith-induced damage, the significance could be dramatic. Therefore, feline patients with an already compromised GFR from chronic stone disease may develop a clinically significant decline in renal function after nephrotomy. Since over 30% of adult cats eventually develop chronic kidney disease associated with a 75% decline of renal function, a 10–20% further decline in GFR from a nephrotomy may be poorly tolerated. Hence, nephrotomy should be avoided when possible in all cats, especially those with existing renal disease. In dogs undergoing traditional surgery for nephrolithiasis, there was a very high complication rate (23%) following the procedure, as well as remaining fragments in more than 40%. In addition, 67% of dogs undergoing nephrectomy developed renal azotemia.

Typically, unless the stone results in a ureteral obstruction or severe perisitent hematuria, is the cause of chronic UTIs, or is so large that it is overtaking the renal parenchyma, nephroliths remain clinically silent for the life of the dog or cat and removal is currently not being recommended. The 2016 ACVIM consensus statement on the management of urinary tract stone disease recommends management of upper urinary uroliths by minimally invasive techniques rather than standard surgery when possible.

Ureteroliths

Traditional surgical intervention to address ureteroliths includes ureterotomy, neoureterocystostomy, ureteronephrectomy, or renal transplantation. Kyles *et al*. reported procedure-associated complication and mortality rates of >30% and 18–38%, respectively, in more than 150 cats that underwent at least one of these procedures. These cases were seen at two universities where microsurgical expertise was available and a renal transplant program existed. The morbidity and mortality rates may be higher in environments where operating microscopes and microsurgical experience and expertise are not available.

Many of the complications associated with surgery are due to site edema, recurrence of stones that then pass from the renal pelvis to the surgery site, stricture formation, persistent obstructions, missed ureteroliths, and ureterotomy-associated or nephrostomy tube-associated urine leakage. In the Kyles *et al*. study, patients that underwent a ureterotomy for treatment of a ureteral obstruction (the most commonly performed procedure in practice) had a perioperative mortality rate of 25%. Uroabdomen occurred in 15% of cats in which a ureteroneocystotomy was performed.

When ureterotomy or ureteroneocystotomy is unsuccessful, a ureteronephrectomy may be required, which is not ideal due to the high risk of subsequent stone-induced obstruction of the contralateral kidney and the majority of cats being azotemic at the time of diagnosis with a unilateral ureteral obstruction. Chronic kidney disease is common in cats when a ureteral obstruction is diagnosed, with 75–97% of cats with a unilateral obstruction reported to be azotemic. For this reason, removing a kidney for a diseased ureter should never be encouraged.

Another major concern is that in one study, 40% of cats developed a second ureteral obstruction over a 1–2-year follow-up, and of these cats, 62% had evidence of nephrolithiasis documented at the time of the first surgery. Unfortunately, removing a nephrolith in a cat is challenging and potentially harmful, and it is impossible to predict whether a nephrolith will become an obstructive ureterolith, so nephrotomy should not be encouraged.

Results after ureterotomy, pyelotomy, and/or ureteronephrectomy have been reported in 16 dogs. The mortality rate (death related to azotemia or to clinical signs related to the urinary system) in this study was 25% (4/16 dogs). Of the 12 dogs that were followed, 17% required an additional surgery within four months for ureteral stricture or recurrent ureteroliths. Most dogs (88%) had urinary tract infections at diagnosis, and 50% had concurrent nephrolithiasis. Ten (62.5%) dogs presented to the hospital with elevated blood urea nitrogen and/or creatinine concentrations and 50% remained elevated after successful surgery. Postoperatively, two dogs had worsening azotemia.

Minimally Invasive Management of Nephroliths and Ureteroliths

In humans, minimally invasive procedures are the treatment of choice for nephrolithiasis and ureteroliths due to the high complication rates and morbidity associated with traditional surgery (Table 123.4). These procedures include ESWL for nephroliths <1–2 cm and endoscopic nephrolithotomy (percutaneous nephrolithotomy [PCNL] or surgically assisted endoscopic nephrolithotomy [SENL]) for nephroliths >1–2 cm. Open surgery and laparoscopy are typically only considered after other less invasive options have failed or been deemed inappropriate.

Over the last 10 years, evidence-based data support that minimally invasive treatment of upper urinary tract uroliths in dogs and cats is associated with a lower morbidity and mortality rate compared to surgical procedures. Selection of the most kidney-sparing procedure should always be a priority to treat upper urinary tract uroliths in small animals.

Table 123.4 Considerations for various interventional procedures in patients with partial or complete ureteral obstruction[a]

Procedure	Cats	Dogs
Medical management (aggressive diuresis)	• Indicated within 48 h of ureteral obstruction • Contraindicated if patient is unstable (hyperkalemic, excessively overhydrated, becoming oliguric, or has cardiac disease)	• Indicated within 48 h of ureteral obstruction • Contraindicated if patient is unstable (hyperkalemic, excessively overhydrated, becoming oliguric, or has cardiac disease)
Nephrostomy tube	• Indicated for urgent decompression of the renal pelvis if ESWL and ureteral stenting not available • Renal pelvis must be >10 mm • Surgically placed; percutaneous placement not recommended because of increased risk of uroabdomen due to mobility of feline kidneys	• Indicated for urgent decompression of the renal pelvis if ESWL and ureteral stenting not available • Renal pelvis must be >10 mm • Percutaneously placed
ESWL	• Indicated for ureteroliths <3 mm • Add ureteral stent if ureterolith is between 3 and 5 mm or obstruction is present	• Indicated for ureteroliths <5 mm • Add ureteral stent if ureterolith is >5 mm or obstruction is present
Ureteral stents	• Indicated for obstructive ureteroliths (any degree of hydroureter and hydronephrosis) • Placed antegrade via nephrostomy access • Placed retrograde via cystoscopy or ureterotomy	• Indicated for any obstructive ureterolith • Placed retrograde (cystotomy or cystoscopy) or antegrade (percutaneous or surgical nephrostomy access)
Ureteroscopy	Not performed because of small patient size	• Indicated for dogs >18 kg • Ureteral stents placed when complete obstruction
SUB	• Current preferred method for ureteral obstruction in cats • Indicated for ureteral strictures or very proximal ureteral obstructions • Indicated for ureteral stent reactions	• Indicated for ureteral stent reactions or intolerance or recurrence of occlusion
Ureterotomy or ureteral reimplantation	If deemed appropriate by attending surgeon	If deemed appropriate by attending surgeon

[a] Immediate treatment of partial ureteral obstruction is typically recommended.
Source: Reproduced with permission from Defarges A, Berent AC, Dunn M. New alternatives for minimally invasive management of uroliths: ureteroliths. *Compend Contin Educ Vet* 2013; **35**(3): E1–E7.
ESWL, extracorporeal shock wave lithotripsy; SUB, subcutaneous ureteral bypass.

Extracorporeal Shock Wave Lithotripsy

Extracorporeal shock wave lithotripsy is used to fragment uroliths fixed in one location. It has been successfully used to fragment nephroliths and ureteroliths in dogs and ureteroliths in cats. The patient is placed under general anesthesia to permit positioning and provide analgesia. Fluoroscopy is used to position the ESWL unit to target the urolith. If compromised renal function is of concern, or if bilateral ESWL is to be performed concurrently, limiting treatment to a maximum of 2000–2500 shock waves per kidney is recommended. For uroliths in the distal ureter or urinary bladder, higher doses are possible because the kidney is not within the treatment focal zone and collateral damage to surrounding tissues seems to be minimal.

Extracorporeal shock wave lithotripsy is most commonly recommended for the treatment of nephroliths and ureteroliths in dogs, rather than cats, for two reasons. First, the feline ureter does not routinely accommodate nephrolith fragment passage. Therefore, a nonobstructive nephrolith could become an obstructive ureterolith after ESWL. Post ESWL, nephrolith fragments are typically ≥1 mm in diameter, and the typical unstented feline ureter is 0.3–0.4 mm in diameter. Second, there is some concern that feline kidneys are more sensitive than canine kidneys to shock waves and could experience bleeding.

Extracorporeal shock wave lithotripsy treatment was reported to be successful in approximately 85% of dogs with calcium-containing nephroliths and ureteroliths. Successful fragmentation of renal stones was achieved in 90% of dogs, but some dogs required multiple treatments. Overall, 30% of dogs required more than one ESWL treatment for adequate fragmentation of nephroliths when lithotripsy was used; when an older model dry unit (Modulith SL-20) was used, up to 50% of dogs required more than one treatment. Success rates approach ~85% with one treatment when ureteral stenting is concurrently performed. In one study of five cats with ureterolithiasis treated by ESWL (wet unit),

only one cat had complete resolution of the ureterolith, and partial fragmentation occurred in two other cats; however, these fragments were still too large to pass down the ureter. In the authors' (AB) experience, success in stone fragmentation and passage was seen in two of an additional five cats, suggesting an approximate 30% passage rate overall (3/10). However, larger studies are needed to confirm these results and this procedure is not currently recommended in cats by the authors.

Extracorporeal shock wave lithotripsy is believed to be safe and well tolerated by canine kidneys. In a series of 140 dogs with nephroliths or ureteroliths treated by ESWL, the most common complication was ureteral obstruction by stone fragments, which occurred in approximately 10% of dogs. With the advocacy of ureteral stent placement for larger nephroliths (>10–20 mm) before ESWL, this risk has declined. In dogs, it has been shown that the renal changes observed after ESWL typically result in minimal decreases in GFR and renal blood flow during the first 24 hours of treatment, and both return to baseline within one week. Extrarenal complications with ESWL include abdominal pain, diarrhea, and pancreatic injury (i.e., increased enzymes levels not associated with clinical signs). Shock wave-induced dysrhythmias have been described in a few human patients (<8%).

Hospitalization typically ranges from eight to 24 hours to monitor for the passage of urolith fragments and to allow postprocedure analgesia and diuresis with intravenous fluid therapy. Stone fragments may be voided 1–2 days after the procedure and collected in a strainer or cheesecloth to be analyzed. Animals with ureteral stents often require shorter hospital stays, as the concern for post-ESWL ureteral obstruction is diminished. Patients are discharged with instructions for monitoring urination and urine appearance, lethargy, abdominal pain, or vomiting. Follow-up radiography and ultrasonography are typically recommended one day after treatment, then in 2–4 weeks, and then every month thereafter until all stones are passed. If fragments that have passed into the urinary bladder are not voided within 1–2 months after ESWL, VUH or cystoscopic stone basketing is recommended. If stone fragments remain in the kidney or ureter after 2–3 months, repeat ESWL is suggested as long as there is no concurrent ureteral obstruction. A second treatment is required in 15–35% of cases to achieve effective fragmentation if the remaining fragments appear too large to safely pass through the ureter. In cases of ureteral obstruction, placement of a ureteral stent would be recommended.

Ureteral Stents

The use of ureteral stents in dogs and cats has been investigated for the last 14 years as a less invasive alternative to traditional surgery. Placement of a double-pigtail ureteral stent (Figure 123.18), via either minimally invasive techniques (endoscopy and fluoroscopy in most dogs) or surgically assisted (nephrostomy access in most cats), can circumvent many of the perioperative complications of surgery (e.g., leakage, stricture, reobstruction)

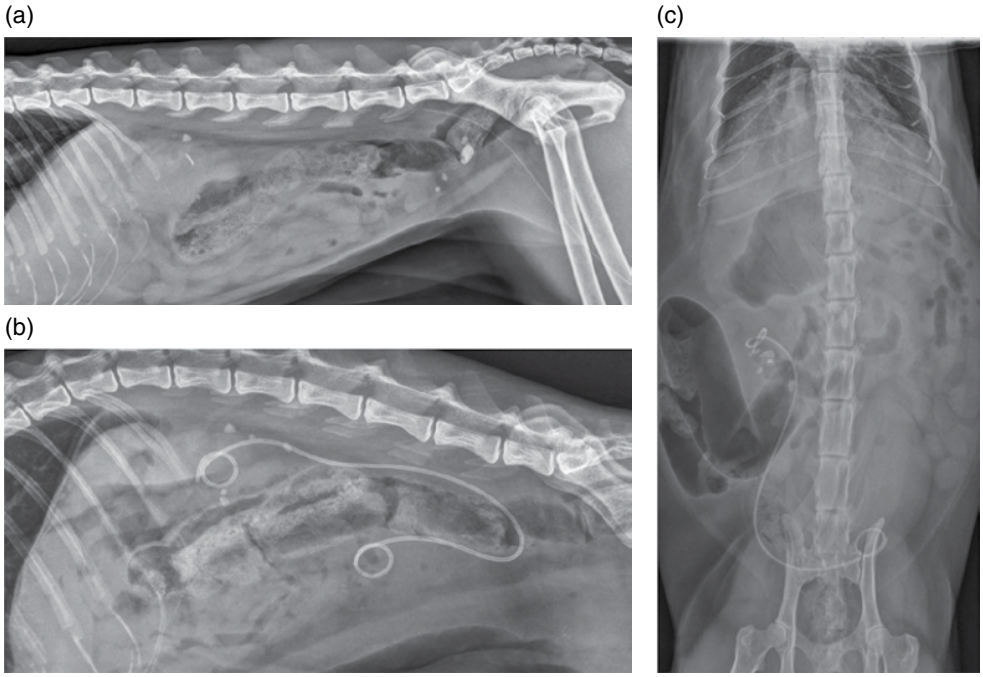


Figure 123.18 Preoperative lateral (a), postoperative lateral (b) and ventrodorsal (c) radiographs following ureteral stent placement in a cat.

and quickly stabilize the patient. Typical ureteral stent sizes are 2.5 Fr for cats and 3.7 or 4.7 Fr for dogs. Ureteral stents have many benefits:

- immediate decompression of the renal pelvis
- passive ureteral dilation for urine and stone passage
- prevention of strictures and leakage associated with surgical or nonsurgical procedures
- prevention of a ureteral obstruction after ESWL
- can be easily removed.

In cases of obstructive pyonephrosis, endoscopic ureteral and renal pelvic catheterization can lavage the renal pelvis and ureter of infected debris and a ureteral stent can then be placed to maintain ureteral patency. All of these benefits have been clearly documented in human medicine and, more recently, in veterinary medicine.

Ureteral stenting in dogs and cats performed by an experienced operator is associated with a lower morbidity and mortality rate (<2% and 7%, respectively) than traditional surgery. Surgical placement with fluoroscopic guidance has a procedural success rate of more than 95% in cats and 100% in dogs; with endoscopic and fluoroscopic guidance, the success rate is 20% in cats and over 90% in dogs. There are relatively few major long- or short-term complications (Table 123.5), and the stents are typically left in place long term. In the authors' (AB) experience to date, the longest duration of stent patency in a feline ureter is more than seven years and in dogs more than 10 years.

The risks of stent placement need to be understood, and owners must be educated on these risks before considering this option (see Table 123.5). The greatest risks are associated with device placement, as the stent can be very difficult to place in some feline patients, and appropriate training and experience with the procedure are critical to its success. Risks seen months to years after stent placement are typically not life threatening, and are relatively easy to address on an outpatient basis

Table 123.5 Immediate, short-term, and long-term complications of various minimally invasive procedures to manage ureteroliths in dogs and cats

	Complications			
Procedure	**Operative**	**Postoperative (<1 week)**	**Short-term (1 week–1 month)**	**Long-term (>1 month)**
Feline ureteral stent	Ureteral perforation with guidewire (little clinical consequence) Leakage if concurrent ureterotomy needed Eversion of ureteral mucosa during stent passage Ureteral tear during stent passage	Fluid overload during postobstructive diuresis (<5%) Failure of creatinine to improve (<5%) MORTALITY (<8%) typically due to nonurinary causes (pancreatitis or congestive heart failure)	Dysuria (self-limiting 7–14 days) Inappetence (temporary)	Dysuria (38%) nearly all respond to prednisolone and/or prazosin UTI (30%; 34% pre-op) Reobstruction (19%) – Stricture recurrence (54%) – Adhesions around ureter (23%) Obstructive pyelonephritis (8%) Chronic hematuria (18%) Stent migration (6%) Ureteral reflux (1%)
Canine ureteral stent	Endoscopic failure (~3%) Ureteral perforation (<1%) Leakage (<1%) Ureteral tear (<1%)	MORTALITY (<1%)	Dysuria (<1%)	Proliferative tissue at ureterovesicular junction (25%) UTIs (~10%; >60% pre-op) Migration (<5%) Occlusion (<5%) Dysuria (<3%)
SUB	Renal pelvis penetration by guidewire (<5%) Kinking of catheters (~5%) Inability to place SUB device (<1%)	Leakage (5%) Fluid overload (<5%) Failure of creatinine to improve (<5%) Blockage of system (3%) (blood clot, purulent material, device failure) MORTALITY 5.6%	Dysuria (<2%) Inappetence (temporary)	UTI (15%; 35% pre-op) Blockage of system (9%) (stones 8%, purulent material 1%) Dysuria (<2%)

Source: Reproduced with permission from Defarges A, Berent AC, Dunn M. New alternatives for minimally invasive management of uroliths: ureteroliths. *Compend Contin Educ Vet* 2013; **35**(3): E1–E7.
SUB, subcutaneous ureteral bypass; UTI, urinary tract infection.

and include reocclusion, migration, or dysuria. In dogs, ureteral stents have replaced standard surgery to decompress upper urinary tract obstruction. Long-term complications include urinary tract infection (26%), occlusion of the stent (9%), ureteritis (5%), stent migration (5%), encrustation (2%), and hematuria (7%). More than three-quarters of the patients were able to clear the infections if present before ureteral stent placement. In cats, ureteral stent placement can be challenging and is associated with a 38% rate of long-term dysuria (responsive to steroid therapy). Since subcutaneous ureteral bypass has been associated with lower complication rates (see later) than ureteral stenting in cats, it is now considered the treatment of choice to relieve upper urinary tract obstruction in cats in the authors' practices.

Endoscopic Nephrolithotomy

In humans, PCNL is typically performed for large or embedded nephroliths (>15–20 mm). In small animals, PCNL/SENL is considered if ESWL fails or is not available, cystine stones (which are resistant to EWSL) are present, or the stone is >15–20 mm (depending on patient size).

Typically, a combination of ultrasonographic, endoscopic, and fluoroscopic guidance is used for both PCNL and SENL. PCNL has been performed in 11 dogs and one cat to date. The smallest patient to date having a PCNL/SENL was 5 lbs (2.3 kg), making patient size less of an issue than other alternatives.

Typically, for PCNL, a renal access needle is used to access the renal pelvis through the greater curvature of the kidney under ultrasonographic guidance. Subsequently, a nephroscope is inserted through a sheath and into the renal pelvis to visualize the stone. If the latter is small enough, a stone retrieval basket is used to remove the stone. If the stone is larger than the sheath, intracorporeal lithotripsy (ultrasonic, pneumonic, electrohydraulic, or Ho:YAG laser) is used to fragment it. Once the stone fragments are small enough to fit through the sheath, they are removed and a locking-loop nephrostomy tube (5 or 6 Fr) is left in place to allow the small hole to seal and form a nephropexy.

Surgical-assisted endoscopic nephrolithotomy can be performed similarly to that described for PCNL, only the abdomen is opened to assist in nephrostomy access closure, to prevent the need for a nephrostomy tube. For both PCNL and surgical-assisted endoscopic nephrolithotomy, because a balloon is used to dilate the renal parenchyma (no incision is performed), minimal nephron loss occurs. PCNL and SENL are considered the most "kidney-sparing" procedures with the highest urolith-free rate and minimal effect on GFR. For these reasons, they are recommended as the first treatment for patients with staghorn calculi according to the American Urologic Association Guidelines.

The author (AB) has performed endoscopic nephrolithotomy in 11 dogs and one cat (16 renal units) using the PCNL approach (n = 4 renal units) or SENL (n = 12 renal units) to remove complicated nephroliths (median diameter 2.5 cm; range, 0.5–5.7 cm). No kidney required conversion to traditional surgical nephrotomy or nephrectomy. Median procedure time was 180 minutes (range, 90–270 minutes). Patients were discharged within 48 hours (range, 48–144 hours). The procedure was successful (resolution of complicated nephroliths) in 14 renal units. Ureteral stents were placed in all cases during the PCNL/SENL and removed after 1–20 weeks minimally invasively. No recurrence was reported during the follow-up period (median duration 557 days). Owners tolerated recovery from the SENL better than the PCNL because a nephrostomy tube was not required.

Overall, this series of cases demonstrates that PNCL and SENL have a greater stone-free rate (93% vs 85%) and lower recurrence rate (0% vs 10%) than ESWL for large problematic nephroliths. The results of this study suggest that the median survival time is higher for dogs with IRIS stage 1, 2 or 4 disease treated with ENL compared to previously reported survival times for the same IRIS stage diseases. However, further prospective studies are required to draw conclusions as this was only a small number of cases.

Ureteroscopy

Contrary to human medicine, ureteroscopy is rarely performed in veterinary patients. For minimally invasive treatment, dogs with a ureteral obstruction could have an endoscopic ureteral stent placed and/or may also undergo ESWL. If the patient is large enough (at least 39.6–44 lb [18–20 kg]), ureteroscopy can be considered. However, most dogs with ureterolithiasis are small terrier or toy breeds, making this an uncommon procedure. If this is to be performed, then the preplacement of a ureteral stent to allow for passive ureteral dilation, prior to ureteroscopy, is typically recommended.

Subcutaneous Ureteral Bypass

Feline ureteroliths are typically more frustrating than canine ureteroliths due to the small diameter of the feline ureter (<0.4 mm) and the endoscopic and surgical limitations. In cats, ESWL is not typically advised and ureteroscopy is not possible.

A subcutaneous ureteral bypass (SUB) involves the placement of a nephrostomy tube and a cystostomy tube that are connected subcutaneously to a shunting port, allowing for urine drainage from the kidney directly to the bladder, bypassing the ureter (Figure 123.19). Initially, this procedure was primarily performed for cats with

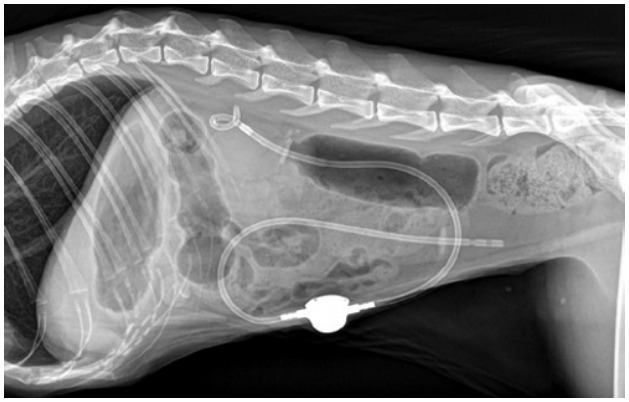


Figure 123.19 Lateral radiographs of a feline patient following the placement of a subcutaneous ureteral bypass.

ureteral strictures, very proximal ureteral obstructions, or in which stent placement was unsuccessful. Based on experience in over 300 cats in the authors' practice, it is now preferred over the feline ureteral stent due to the minimal complications both shortterm and longterm. Over 93% of cats survived to hospital discharge after admission. The longest period for which an SUB device has remained in place is nine years (personal communication AB), and the short- and long-term complications seen with this device are fewer and less severe than those seen with ureteral stents in cats (see Table 123.5).

The use of a SUB device to treat cats with ureteral obstruction has been associated with the highest survival rate to date. In that study, 135 out of 144 (94%) cats survived to hospital discharge, and 90%, 83%, 80% and 74 % of cats were alive after one, three, and six months and one year respectively after SUB placement. The most common complication was stent obstruction (25%) requiring SUB system replacement. However, with the use of tetrasodium ethylenediaminetetraacetic acid (tEDTA) solution, the rate of reobstruction declined to 4.5%.

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Further Reading

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124

Prostatic Diseases

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Both male dogs and cats have prostate glands, but cats rarely develop prostatic diseases. Prostatic diseases are relatively common in middle-aged to older, intact male dogs and rare in neutered males, with a higher reported frequency in medium- and large-breed dogs. Most companion male dogs and cats are neutered, which prevents the majority of prostatic diseases.

The prostate is the only accessory sex gland in male dogs, and it surrounds the urethra in the pelvic region caudal to the trigone of the bladder and distal to the internal urethral sphincter. It is oval in shape and bilobed, with the two lobes separated by a prominent median septum (Figure 124.1). The size of the prostate is greatly influenced by hormonal stimulation. Castration of dogs removes the important trophic factors necessary for prostatic growth and function, estrogen and testosterone, and leads to prostatic atrophy (Figure 124.2).

The prostate itself is an exocrine gland that produces continuous secretions that flow into the urethra through multiple prostatic ducts. These secretions make up the largest component of spermatic ejaculate (90–95%). Normal prostatic acini are lined with tall columnar to cuboidal epithelium. The prostate reaches normal size by age 2, but it continues to grow with age in the intact male.

Most problems associated with the prostate result in prostatomegaly, but many of the diseases do not result in pain upon palpation of the prostate or lower urinary tract signs. The most common prostatic diseases are benign prostatic hyperplasia (BPH), bacterial acute and chronic prostatitis, prostatic abscesses, prostatic and paraprostatic cysts, and prostatic neoplasia (discussed in further chapters).

Benign Prostatic Hyperplasia and Prostatic Cysts

Etiology

Benign prostatic hyperplasia is by far the most common prostatic disease in intact male dogs, and it develops due to long-term exposure of the prostate trophic hormone testosterone's active metabolite dihydrotestosterone (DHT). Over time, an imbalance in the ratio of androgens to estrogens develops, and there is also both an increase in prostatic tissue sensitivity to androgens and an increase in androgen receptors. Over 50% of intact male dogs will develop symptoms from BPH by age 5, and by the age of 6 years 80% will manifest symptoms.

Fluid-filled cysts may develop within the prostate and are secondary to the hormonal influences that also cause BPH. Theses cysts may not cause clinical signs until either they get infected and develop into an abscess, or affect the flow of urine through the urethra due to their size.

History and Clinical Signs

Not all dogs with BPH develop clinical signs. In others, as the prostate becomes enlarged, observed clinical signs with BPH include intermittent or continuous serosanguinous discharge or hematuria, and less commonly straining to defecate, and lower urinary tract signs. Dogs may experience pain upon ejaculation, and BPH can lead to infertility in some cases. Dogs with BPH are not usually systemically ill but they do have a higher incidence of developing prostatitis, prostatic abscesses, and urinary tract infections.

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Figure 124.1 Ultrasound transverse view image of a normal prostate of an intact male dog. Note the homogenous echotexture and relatively uniform but prominent size of the prostate. *Source:* Image courtesy of Dr Tim Spotswood.

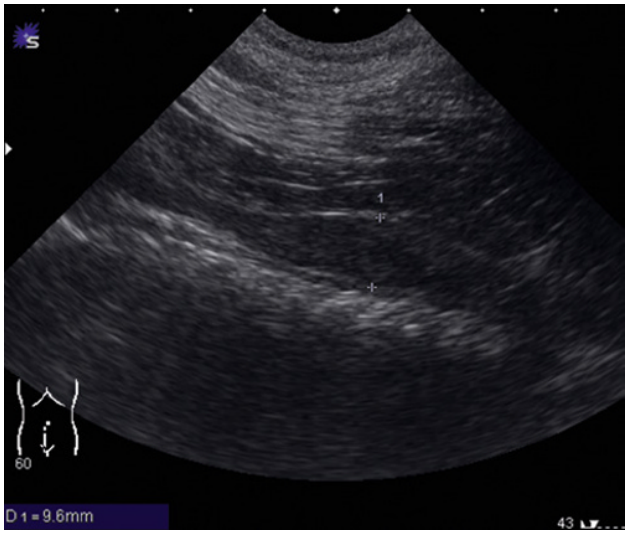


Figure 124.2 Ultrasound transverse view image of an atrophied prostate in a neutered male dog. The prostate is very small and barely recognizable. The + symbols delineate the prostate. *Source:* Image courtesy of Dr Tim Spotswood.

Diagnosis

With all suspected prostatic diseases, it is important to put the entire clinical picture together: history, clinical signs, physical exam, imaging results, laboratory results, and cytology or histopathology.

Performing a rectal examination is of the utmost importance. Neutered males rarely develop prostatic diseases but they can still develop prostatic neoplasia, so it is important not to rule out prostatic diseases in castrated males. In most patients, the caudal portion of the prostate can be palpated on the ventral floor of the colon. This may be difficult in larger dogs. The normal prostate should not be painful and should be soft. With BPH, the prostate tends to feel enlarged but it is smooth, symmetric, and rarely painful. The median raphe may not be as obvious to palpate. The enlargement may cause the prostate to move cranially into the abdominal cavity, and therefore can be difficult to palpate rectally without the help of concurrent abdominal palpation. Prostatic cysts can rarely be identified. Rectal palpation should also include the dorsal portion of the distal colon to feel for enlarged iliac lymph nodes. With BPH, lymphadenopathy should not be present. Constipation may be possible, but the rest of the physical exam is usually within normal limits.

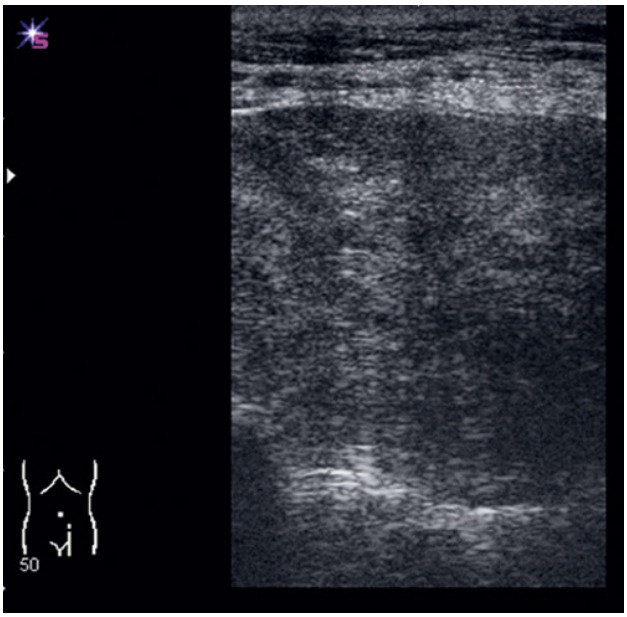
Complete blood count (CBC) and chemistry panel are unremarkable in dogs with BPH and noninfected prostatic cysts. Human prostate-specific antigen (PSA) has not been shown to correlate with prostatic disease in dogs. Abdominal radiographs may reveal an enlarged soft tissue opacity in the caudal abdominal region usually near or within the pelvic canal and caudal to the bladder, especially on a lateral radiograph. Radiographs are not very sensitive or specific for identifying the etiology of prostatic disease but they do give a good indication of size and shape of the prostate. Prostatic mineralization can be seen in both neutered and intact dogs. In neutered dogs, mineralization strongly indicates neoplasia, whereas in intact dogs, mineralization can indicate neoplasia, prostatitis, BPH, and prostatic cysts. Constipation can be noted on radiographs. The prostate is harder to recognize on abdominal radiographs in a neutered male.

Retrograde contrast urethrocystography can aid in the diagnosis of prostatic and urethral disease. Prostatic disease may result in the uptake of contrast into glandular tissue, and the degree of uptake can correlate with severity of disease. With BPH, there should be minimal to no contrast uptake. It may be possible to appreciate a narrowed prostatic urethral diameter due to compression by an enlarged prostate.

Ultrasonography has become the gold standard for visualizing the prostate. In the intact male, the normal prostate usually appears as a bilobed structure on short axis and oval on long axis, its architecture uniform and with a homogenous echogenicity similar to the spleen. In BPH, the prostate appears enlarged and there may be a loss of visualization of the median septum. Echogenicity should not differ from the normal prostate or the prostate may be slightly more hyperechoic (Figure 124.3). Prostatic cysts can be seen within the parenchyma and usually contain anechoic fluid (Figure 124.4). Cysts may vary in size and number.

For a specific diagnosis of prostatic disease, a sample of prostatic cells, fluid, or tissue is recommended. Often with typical clinical signs and diagnostic results, BPH can be tentatively diagnosed and treated, but it is important to note that other diseases cannot be excluded.

(a)



(b)

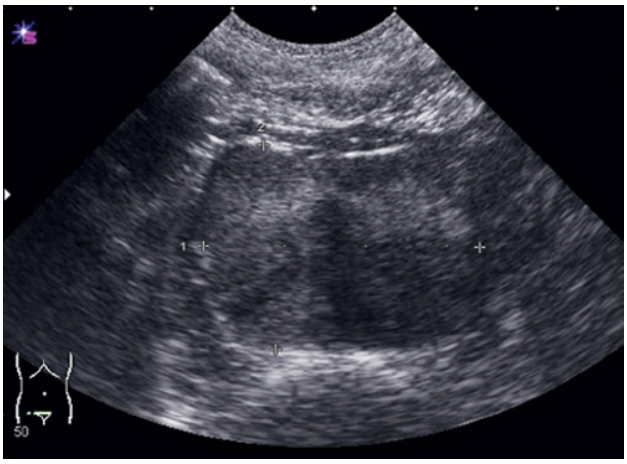


Figure 124.3 Benign prostatic hypertrophy as seen on ultrasound in both transverse and sagittal planes. The prostate is larger than normal and appears slightly more echogenic. *Source:* Image courtesy of Dr Tim Spotswood.

Obtaining a biopsy of the prostate can be difficult due to its location in the caudal abdomen. Biopsies may be obtained using ultrasound guidance and a Tru-Cut biopsy instrument, or surgically via laparotomy/laparoscopy. Biopsies may also be obtained in a blind fashion but this is not recommended. With BPH, histopathology should indicate only evidence of hyperplasia and hypertrophy.

Cytology of prostatic cells and fluid has been shown to agree most of the time with histopathology, and is more sensitive in the detection of infectious processes. However, a negative cytology does not rule out prostatic diseases. Ultrasound-guided fine needle aspirates of the prostate for cytology and culture are possible and relatively easy to do. Other cytology and/or culture techniques include semen collection, prostatic massage and wash, prostatic brush cytology, and traumatic prostatic wash (Table 124.1). Cytology of a normal prostate contains cuboid to columnar epithelial cells in clusters. Cytology of BPH usually reveals normal-appearing epithelial cells arranged in clusters characteristic of a honeycomb appearance.

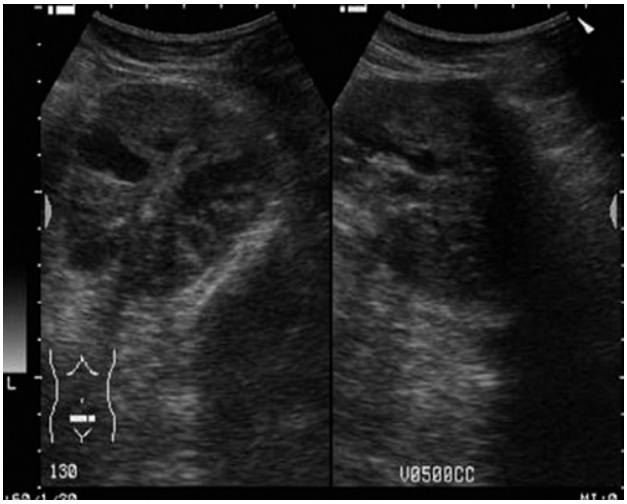


Figure 124.4 Benign prostatic hypertrophy with prostatic cysts as seen on ultrasound in both transverse and sagittal planes. *Source:* Image courtesy of Dr Tim Spotswood.

A urinalysis and urine culture is usually always indicated with any prostatic disease due to the higher incidence of urinary tract infections. With BPH, urinalysis may be normal or show increased red blood cells with an inactive sediment and negative culture.

Therapy

Therapy is not always indicated for BPH as not all dogs develop clinical signs. These patients should be monitored for the development of clinical signs over time by their owners. Surgical castration is the treatment of choice for BPH, and prostatic atrophy begins within days to weeks following surgery, with completion usually by 12 weeks. The larger the prostate prior to surgery, the longer the involution period. Clinical signs begin to resolve before involution is complete. Prostatic cysts will usually resolve with castration unless they are infected. Large prostatic cysts may rarely require surgery.

In breeding dogs, medical therapy can be used to reduce prostatic size and clinical signs of prostatomegaly. Finasteride, a 5-alpha-reductase enzyme inhibitor, is the treatment of choice in men and has been shown to be effective in dogs. The medication blocks the conversion of testosterone to DHT in the prostate. Finasteride does not affect fertility and has no known side-effects in dogs.

Table 124.1 Procedures for collecting cytologic samples from the prostate

Procedure	Specialized equipment	Advantages	Disadvantages
Percutaneous ultrasound-guided aspirate	Ultrasound machine, probe capable of reaching higher frequencies; needles (22 G, 1.5 inch in length) or catheters; syringes (6 cc) and extension set	Quick and relatively effective at obtaining diagnostic samples; can be used to target specific areas of the prostate, more sensitive	May require sedation; technique requires learning curve and specialized equipment; risk of seeding infectious organisms or neoplastic cells into abdominal cavity; risk of abscess rupture
Brush cytology	Bronchoscopy airway brush	Quick and easy to do; minimal learning curve	May not reach the prostate; nondiagnostic sample if more localized disease; brush can only be used once; sedation may be necessary
Ejaculate collection	None	Easy and safe to do; sedation not necessary	Difficult in painful animals; patients may not cooperate; sample only useful for culture and is not specific to prostatic disease
Prostatic wash	Urinary catheters of various French sizes (red rubber catheters, Argyle feeding tube catheters); syringes (30–60 cc) and extension set; nonsterile gloves	Safe, relatively easy; sedation may not be necessary; more sensitive; less risk of bacteria or neoplastic cell abdominal seeding	Urine contamination possible; prostate may be too far to reach; potential risk of abscess rupture; requires multiple people
Traumatic wash	Urinary catheters of various French sizes (red rubber catheters, Argyle feeding tube catheters); syringes (30–60 cc) and extension set; nonsterile gloves	Safe, relatively easy; may yield a more diagnostic sample than simple prostatic wash; less risk of bacteria or neoplastic cell abdominal seeding	Urine contamination possible; prostate may be too far to reach; potential risk of abscess rupture; sedation usually necessary; requires multiple people

However, care must be taken in its administration and the drug may cause birth defects in pregnant women. Dosages range from 0.1–1 mg/kg orally once daily to 5 mg per dog per day, and a decrease in prostatic size by 50–70% is usually seen by 2–3 months. Flutamide is androgen receptor antagonist and prevents DTH from binding to the receptor. It has been reported to be effective at a dosage of 5 mg/kg orally once daily with no known side-effects. Cost is the limiting factor for both drugs.

Estrogen therapy can also be used to treat BPH and will cause a decrease in testosterone production. However, long-term therapy with estrogen may cause bone marrow suppression, symptoms of feminization, and prostatic squamous metaplasia. Estrogen and its derivatives are no longer recommended as first-line therapy to treat BPH.

Lastly, gonadotropin-releasing hormone (GnRH) agonist implants have shown great promise and effectiveness with no reported adverse effects in treating BPH in intact male dogs. Their limited availability limits their use at this time.

Prognosis

Prognosis from uncomplicated BPH causing clinical signs is excellent with surgical castration as treatment is curative, and good with medical therapy depending on response to pharmacologic therapy. Fertility is usually restored with finasteride therapy once the prostate beings to atrophy. Prostatic cysts that are not infected should shrink and disappear with surgical castration.

Paraprostatic Cysts

Etiology

Paraprostatic cysts are fluid-filled structures that develop beside and outside the prostate secondary to the retention of the embryonic muellerian duct system (uterus masculinus). These cysts may become quite large, usually are thin-walled, and contain anechoic to debris-filled fluid.

History and Clinical Signs

These cysts often do not cause appreciable clinical signs, or they may grow large enough to compress and obstruct the urethra or the colon.

Diagnosis

Abdominal ultrasound is the modality of choice for detection of these cysts (Figure 124.5). They often resemble a second urinary bladder.

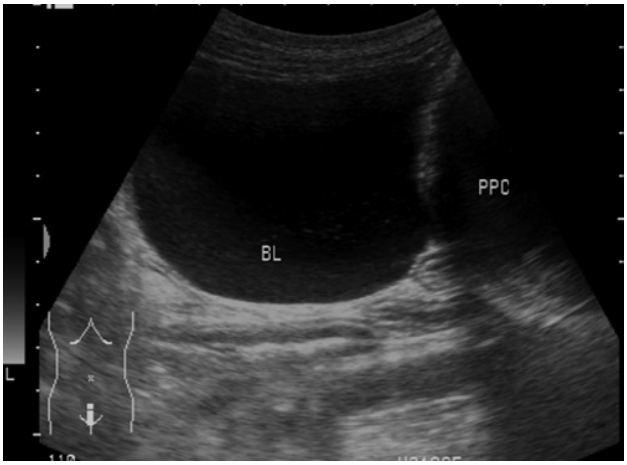


Figure 124.5 Paraprostatic cyst as seen on sagittal ultrasound view. BL, urinary bladder; PPC, paraprostatic cyst. *Source:* Image courtesy of Dr Tim Spotswood.

Therapy

Surgery is required to completely or partially remove these cysts. Concurrent castration is recommended.

Prognosis

Prognosis is good to excellent depending on the ability to surgically remove the cysts.

Prostatitis and Prostatic Abscesses

Etiology

Bacterial prostatitis is usually the result of an ascending infection via the urethra and into the communicating prostatic ducts. The presence of other prostatic conditions such as BPH, prostatic cysts, or prostatic neoplasia may increase the incidence of prostatitis. Alterations in urine flow and urinary tract infections also increase the risk of prostatitis in intact males. Hematogenous infection is also possible but less likely. Prostatitis is reported in all age groups in intact males and is exceedingly rare in neutered males.

The most common bacterial organism to cause prostatitis is *Escherichia coli*. Other common infectious etiologies include *Staphylococcus* spp., *Streptococcus* spp., *Mycoplasma* spp., *Pseudomonas* spp., and *Proteus* spp. Brucellosis is possible secondary to venereal and hematogenous transmission. Prostatic abscesses can develop secondary to prostatitis or within prostatic cysts. Chronic prostatitis is reported to be more frequent than acute prostatitis but with less evident clinical signs.

History and Clinical Signs

Acute prostatitis is usually a very painful condition and these patients tend to have a greater frequency of systemic signs: depression, dehydration, anorexia, abnormal discharge, painful gait, difficulty urinating, inability to mount or ejaculate, and trouble defecating. Lower urinary signs such as stranguria, purulent urethral discharge, hematuria, pollakiuria, and abnormal discharge are often present. Patients may also vocalize when attempting to urinate or defecate. Stool quality may change due to compression of the colon. Other common clinical signs and physical examination findings include fever, vomiting, diarrhea, dehydration, tenesmus, and constipation. Abscesses may rupture within the abdominal cavity and cause symptoms of acute abdomen, endotoxemia, sepsis, and peritonitis.

Dogs with chronic prostatitis may sometimes have no evident clinical signs. History may include decreased mounting behavior, decreased sperm count or quality, recurrent and chronic urinary tract infections, lethargy, decreased appetite, intermittent urethral discharge, and potentially other vague and nonspecific clinical signs.

Diagnosis

Rectal palpation usually reveals either an enlarged and symmetric prostate or the prostate can be abnormally shaped, especially when abscesses are present. Acute prostatitis may be very painful on palpation. Iliac lymph node enlargement is possible.

With acute bacterial prostatitis, the CBC may be normal or may display a neutrophilic leukocytosis of varying severity with a left shift. The biochemistry panel may reveal azotemia of varying degrees which may be a combination of postrenal (secondary to prostatic enlargement and urethral obstruction), intrinsic renal (ascending pyelonephritis) or prerenal (dehydration) factors. Hepatic enzymes, especially alkaline phosphatase enzyme, may be elevated. Urinalysis collected by cystocentesis may reveal hematuria, proteinuria, and an active sediment but this is not sensitive or specific for diagnosing prostatitis. Urine culture is usually positive. Abdominal radiographs may indicate an enlarged and irregular prostate, and mineralization is possible. Peritonitis is sometimes noted caudal to the bladder due to inflammation and secondary to abscess rupture. The bladder may also be pushed cranially into the abdominal cavity. Abdominal ultrasound findings include an enlarged and sometimes irregular prostate that is diffusely heterogenous with or without abscesses, sometimes giving the appearance of being mottled (Figure 124.6). Contrast urethrocystogram may indicate prostatic contrast uptake of varying degree.

Cytology is necessary for a diagnosis and for targeted therapy, but caution must be exercised in obtaining samples (see Table 124.1). Typical cytology findings include free and phagocytosed bacteria, intact and degenerate neutrophils, macrophages, necrotic debris, and hyperplastic epithelial cells with mild anisokaryosis.

Therapy

Targeted antibiotic therapy is indicated in both acute and chronic prostatitis and prostatic abscesses. Antibiotics must be chosen based on culture and sensitivity results as well as their ability to penetrate prostatic tissue. The ideal antibiotic needs to be lipid soluble and have lower serum protein binding to be able to cross into the prostate (Table 124.2). If higher protein binding is a characteristic of a particular desired antibiotic, using a higher dosage range is necessary. While awaiting cytology and culture results, therapy should be started with enrofloxacin.



Figure 124.6 Prostatic abscess and prostatitis as seen on ultrasound transverse image plane. Note the mottled appearance of the prostate surrounding the abscessed region. *Source:* Image courtesy of Dr Tim Spotswood.

There are unfortunately very few clinical data or trials in veterinary medicine looking at the efficacy of specific antibiotics and their effectiveness in crossing into the dog prostate and treating prostatitis. In the presence of sepsis, the antibiotic spectrum should be broadened (beta-lactam, third-generation cephalosporin, aminoglycosides, imipenem). The blood–prostate barrier is compromised in these situations and antibiotics that would not generally penetrate the prostate will do so.

Ciprofloxacin is not indicated in infectious prostatitis as not only does it have poor oral bioavailability in dogs and cats, it also does not penetrate the prostate as well as enrofloxacin. Antibiotic therapy should be continued for a minimum of 4–6 weeks, and prostatic culture should be rechecked 3–5 days after discontinuation of antibiotics. Specific treatment for sepsis and peritonitis is detailed elsewhere, as is the treatment for acute azotemia.

Surgery may be necessary for prostatic abscesses. Medical drainage of abscesses by percutaneous ultrasound-guided aspiration combined with targeted antibiotic therapy rarely results in the resolution of abscesses. However, ultrasound-guided drainage may facilitate stabilization of a patient if surgery is delayed. Multiple surgical techniques have been described including omentalization, marsupialization, placement of drain tubes, and partial or total prostatectomy, with omentalization seeming to offer the best results and fewer complications.

It is always recommended to neuter dogs with prostatitis and prostatic abscesses as this can accelerate recovery and also prevent recurrence. Finasteride therapy may be used in breeding dogs to shrink the prostate but its efficacy in prostatitis is unknown.

Prognosis

Prognosis is good to guarded in acute prostatitis without abscessation or sepsis. Chronic prostatitis may be more

Table 124.2 Antibiotics used for bacterial prostatitis

Antibiotic	Dosage	Route	Notes
Enrofloxacin	10 mg/kg q24h	IV, PO, SC	Risk of permanent cartilage damage in large-breed dogs <18 months; usually the first-line drug of choice
Chloramphenicol	50 mg/kg q6–8h	PO	Dosage listed is at higher end of therapeutic range; monitor CBC for evidence of bone marrow suppression
Trimethoprim-sulfamethoxazole	15 mg/kg q12h	IV, PO, SC	Potential complications include keratoconjunctivits sicca, acute hypersensitivity reactions, polyarthropathy, blood dyscrasias, vomiting, anorexia, hepatopathy and icterus; rarely used as first-line therapy
Clindamycin	11–20 mg/kg q12h	PO, IV, IM, SC	Capsules or divided tablets may cause esophagitis; not usually indicated for prostatitis unless indicated by culture
Erythromycin	10–25 mg/kg q8–12h	PO	May cause anorexia, vomiting, diarrhea; usually not indicated for prostatitis unless indicated by culture

CBC, complete blood count; IM, intramuscular; IV, intravenous; PO, by mouth (*per os*); SC, subcutaneous.

difficult and take longer to treat and there may be a higher incidence of relapse. The prognosis is guarded to poor with abscessation even with surgical intervention.

Squamous Metaplasia of Prostatic Epithelial Cells

This condition is quite rare and usually develops secondary to exogenous estrogen administration (such as to treat BPH or transdermal patches and creams used as hormone replacement therapy in women) or to an estrogen-secreting tumor such as a Sertoli cell tumor. Dogs may be asymptomatic or develop clinical signs similar to dogs with prostatitis. Diagnosis is obtained via biopsies. Treatment involves antibiotic therapy for potential secondary prostatitis, identifying and treating the cause of the metaplasia (surgery and potentially chemotherapy for Sertoli cell tumors, discontinuation of estrogen compounds). Prognosis is guarded as chronic prostatitis may develop.

Further Reading

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125

Management of Chronic Kidney Disease

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Chronic kidney disease (CKD) is defined as the presence of structural or functional abnormalities in one or both kidneys that has been present for three or more months. In most cases with renal dysfunction, this is a progressive disease, and currently no treatment short of renal transplantation has been shown to reverse or halt declining renal function for any significant period of time. Renal transplant and dialysis are less widely available and are expensive therapies. Additionally, not all CKD patients are acceptable candidates for transplantation or dialysis. Medical management therefore is the mainstay of treatment and can help patients cope with metabolic complications of the disease and improve quality of life.

Disease Staging

The severity of signs associated with kidney disease varies depending on the degree of kidney dysfunction. In order to better tailor therapy to the individual patient and to provide some assessment of prognosis, staging of disease is recommended. The International Renal Interest Society (IRIS), a panel of experts in veterinary nephrology, has developed a staging system for chronic kidney disease in dogs and cats (www.iris-kidney.com) that has been accepted by the American and European Societies of Veterinary Nephrology and Urology. With this system, once diagnosed with CKD, animals are grouped into four stages (IRIS 1–4) based on serum creatinine, as well as substages based on proteinuria and blood pressure. The recent guidelines also incorporate SDMA results. Assessment of kidney function is based on fasted serum creatinine measurements assessed on at least two occasions in a stable, hydrated patient (Table 125.1). Caution should be exercised in staging elderly patients in poor body condition as muscle mass contributes to daily creatinine production; very thin animals may have lower than expected serum creatinine concentrations. The biomarker SDMA is correlated with glomerular filtration rate (GFR) and as it is not affected by muscle mass, has been incorporated into the IRIS guidelines to help determine staging in patients with muscle loss.

Due to variability in normal ranges for serum creatinine, some patients staged as IRIS 1 or 2 may have serum creatinine within the reference range. The patient's overall clinical status should be taken into account and serum creatinine should not be interpreted without a concurrent urine specific gravity. For example, creatinine >1.6 mg/dL in a feline patient with a urine specific gravity <1.035 may be indicative of kidney disease even though it is within a published reference range.

Substaging is performed to further characterize the disease based on the measurement of arterial blood pressure and proteinuria, both of which are a concern as they potentially hasten disease progression. Classification of proteinuria is determined by measuring urine protein:creatinine ratio (UPC) in a culture-negative sample with an inactive sediment (Table 125.2). Unless the UPC is markedly elevated or less than 0.2, classification should ideally be based on multiple UPC determinations (2–3) over at least a two-week period.

Blood pressure substage is determined by incorporating both arterial blood pressure measurement and assessment of the presence of end-organ damage such as retinal lesions and neurologic signs (Table 125.3). With the exception of animals who have a blood pressure >200 mmHg and/or evidence of end-organ damage, blood pressure classification should be determined based on at least three independent measurements, ideally over several days to weeks. The lowest measurement is the one utilized.

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Companion website: www.wiley.com/go/bruyette/clinical

Table 125.1 IRIS chronic kidney disease stages in cats and dogs

	Serum creatinine values (mg/dL)	
	Cat	**Dog**
Stage 1	<1.6	<1.4
Stage 2	1.6–2.8	1.4–2.0
Stage 3	2.9–5.0	2.1–5.0
Stage 4	>5.0	>5.0

www.iris-kidney.com

Table 125.2 Classification of proteinuria in cats and dogs

	Urine protein:creatinine ratio	
	Cat	**Dog**
Nonproteinuric	<0.2	<0.2
Borderline proteinuric	0.2–0.4	0.2–0.5
Proteinuric	>0.4	>0.5

www.iris-kidney.com

Medical Management of Chronic Kidney Disease

Medical management of CKD consists of treatments designed to provide supportive and symptomatic care for the animal, with the goal of correcting nutritional, fluid, electrolyte, endocrine, and acid–base imbalances. These treatments aim to minimize the clinicopathologic and pathophysiologic effects of kidney dysfunction. Unfortunately, medical management is not expected to halt, reverse or cure kidney dysfunction or any associated renal lesions. If any treatable underlying cause of disease is identified, such as infection or obstruction, it is imperative that it be addressed. The management guidelines presented in this chapter are intended for animals with stable chronic disease, not those currently undergoing a uremic crisis.

Nutrition and Dietary Therapy

Several studies have documented the therapeutic value of specially formulated diets in the management of CKD, including evidence of decreased incidence of uremic crisis and increased survival and modulation of biomarkers. It is perhaps a common misconception that the sole purpose of these diets is protein restriction. Other modifications present in these diets are as important, or potentially even more important than protein restriction. In comparison to a maintenance diet, renal diets are typically formulated to contain modified amounts of high-quality protein, increased caloric, soluble fiber and B vitamins, omega-3 polyunsaturated fatty acid and antioxidant content, reduced amounts of phosphorus and sodium, and to have a neutral effect on acid–base balance. In addition, feline renal diets are supplemented with potassium. Recently, early-stage renal diets that are phosphorus restricted but with less restricted protein content have also become available for cats.

The greatest clinical challenge with recommending a renal diet is acceptance by the animal. The failure of the patient to eat the formulated diet negates the benefit of dietary management, and therefore a key therapeutic target for these patients is the maintenance of appetite and food intake. Poor body condition is associated with decreased prognosis in several species and it also has a negative effect on owner perception of quality of life. As animals with CKD often suffer from poor appetite, this should be actively addressed in a management plan. Nonacceptance of renal diets can potentially be overcome by addressing underlying metabolic complications of CKD as well as gradually introducing the renal diet over several weeks. Many animals will readily accept and continue eating a renal diet provided the transition period is adequately slow. Other tips to encourage acceptance of renal diet include increasing owner compliance with education regarding the benefits of the diet, avoiding transitioning to the renal diet during a uremic crisis event to prevent food aversion, trying different temperatures, textures and brand formulations of food, and medically managing nausea and inappetence associated with uremic syndrome.

It is particularly important that the patient eat sufficiently to satisfy caloric requirements. A nutritional assessment should be performed at each visit including body weight, body condition score, muscle mass score, and a thorough nutritional history (www.wsava.org/nutrition-toolkit). Insufficient caloric intake could potentially lead to protein malnutrition as evidenced by decreased muscle mass, anemia and decreased serum albumin or total protein concentrations.

If caloric requirements are not being met, yet metabolic complications are controlled and medical management of inappetence is unsuccessful, supplementation with a diet palatable to the animal or assisted feeding should be considered. Assisted feeding options include placement of an esophagostomy or percutaneous gastrostomy tube for long-term nutritional management. Tube feeding has the additional advantage of allowing the owner to deliver oral water and medications to the patient and can be a valuable tool for long-term management of CKD. Disadvantages of tube feeding include the anesthesia required for placement and tube site complications.

Table 125.3 Classification of blood pressure in cats and dogs

IRIS blood pressure (BP) stage	Systolic BP (mmHg)	Diastolic BP (mmHg)	Risk of target organ damage
Normotensive	<150	<95	Minimal
Borderline hypertensive	150–159	95–99	Mild
Hypertensive	160–179	100119	Moderate
Severely hypertensive	>180	>120	Severe

IRIS, International Renal Interest Society.

Antinausea and Appetite Stimulant Therapy

Patients with CKD can suffer from nausea, vomiting, and inappetence likely as a result of uremic toxins that are sensed in the chemoreceptor trigger zone in the brain. Several potent antiemetic/antinausea therapies are now available. These include the 5-HT3 receptor antagonists ondansetron and dolasetron and the NK1 receptor antagonist maropitant citrate. These drugs work at the chemoreceptor trigger zone and vomiting center in the brain, as well as receptors in gastrointestinal tract, and can be given orally or as an injection.

Maropitant is commonly used for acute vomiting but a pharmacokinetic and toxicity study in cats indicated that longer-term usage appears safe and it is often used for long-term therapy in chronically ill patients. When given daily for two weeks at a dose of 4 mg/cat, maropitant was demonstrated to palliate vomiting associated with CKD in cats with stage II and III CKD. Maropitant citrate is administered at 1 mg/kg.

Ondansetron has been documented to be twice as effective as metoclopramide in palliating uremic nausea and vomiting in human CKD patients. Ondansetron and dolasetron are frequently used as antiemetics, but recent studies have called into question their efficacy at currently recommended doses in cats (0.5 mg/kg BID). Pharmacokinetic studies in cats have demonstrated that oral bioavailability of ondansetron is poor in this species (~35%) and the half-life is very short (approximately one hour), making it most appropriately a q8h medication. Subcutaneous ondansetron had a slightly longer half-life of three hours. Ondansetron is also not appropriate as a transdermal medication as a recent paper assessing transdermal absorption in cats demonstrated no clinically relevant blood levels after administration. The ideal dosing regimen of ondansetron for dogs is also unknown and there is some evidence that oral bioavailable in dogs is extremely poor (<10%). However, a recent study demonstrated that ondansetron had superior antinausea effects in comparison to maropitant in a cisplatin model. Dolasetron has traditionally been recommended as a once-daily medication at doses of 0.5–1 mg/kg; however, a recent paper demonstrated that after a 0.8 mg/kg subcutaneous dose the drug is not detectable in the serum at 12 hours and does not palliate xylazine-induced emesis.

Although more commonly used as an appetite stimulant, mirtazapine also demonstrates antiemetic properties, acting at the 5-HT3 receptor similar to ondansetron. In cats, mirtazapine has been shown to significantly reduce vomiting associated with CKD.

Limiting gastric acidity with the use of H2 blockers like famotidine or proton pump inhibitors such as omeprazole anecdotally appears to palliate inappetence in some CKD patients. However, these medications have never been evaluated in a clinical trial despite famotidine being one of the most commonly prescribed medications in CKD cats. Recent studies of the effect of omeprazole on the gastric pH in normal cats indicate that at 1 mg/kg twice daily, it is superior to famotidine in its ability to inhibit acid production, but again no clinical trials have been performed in CKD cats and CKD cats do not appear to experience hyperacidity as previously assumed. Additionally, proton pump inhibitors have recently been linked to an increased risk of kidney disease in humans. The applicability of this finding to veterinary patients is entirely unknown, and a recent retrospective study found no correlation between acid-suppressing medications and increased risk for kidney disease or progression of disease. Due to lack of evidence for a high incidence of ulcerative gastritis associated with CKD, sucralfate is recommended only if gastric ulceration and hemorrhage are suspected as it is sometimes poorly tolerated and may lead to further inappetence.

In addition to addressing uremic nausea and vomiting, appetite stimulants can also be used to encourage food intake, particularly in late-stage patients. Cyproheptadine has been used for some time as an appetite stimulant and has anecdotal efficacy in many patients, although its efficacy has never been scientifically evaluated. Mirtazapine has become more commonly used, particularly in cats, and recent exploration of its pharmacodynamics and pharmacokinetics has provided information for more effective use in animals. Pharmacodynamic studies in cats have illustrated that it can be a potent appetite

stimulant, but higher doses are more commonly associated with side-effects (hyperexcitability, vocalization, agitation). Smaller, more frequent doses are recommended: 1.88 mg q48h orally in cats with CKD and 0.6–1 mg/kg once to twice daily in dogs. In dogs, twice-daily dosing may be required due to relatively shorter half-life than in other species. Mirtazapine is also amenable to transdermal administration, and has recently become FDA approved for use in cats (Mirataz®, KindredBio).

Owners should be aware that mirtazapine and cyproheptadine cannot be administered concurrently; cyproheptadine is used as an antidote for serotonin effects of mirtazapine overdose and thus negates the efficacy of the latter.

Capromorelin (Entyce®, Aratana Therapeutics), a ghrelin agonist, has recently become FDA approved as an appetite stimulant for dogs.

Systemic Hypertension

Systemic hypertension appears to be common in dogs (31–54%) and cats (20–65%) with CKD, but the exact pathophysiologic relationship is unknown. Systemic hypertension can have deleterious effects such as retinal hemorrhage and detachment, neurologic and cardiac impairment. Therefore, the diagnosis and treatment of hypertension are important in this patient population.

Once hypertension has been classified (see Table 125.3), the decision to initiate therapy is based on the degree of hypertension and the animal's IRIS stage. Patients with CKD stage 2–4 and blood pressure persistently over 160 mmHg are candidates for treatment. Antihypertensive therapy should be considered for IRIS 1 patients with arterial blood pressure persistently greater than 180 mmHg. It is unknown what the optimal arterial blood pressure is for patients with CKD. A general guideline is to reduce the blood pressure to between 100 and 160 mmHg. Aggressive reduction of blood pressure is only necessary in patients experiencing ocular and neurologic complications and otherwise it may take weeks, particularly in dogs, to achieve adequate control.

Treatment strategies for cats and dogs differ slightly based on the efficacy of currently available antihypertensive medications for each species. Currently utilized antihypertensive medications in dogs include angiotensin-converting enzyme (ACE) inhibitors (enalapril and benazepril), calcium channel blockers (amlodipine) or angiotensin receptor blockers (ARB) such as telmisartan. These medications are thought to be most effective at reducing hypertension in dogs although most patients require multiple medications and few studies have been done in this area. ACEI and ARB are also used for the management of concurrent proteinuria. Typical starting doses of ACEI are 0.25–0.5 mg/kg every 12–24 hours with increases based on effect on blood pressure up to 2 mg/kg/day. In dogs, amlodipine doses range from 0.1 to 0.5 mg/kg/day and are typically combined with an ACEI. Recommended dose for telmisartan is 1 mg/kg once daily.

Amlodipine is documented to be an effective treatment for hypertension in the cat and has traditionally been the drug of choice in this species. ACEI have not been demonstrated to adequately reduce blood pressure in cats when used as sole therapy. Amlodipine is prescribed at an initial dose of 0.625 mg/cat <5 kg and 1.25 mg/cat >5 kg. Alternative formulations of the drug have been explored including transdermal amlodipine and a chewable form which may provide some degree of efficacy. Amlodipine has also been documented to decrease proteinuria in cats. Telmisartan is also an effective antihypertensive medication in cats and has recently become approved for this indication in cats (United States) as well as an antiproteinuric (UK and Europe).

For all antihypertensive therapy, blood pressure should be rechecked within 7–10 days after initiating treatment. Monitoring renal values and electrolytes is also important; ACEI can decrease GFR and result in increasing azotemia, in which case therapy should be reassessed. Hyperkalemia is also a common side-effect of ACEI and ARB in dogs and may limit the dose that can be administered. Additional guidelines for the use of ACEI and ARB can be found in the consensus statement for the standard treatment of proteinuria.

Proteinuria

Proteinuria is associated with poorer prognosis in several species. The renal tubular epithelial cells are responsible for processing protein and this increases their metabolic load and oxidative stress. Although reducing proteinuria has been demonstrated to significantly slow disease progression in humans, studies in dogs and cats have documented decreased proteinuria secondary to ACEI administration, but results so far are only suggestive of long-term benefit. Nonetheless, it is considered standard of care that dogs and cats with stage 2, 3 and 4 CKD with UPC greater than 0.5 and 0.4 respectively, and cats and dogs with stage 1 CKD and UPC greater than 2.0 be treated with antiproteinuric drugs such as ACEI or ARB. Additionally, systemic hypertension exacerbates proteinuria and should be addressed as previously described. Therapeutic renal diets are considered to be standard of care and have been demonstrated to be helpful in the management of proteinuric CKD and typically are restricted in phosphorus, contain conservative amounts of high-quality protein, adequate nonprotein calories, as well as omega-3 fatty acids, antioxidants, and buffers to help control acidemia. Management of nutrition to meet caloric intake is a key goal.

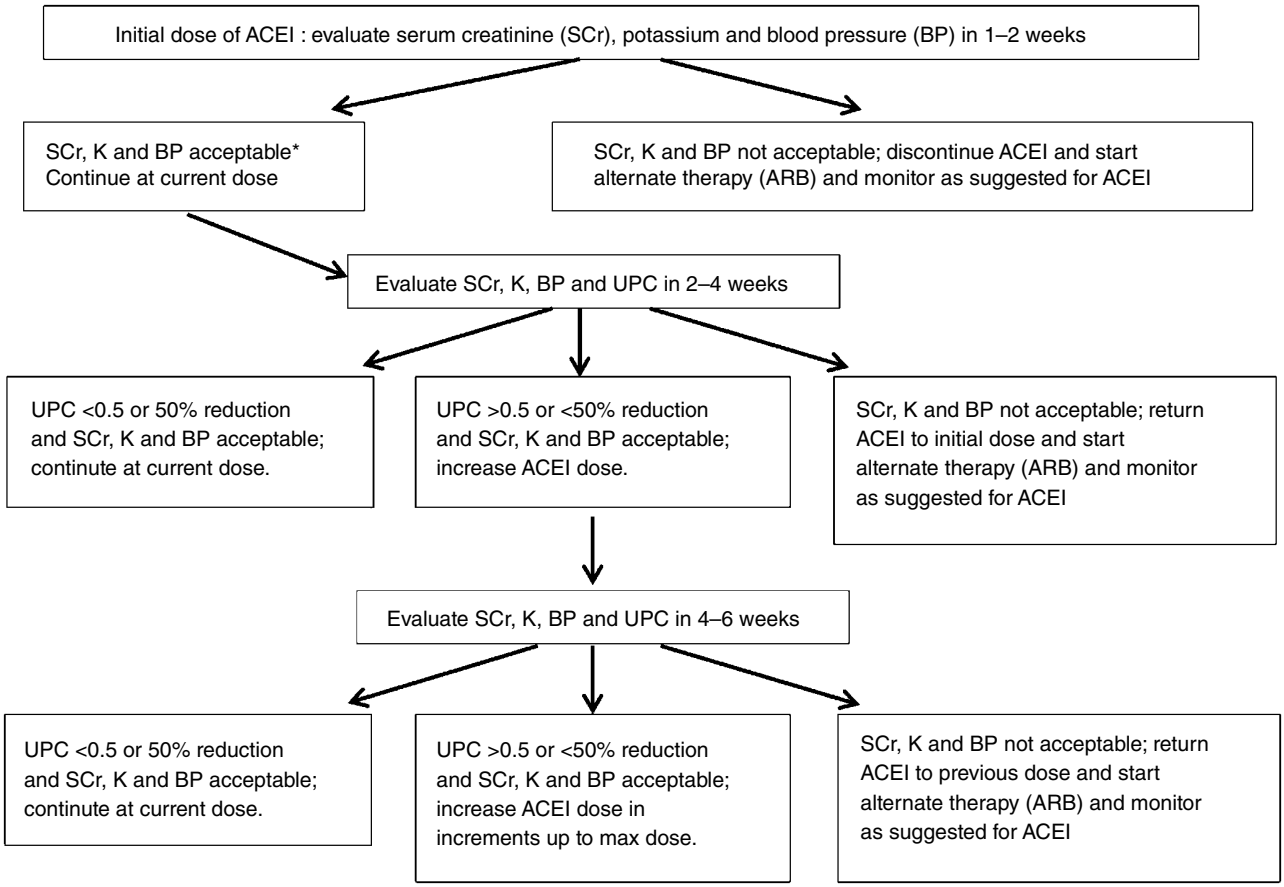


Figure 125.1 Flowchart for adjusting ACEI therapy. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; UPC, urine protein:creatinine ratio. *Source:* Modified from Brown S, Elliott J, Francey T, *et al*. Consensus recommendations for standard therapy of glomerular disease in dogs. *J Vet Intern Med* 2013; **27**(Suppl 1): S27–43.

Angiotensin-converting enzyme inhibitor or ARB therapy is instituted with a therapeutic goal of normalizing (<0.5) or, when impossible, at least reducing the UPC by 50% (Figure 125.1). Dosing, side-effects, and monitoring for ACEI are as described for antihypertensive therapy; starting at the low end of the range and cautiously increasing the dose to maximize effect on proteinuria while monitoring for adverse effects is recommended (see Figure 125.1). Unacceptable side-effects of ACEI or ARB therapy include an increase in serum creatinine >30% in IRIS 1–2 dogs, >10% in IRIS 3 dogs or any increase in creatinine in stage 4 dogs; serum potassium >6.0 mmol/L; blood pressure <120 mmHg. Extreme caution should be used in prescribing ACEI or ARB in dogs with IRIS stage 4 disease. In these patients, side-effects may outweigh benefits at this stage of disease progression.

Additional guidelines for the use of ACEI and ARB can be found in the consensus statement for the standard treatment of proteinuria.

Protein-losing nephropathies are associated with an increased risk for thromboembolism and the prevalence in dogs has been reported to be as high as 25%. Few studies have assessed the efficacy of antithrombotic therapies specifically in glomerulonephropathy (GN) patients. Currently consensus recommendations consist of 1–5 mg/kg low-dose aspirin daily for thromboprophylaxis. Clopidogrel (1.1 mg/kg daily) is likely similarly effective to low-dose aspirin. No studies have demonstrated superior efficacy to justify the higher cost.

Polyunsaturated fatty acids (PUFAs) are antiinflammatory and the underlying process in CKD is inflammatory in nature; supplementation is thought to be beneficial. Several studies have demonstrated evidence of benefit in human CKD patients and rodent models demonstrate decreased oxidative stress, inflammation, and scarring. Many renal diets are now supplemented with PUFAs in appropriate ratios. The need to supplement omega-3 fatty acids beyond that present in renal diets is not fully known at this time. However, supplementation at 0.25–0.5 g of omega-3 PUFA/kg containing eicosapentaenoic acid and docosahexaenoic acid has been described as a dose extrapolated from human literature.

Approximate 50% of dogs with protein-losing nephropathy have immune-mediated disease. The goals of performing a renal biopsy are to identify subtypes of GN that involve immune complexes, guide the decision regarding the necessity of immunosuppressive therapy, and assess prognosis. Renal biopsy should be avoided in patients with bleeding disorders, uncontrolled hypertension, chronic end-stage disease and in very small patients (cats and dogs <5 kg). It is highly recommended that if taking the time and trouble to biopsy, samples are sent to a nephropathologist (International Veterinary Renal Pathology Service, Ohio State University, https://vet.osu.edu/vmc/international-veterinary-renal-pathology-service-ivrps). Immune suppression is indicated when electron-dense deposits are seen on electron microscopy or if there is positive immunofluorescent staining. A typical therapeutic regimen is mycophenolate 10 mg/kg BID and adding prednisolone when rapidly progressing (1 mg/kg BID). Steroids should not be used as monotherapy and the goal in using them is to taper relatively quickly. If biopsy is not possible or safe, empiric immunosuppressive therapy can be considered in patients where standard therapy is not effective, serum creatinine is >3 mg/dL, and there is rapid progression of disease or severe hypoalbuminemia. It is generally considered that if a response to immunosuppressive therapy is not seen in eight weeks, it is unlikely to occur.

Fluid Therapy

As CKD progresses, GFR decreases and azotemia worsens, yet the patient is not able to compensate by concentrating urine and maintaining hydration. Dehydration is therefore a common complication of CKD and can lead to inappetence, lethargy, weakness, constipation, and increased susceptibility to uremic crisis. Owners should be aware that concurrent illness, vomiting and diarrhea, household changes/stress or inadequate water sources promote dehydration and can have more serious effects in CKD patients, potentially precipitating a uremic crisis. Maintaining hydration by administering subcutaneous balanced electrolyte solutions appears to anecdotally improve appetite, activity, and quality of life and reduce constipation in CKD patients, although no clinical trials have been performed. Subcutaneous fluid administration is generally feasible in cats and small dogs and can be a very helpful tool for owners in management of disease, particularly in stage 3 and 4. With instruction, many owners find the procedure to be feasible, and tolerated by the patient. Additionally, feeding canned food instead of dry kibble, or adding water to food is another way to increase water consumption. Paying special attention to water sources in the house – fresh, accessible, water fountains for cats, etc. – is also an important tip for owners.

Anemia

As kidney disease progresses, renal production of erythropoietin decreases and anemia can result. Other factors that can contribute to anemia include poor nutrition, blood loss, concurrent infection, and reduced red blood cell lifespan. Anemia may exacerbate the hypoxic environment in the kidney by reducing oxygen delivery to the area, thus potentiating oxidative stress, renal damage, and progression of disease. Anemia has been identified as a negative predictor of survival in CKD. Therapeutic action should be taken when hematocrit nears or drops below 20%. Although gastric ulceration is thought to be relatively uncommon with CKD, chronic gastrointestinal hemorrhage is suspected when melena, elevated BUN, iron deficiency or anemia disproportionate to level of azotemia is noted. Empiric treatment with antacid and sucralfate with an increase in hematocrit supports the diagnosis.

Hormone replacement therapy is the most effective treatment for anemia secondary to CKD and can be addressed with artificial products such as recombinant human erythropoietin (Epogen®, Amgen) or darbepoetin alpha (Aranesp®, Amgen). Epogen is given as a SC injection and is effective in treating anemia secondary to CKD. However, as it is a foreign protein, approximately one-third of animals will develop antibodies against both the foreign erythropoietin and their own, and potentially become transfusion dependent. For this reason, the product is not recommended until packed cell volume (PCV) falls below 20% and owners should be informed of this risk. Close monitoring of hematocrit is crucial so that possible antibody formation and subsequent drop in hematocrit are caught quickly. If therapy is stopped appropriately, suppressed erythropoiesis may be reversible.

Darbepoetin is a longer-acting form of erythropoietin and appears to have less association with anti-epo antibodies. It is currently the product of choice, but expense can limit its use for some owners. Therapy with darbepoetin consists of an induction phase and a maintenance phase. Initially, darbepoetin is administered 0.5–1.0 μg/kg subcutaneously once weekly. Blood pressure as well as PCV should be checked weekly during the initiation period; hypertension associated with too quick an increase in PCV is the main side-effect. Other reported side-effects include pure red cell aplasia, arthralgia, fever, seizures, polycythemia, and iron deficiency. Previous estimates of treatment success have been 60–65% in cats (multiple concurrent disease) and 85% in dogs. Typical response time is 2–4 weeks.

Once the hematocrit has reached the lower end of the normal range, the frequency of administration can be decreased to every other week to maintain the animal long term. Stimulating erythropoiesis is associated with

a high iron demand and due to the functional iron deficiency associated with CKD, iron supplementation is recommended when therapy is initiated, as well as every few months through the course of therapy. Iron injections (iron dextran 50 mg/cat IM, 10–20 mg/kg dogs IM, typically well tolerated) are considered better that oral iron supplementation as the latter tends to be bitter and likely to exacerbate an already poor appetite, as well as being poorly absorbed from the GI tract. B vitamins are necessary for red blood cell (RBC) synthesis and the degree to which they are deficient in CKD patients and an active contributor to anemia is poorly understood. Given their benign nature, supplementation is unlikely to be harmful but no information about efficacy currently exists. However, B vitamins are not considered effective as sole therapy for anemia.

Hypokalemia

Hypokalemia is a common finding in cats with stage 2 and 3 CKD likely due to a combination of increased urinary loss, inadequate dietary intake, and activation of the renin-angiotensin-aldosterone system. Hypokalemia is less common in stage 4 cats due to markedly decreased glomerular filtration, and less common in dogs due to ACEI therapy. In cats, common presenting signs of profound hypokalemia are hypokalemic myopathy and constipation. Fortunately, profound hypokalemia is less common since the advent of renal diets supplemented with potassium. Hypokalemia is associated with development and worsening of CKD in humans and appears to exacerbate damage to tubular epithelial cells.

Potassium supplementation may be provided orally as potassium gluconate (1–4 mEq/cat twice daily), or potassium citrate (40–75 mg/kg PO divided twice daily), to effect. Various forms of potassium supplements are available including pill, powder, and gel. Potassium citrate has the added advantage of being an alkalinizing agent, but the degree to which this is effective for treatment of metabolic acidosis has not been evaluated. Potassium chloride is not recommended as an oral supplement because it is acidifying and unpalatable, but may be added to subcutaneous fluids at concentration up to 30 mEq/L (higher concentrations can be associated with irritation).

Serum potassium levels are not representative of systemic tissue potassium levels and animals with low normal serum potassium may be systemically depleted, which is exacerbated by metabolic acidosis. Some clinicians advocate prophylactic supplementation even when serum potassium is in the low normal range, with a goal of maintaining serum potassium levels above 4 mg/dL. The value of prophylactic potassium supplementation has not yet been established.

Mineral and Bone Disorder: Hyperphosphatemia

The disturbances in calcium, phosphorus, and magnesium, and associated clinical syndromes in CKD are referred to as CKD-mineral and bone disorder (CKD-MBD). Renal secondary hyperparathyroidism is a major component in this process involving excess phosphorus, parathyroid hormone (PTH), and fibroblast growth factor (FGF)23. The kidneys are the main route of phosphorus excretion and as kidney function declines, hyperphosphatemia develops. Hyperphosphatemia is detrimental because it contributes to renal secondary hyperparathyroidism, tissue mineralization, and progression of CKD. Thus, controlling phosphorus intake through diet and phosphate binders is an important part of CKD management. Feeding a phosphorus-restricted diet is the first recommended step for managing CKD-MBD and studies have demonstrated efficacy in decreasing serum concentrations of phosphorus, PTH, and FGF23 as well as improved outcome. Evidence suggests that feeding a phosphorus-restricted diet even if serum phosphorus is normal is potentially beneficial. If a renal diet is initiated and phosphorus is still elevated after 4–6 weeks, then a phosphate binder is recommended with the goal of keeping serum phosphorus in the low normal range if possible (Table 125.4). These medications bind the phosphorus in the food, making it less bioavailable, so it is critical that the medication is given with each meal. Several different phosphate binders are available, including aluminum hydroxide, calcium carbonate, and lanthanum carbonate, but the main problem with administration is palatability.

Therapy is initiated with a starting dose of 30–100 mg/kg/day for aluminum hydroxide, 150 mg/kg/day for calcium carbonate, and 30 mg/kg/day for lanthanum carbonate. Doses are to effect, and generally therapy begins at the lower end of the dose range and is increased every 4–6 weeks until serum phosphorus concentrations are within the desired range. Use of calcium-containing phosphate binders is potentially associated with the development of hypercalcemia, particularly if calcitriol is also being administered. Serum ionized calcium should be monitored during use.

Table 125.4 Recommended serum phosphorus concentrations at each IRIS stage

Stage	Target serum phosphorus concentration
2	3.5–4.5 mg/dL
3	3.5–5.0 mg/dL
4	3.5–6.0 mg/dL

Calcitriol

Calcitriol, the active form of vitamin D, is produced in the kidney. Production is decreased in CKD and hyperphosphatemia further inhibits its synthesis. Calcitriol is an important inhibitor of parathyroid hormone and low levels lead to renal secondary hyperparathyroidism which has multiple deleterious consequences. In early CKD, controlling phosphorus levels may be sufficient to maintain levels. As kidney disease progresses, supplementation of calcitriol may be necessary. In dogs and people, supplementation of calcitriol has been shown to be beneficial, resulting in slower progression of disease; however, a preliminary study performed in cats was not supportive of supplementation. Further evaluation of calcitriol therapy, or other types of vitamin D analogs is necessary to determine efficacy.

When prescribed, calcitriol therapy is initiated at a dosage of 2.0–2.5 ng/kg daily and should not exceed 5 ng/kg/day. Calcitriol should be given on an empty stomach as administration with food increases calcium absorption and the risk of hypercalcemia. Cost may be a concern for many owners as the drug and required monitoring are costly; careful monitoring of ionized calcium, phosphorus, and PTH levels is required as hypercalcemia can result from oversupplementation. If hypercalcemia results, the daily dose can be doubled and given every other day to decrease intestinal absorption of calcium.

Alkalinization Therapy

Metabolic acidosis is common in animals with overt signs of uremia and may promote progression of disease. In humans with CKD, bicarbonate therapy has been demonstrated to slow progression and improve nutritional status. Blood gas analysis should be used to determine acid–base status and whether treatment is warranted. Therapy is initiated when blood pH and bicarbonate concentration drop below the normal range. Changing to a renal diet may improve acid–base balance as these diets are pH neutral. Potassium citrate administration has the advantage of serving both as an alkalizing agent and a potassium supplement; typical doses are 40–60 mg/kg two to three times daily, but degree of efficacy has not been demonstrated.

Antioxidant Therapy

The kidney is the site of substantial aerobic metabolism that results in the production of reactive oxygen species. Additionally, several processes in the diseased kidney potentially result in increased oxidative stress, including hypoxia, anemia, proteinuria, and inflammation. Oxidative stress has been documented in humans with CKD and potentially contributes to the progression of disease. Oxidative stress and decreased antioxidant capacity have been demonstrated in cats with CKD, and vitamins E, C, and B-carotene have been shown to decrease oxidative stress in CKD cats. Animals with CKD may benefit from antioxidant therapy, but randomized clinical trials are needed to determine the effect on progression and survival.

Fatty Acid Therapy

Omega-3 fatty acids are antiinflammatory and the underlying process in CKD is inflammatory in nature, so supplementation is thought to be beneficial. Several studies have demonstrated evidence of benefit in human CKD patients and rodent models demonstrate decreased oxidative stress, inflammation, and scarring. Many renal diets are now supplemented with fatty acids.

Enteric Dialysis and the Microbiome

Alterations in the gut microbiome and increased production of uremic toxins have been associated with CKD in several species, including cats. Enteric dialysis refers to the oral administration of prebiotic-probiotic bacteria which metabolize urea, creatinine, indoles, and phenols in the gut, preventing absorption and therefore decreasing azotemia (Azodyl®). Enteric dialysis has some demonstrated efficacy in humans and rat models and it is a popular supplemental therapy in feline CKD. A recent study demonstrated that sprinkling the pill in the food, contrary to manufacturer's instructions, negated any potential benefit. Controlled clinical studies are still needed to determine the effect of enteric dialysis on serum creatinine or uremic toxins in dogs and cats.

Monitoring CKD Patients

Chronic kidney disease is progressive and as such, patients' metabolic state, clinical signs, and supportive care needs change over time. Factors such as hypertension and proteinuria may not initially be present at diagnosis, but can develop later in the course of the disease. Patients in stage 1 and 2 CKD are typically monitored every 4–6 months once stable kidney function has been established. Patients in stage 3 and 4 require more frequent monitoring, especially if metabolic complications are present, and should be assessed minimally every 3–4 months. A typical visit should include clinical history, medication review, physical examination, nutritional assessment, and labwork consisting of CBC, serum biochemistry, urinalysis, and blood pressure. Urine cultures and UPC are performed at regular intervals as well. Establishing a relationship and providing client education

regarding the importance of monitoring and follow-up will improve compliance.

Prognosis

Predicting prognosis in CKD can be somewhat challenging as the progression of disease varies substantially between individuals. Poor body condition, proteinuria, hypertension, hyperphosphatemia, and anemia have all been associated with a poorer prognosis and should be targets for disease management to maximize survival. Typically, CKD progresses much more slowly in cats than in dogs. Dogs with stage 3 and 4 CKD quickly progress and within months to a year or two may be euthanized due to the disease. Cats with early CKD can have stable disease, typically for years, and may die of another disease process. Cats with stage 3 and 4 typically progress more slowly than dogs at a similar disease stage and may still live months to years.

Further Reading

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126

The Role of Dialysis

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Peritoneal dialysis, intermittent hemodialysis, and continuous renal replacement therapy are being used in companion animal medicine with increasing frequency for the treatment of both acute kidney injury and chronic kidney disease. Peritoneal dialysis, intermittent hemodialysis and hemofiltration, and continuous renal replacement therapy (the three modalities are hereafter referred to as "dialysis," unless they are discussed as separate entities) are employed with the goals of removing accumulated uremic toxins and fluid and reestablishing physiologic acid–base and electrolyte balance when the kidneys are damaged to an extent that renders them incapable of performing these duties. The goal of this chapter is to introduce the reader to the indications, treatment goals, complications, and prognostic considerations relevant to dialysis. A discussion of the technical aspects of each therapeutic modality is beyond the scope of this chapter, but excellent resources exist for the interested reader.

Dialysis Modalities

Renal replacement therapy is a term used to describe various treatment modalities designed to perform the excretory, regulatory, and, in some cases, synthetic responsibilities of the kidney. Renal replacement therapies can be classified as intracorporeal (e.g., renal transplantation, peritoneal dialysis) and extracorporeal (e.g., intermittent hemodialysis and hemofiltration, continuous renal replacement therapy). Renal transplantation relies on the provision of a donor kidney graft intended to perform the function of the native kidneys, and is reserved for cases of end-stage kidney disease. This modality is not discussed further here.

The remaining modalities are based on the principles of diffusion, convection, and adsorption for uremic solute clearance and restoration of acid–base and electrolyte balance. Diffusion occurs when uremic solutes redistribute in solution from areas of higher concentration (blood) to lower concentration (dialysate). The use of a semipermeable membrane to separate the dialysate from the blood allows for the restriction of movement of larger substances (protein and cellular components), while smaller substances (uremic toxins) are able to redistribute freely through the pores of the membrane. Convection utilizes the application of a hydrostatic or osmotic force to blood to promote fluid (plasma water) movement across a membrane. Any substances dissolved in the plasma water that are small enough to pass through the pores of the membrane are removed. When the removal of fluid, rather than solute, is the primary indication for convective clearance, this modality is referred to as ultrafiltration. Adsorption, which quantitatively contributes the least to uremic solute removal, occurs when substances adhere to the membrane due to physiochemical interactions.

Peritoneal dialysis is performed by infusion of a solution (dialysate) into the peritoneal cavity. The peritoneal membrane serves as a membrane across which uremic solutes diffuse from the blood into the dialysate; solutes (e.g., bicarbonate) of which the patient is deficient can be administered via diffusion from the dialysate across the peritoneal membrane into the patient's blood. Convective clearance of uremic solutes and excess fluid can be achieved by use of hypertonic dialysate, which exerts an osmotic force, drawing plasma water across the peritoneal membrane into the dialysate. Dialysate is intermittently infused and removed from the peritoneal cavity in cycles during peritoneal dialysis. Intermittent hemodialysis and continuous renal replacement rely on the movement of blood through fibers composed of a semipermeable membrane housed in a cartridge (dialyzer for intermittent hemodialysis; filter for continuous

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renal replacement therapy). The fibers are bathed in dialysate, thus providing an arrangement analogous to peritoneal dialysis, with three major exceptions: solute and fluid exchange occur outside the body, the membrane across which exchange takes place is not native to the patient, and blood and dialysate are typically moved in countercurrent directions (as opposed to dialysate remaining stagnant in the peritoneal cavity) to maximize the concentration gradient for diffusion. For intermittent hemodialysis and continuous renal replacement therapy, convective clearance is achieved by application of negative hydrostatic pressure, which draws plasma water across the dialyzer or filter membrane.

Dialysis for Acute Kidney Injury

In companion animal medicine, dialysis is most frequently employed to treat acute kidney injury of various etiologies, including leptospirosis (dogs), ureteral obstructions (cats), and nephrotoxicity (dogs and cats). However, in a recent publication, the etiology was undetermined in 43 of 93 (46%) dogs treated with intermittent hemodialysis for acute kidney injury. While the high proportion of undiagnosed cases was likely due, in part, to an inability to obtain a serologic diagnosis of leptospirosis or confirm the presence of the organism in tissue or fluid, this statistic underscores the degree of prognostic uncertainty that is frequently present when dialysis is initiated in cases of acute kidney injury. The same study reported ureteral obstructions as the most common underlying etiology in cats undergoing intermittent hemodialysis. Figure 126.1 demonstrates the use of intermittent hemodialysis for the treatment of a cat with bilateral ureteral obstruction, and Figure 126.2 demonstrates the use of continuous renal replacement therapy for the treatment of leptospirosis.

Regardless of the underlying cause of acute kidney injury, the decision to implement dialysis is made based on a multitude of factors, all of which are discussed below.

Azotemia/Uremia

Historically, severe uremia (e.g., blood urea nitrogen and creatinine concentrations of ≥100 mg/dL and ≥10 mg/dL, respectively) was considered a major indication for dialysis. However, recent trends favor initiation of dialysis at less severe degrees of azotemia. The reasons for the lessening of this threshold are twofold. First, as the veterinary community gains experience and proficiency with dialytic techniques, the safety and feasibility of this treatment have improved significantly. Consequently, the value in preventing severe complications (e.g., gastrointestinal, neurologic, pulmonary) of uremia has become evident, and favorable outcomes have become more likely when dialysis is initiated in efforts to prevent these complications, rather than reverse them. The window for prevention of severe uremia usually is present at less severe degrees of azotemia than the thresholds reported above. Therefore, the degree of azotemia should be assessed every 24–48 hours, so that dialysis can be initiated when consecutive days of worsening renal function are documented, despite appropriate conventional medical and/or surgical therapy. Second, analogous to the



Figure 126.1 This cat had hyperkalemic acute kidney injury secondary to bilateral ureteral obstruction. Prior to surgical intervention, the patient was given three intermittent hemodialysis treatments which resulted in resolution of hyperkalemia and azotemia.



Figure 126.2 This dog was diagnosed with leptospirosis and was initially treated with conservative medical management. Worsening azotemia and volume overload, however, prompted initiation of continuous renal replacement therapy.

decision to administer a packed red blood cell transfusion (i.e. the "transfusion trigger"), the decision to implement dialysis is based on a variety of factors in addition to the degree of azotemia (the correlate of azotemia, in the transfusion example, would be the hematocrit). These factors include co-morbid conditions, such as cardiovascular disease, pulmonary disease, or a low seizure threshold, which may be exacerbated with less severe degrees of renal dysfunction.

Fluid Overload/Oliguria/Anuria

Parenteral fluid administration is considered a cornerstone of treatment for acute kidney injury and a variety of other kidney diseases. However, misconceptions regarding the potential benefits and adverse effects of aggressive fluid administration are widespread. In cases of severe renal dysfunction, aggressive fluid therapy with the goal of achieving a positive fluid balance has not been shown to improve renal clearance of uremic solutes. While the serum or plasma creatinine concentration may improve with achievement of a positive fluid balance, this improvement is more likely related to accumulation of fluid in the extracellular compartment, which results in an increase in the volume of distribution of creatinine and a dilutional effect on the serum or plasma creatinine concentration. In human patients with acute kidney injury (AKI), a decrease in serum or plasma creatinine concentration has been shown to be directly proportional to the degree of fluid accumulation. Furthermore, fluid overload has been associated with negative outcomes, including increased mortality and decreased renal recovery. Additional data suggesting the association between fluid overload and outcome exists in a canine intensive care unit (renal and nonrenal cases) are emerging. While fluid overload can occur in a patient with normal urine production or polyuria, this complication is most frequently encountered in oliguric or anuric patients. Even restriction of all parenteral fluid therapy cannot prevent fluid overload in anuric patients, due to the obligate fluid load administered with medications and nutrition.

Once fluid overload occurs and manifestations, such as pulmonary, gastrointestinal, and neurologic complications, are recognized, restoration of normal fluid balance can be difficult to achieve. Diuretic therapy (e.g., loop or osmotic diuretics) is frequently ineffective at promoting fluid excretion in severely compromised kidneys, and some diuretics (e.g., mannitol) may even be contraindicated due to the obligatory solute load that accompanies administration. Therefore, dialysis (ultrafiltration) may be the only effective means of removing excess fluid.

Hyperkalemia

Hyperkalemia is frequently the most immediate life-threatening complication of severe acute kidney injury. Arrhythmias that negatively affect cardiac output or result in death can occur when the serum or plasma potassium increases above 6 mmol/L. The likelihood of a clinically significant arrhythmia is increased when acidemia, uremia, or fluid overload is severe. While there are several pharmacologic approaches to the treatment of hyperkalemia in AKI (e.g., intravenous dextrose ±

regular insulin and intravenous calcium gluconate, β2 agonists), the effects of these treatments are typically modest and transient when renal function is severely compromised. In these cases, rapid restoration of renal function (e.g., surgical removal of ureteral obstructions) or provision of dialysis are frequently necessary to normalize serum or plasma potassium concentration. It should be noted, however, that restoration of renal function is superior to intermittent forms of dialysis in restoring whole-body potassium balance, due to the predominantly intracellular distribution and slow redistribution of potassium when it is removed from the extracellular space (as is the case in dialysis).

Severe Acidemia

In humans, provision of supplemental sodium bicarbonate in solution has not been proven to be of benefit in cases of severe acidemia accompanying acute kidney injury. Furthermore, in cases of oliguria or anuria, the fluid volume administered once sodium bicarbonate has been diluted to a physiologically tolerable osmolality may result in complications associated with fluid overload. Bicarbonate, however, can be administered in therapeutic concentrations as an alkali buffer to patients without an obligatory fluid load when the bicarbonate is a component of the dialysate. During dialysis, bicarbonate diffuses from a medium in which it has a high concentration (the dialysate) to a fluid with a lower concentration (the patient's plasma water), resulting in administration of sodium and bicarbonate ions without fluid. The provision of alkali without a concomitant fluid load can safely restore the extracellular pH to within the normal range, allowing for normal function of metabolic machinery in various tissues.

While these four factors are commonly encountered in cases of AKI, the decision to employ dialysis does not only depend on each factor's presence but its degree of severity. In human medicine, the optimal timing of initiation of dialysis for acute kidney injury has been vigorously debated, and no consensus has been reached regarding the benefit of early versus late initiation of therapy. The data presented in the human literature likely cannot be extrapolated to veterinary patients because the degree of renal dysfunction that falls into the "late" category (typically defined as serum creatinine concentrations in the range of 3.5–5 mg/dL and urea concentrations in the range of 60–100 mg/dL) would be considered "early" or "mild to moderate" dysfunction by most veterinarians. It is the author's impression that in veterinary cases of AKI for which dialysis is initiated early, when the serum creatinine concentration is in the mild to moderate range, outcomes are much improved compared to when dialysis is initiated later (serum creatinine concentration >10 mg/dL). Earlier initiation of dialysis allows for the prevention of the sequelae of fluid overload, hyperkalemia, and severe acidemia. Preventing these complications provides the patient with optimal metabolic stability to facilitate renal recovery and reduces the costs associated with measures required to address complications such as pulmonary edema and cardiac arrhythmias. Initiation of dialysis prior to decompensation of the patient may even allow for a rapid transition to outpatient dialysis treatments, which can reduce client costs even further and extend the client's available financial resources.

Dialysis for Chronic Kidney Disease

Although chronic kidney disease is an infrequent indication for dialysis, compared with acute kidney injury, dogs and (less frequently) cats have been treated successfully with chronic intermittent hemodialysis for prolonged periods of time, ranging from a few months to over a year. For patients with end-stage chronic kidney disease, dialysis may be thought of as analogous to palliative chemotherapy or radiation therapy for patients with oncologic diseases. The goals of treatment are maintenance of an acceptable quality of life, rather than the metrics of tumor response in the case of cancer treatment or precise regulation of uremic, acid–base, electrolyte, and fluid balance in the case of chronic dialysis.

Patients that receive the greatest benefit from chronic hemodialysis are typically those with International Renal Interest Society (IRIS) stage 4 chronic kidney disease (CKD) that are free of co-morbidities (e.g., significant cardiovascular, gastrointestinal, neurologic, or orthopedic disease). Dogs that weigh greater than 5 kg typically tolerate chronic treatment better than smaller dogs or cats. The reason for smaller animals' inability to tolerate chronic hemodialysis as well as larger patients has not been determined. However, the author speculates that this difference may be due two possible factors: (1) the large volume of blood, relative to the body mass, that must be outside the patient's systemic circulation at any given time to fill the dialysis circuit, and (2) the repeated loss of blood endured by the patient, caused by residual blood trapped in the dialysis circuit that cannot be returned at the end of each treatment. Despite treatment with erythropoiesis-stimulating agents, smaller patients are reliant upon multiple red blood cell transfusions that must be administered before, during, or after some or all dialysis treatments. The repeated administration of red blood cell transfusion in such a short period of time (the first 2–3 weeks of treatment) can lead to an increasing probability of clinically devastating transfusion reactions during the subsequent weeks/months of treatment. An

additional limitation of chronic hemodialysis is the financial and logistic responsibility of the owner. Not only can chronic hemodialysis be cost prohibitive for most owners, but the practical considerations may be overwhelming. Patients treated with chronic hemodialysis typically require treatments, lasting as long as six hours, three times per week. If a scheduling conflict prevents as few as one treatment from being performed, the patient may have a high probability of suffering from severe uremic complications (e.g., nausea), fluid overload, or hyperkalemia. Despite these limitations, a properly selected patient and its owner can enjoy an excellent quality of life for several months to years when treated with chronic hemodialysis.

Alternative Indications for Dialysis: Acute Intoxications and Therapeutic Plasma Exchange

An additional, often overlooked indication for dialysis is decontamination following acute toxin exposure. There are a variety of intoxications that can be treated effectively with dialysis. However, treatment success is highly dependent on the pharmacokinetic properties of the toxin and timing of treatment in relation to ingestion/exposure. Small (<500 daltons), freely circulating toxins are efficiently removed from the blood compartment with conventional hemodialysis, which utilizes diffusion as the predominant clearance mechanism. Toxins with small volumes of distribution are typically retained in the vascular or extracellular compartment, and are more efficiently accessed for clearance. However, retention of toxins within the vascular compartment is typically a result of a high degree of protein-binding.

Because dialysis employs membrane-based separation techniques that, for most dialyzers and filters, exclude the movement of proteins across the membrane, alternative techniques must be employed for toxins that are highly protein bound. Charcoal hemoperfusion and therapeutic plasma exchange are alternatives to conventional dialysis modalities, and can be employed to circumvent the limitations associated with dialytic removal of protein-bound toxins. Charcoal hemoperfusion employs a large cartridge that, rather than housing membrane-bound fibers bathed in a dialysate solution, contains activated charcoal around which blood percolates as it is moved through the dialysis circuit. Binding interactions between toxins and the activated charcoal are stronger than between the toxins and plasma proteins, resulting in the transfer of the toxin from the plasma protein to the activated charcoal (adsorption). The large volume of blood that is required to fill the commercially available charcoal columns, along with hematologic changes associated with interactions of cellular blood components with the charcoal, are sources of possible adverse effects of this treatment (e.g., hypotension and thrombocytopenia, respectively). There are multiple hemoperfusion columns in the development of veterinary patients that utilize a more biocompatible substrate for adsorption of exogenous toxins. These columns are also of smaller volume than the previous charcoal cartridges, making them an attractive alternative to the existing charcoal cartridges. Therefore, both the potential harm posed to the patient by the toxin to which it has been exposed and the possible adverse effects of charcoal hemoperfusion must be considered if this treatment is to be employed.

Therapeutic plasma exchange may be considered in lieu of charcoal hemoperfusion due to the smaller dialysis circuit size required and the avoidance of exposure of cellular blood components to a substance as reactive as charcoal. Therapeutic plasma exchange employs the same equipment and convective clearance principles described above to remove an offending substance from the blood. However, it differs from conventional dialysis in that semipermeable membranes have pores that are large enough to allow passage of plasma proteins. Therefore, therapeutic plasma exchange allows for removal of a protein-bound toxin, along with its carrier protein. Disadvantages of this technique include the requirement for replacement of the removed plasma with a fluid that has a similar oncotic pressure to the removed plasma and, if the protein composition of the replacement fluid differs significantly from the removed plasma, the potential for coagulopathy associated with clotting factor depletion.

With regard to the financial considerations of these two treatments, the cost is comparable. Charcoal hemoperfusion and therapeutic plasma exchange have been used most commonly by the author for blood purification following ingestion of massive quantities of various nonsteroidal anti-inflammatory drugs. The reader is referred elsewhere for an extensive listing of intoxications that can be treated with dialysis.

In addition to blood purification for the treatment of acute intoxication, therapeutic plasma exchange may also be of benefit for a variety of immune-mediated diseases. Due to the large pore size of the membranes used, blood components as large as immunoglobulins and immune complexes are easily cleared with convection using these membranes. Historically, therapeutic plasma exchange was performed with dedicated equipment that utilized a centrifugal technique for blood component separation. Availability of this equipment is still limited in veterinary medicine. However, the development of dialysis equipment with a wide selection of

interchangeable filters and software has provided the capability to perform this procedure with devices primarily designed for renal replacement therapy. In the past several years, reports of therapeutic plasma exchange performed for the treatment of diseases such as myasthenia gravis and immune-mediated hemolytic anemia have appeared in the veterinary literature, heralding a new era in the evaluation of this modality for the treatment of immune-mediated diseases.

Availability of Dialysis and Prognosis for Dialysis Patients

The veterinary community has witnessed exponential growth in the number of facilities offering dialysis for small animal patients. Peritoneal dialysis requires equipment that is readily available, and this modality is performed in many emergency and specialty hospitals that offer 24-hour care. Effective implementation of intermittent hemodialysis and continuous renal replacement therapy is limited to hospitals that not only have the proper equipment but also employ properly trained individuals. Nonetheless, due to the low cost and ease of acquisition of the necessary equipment, many veterinary facilities now offer intermittent hemodialysis and continuous renal replacement therapy.

Despite the paucity of literature available describing outcome, it appears that the prognosis for veterinary patients treated with dialysis is variable, and dependent on the underlying disease etiology, severity of illness, and co-morbid conditions. In cases of acute kidney injury of any etiology, the survival to hospital discharge for both dogs and cats is approximately 50% with the use of intermittent hemodialysis. When considering all possible etiologies, choice of modality does not appear to dramatically affect survival rate. Certain etiologies of acute kidney injury treated with dialysis, such as leptospirosis in dogs and ureteral obstructions in cats, have higher survival rates, reaching 80–90%. In contrast, the prognosis for acute kidney injury secondary to ethylene glycol intoxication is poor, with only 20% of dialysis patients regaining sufficient renal function to allow discontinuation of dialysis.

While the current overall success rate for treatment of acute kidney injury with dialysis appears disappointing, closer evaluation of the situation provides cause for optimism. The survival rates achieved in veterinary medicine are similar to those achieved in human medicine. This accomplishment is likely due, in large part, to the etiologic differences between human and veterinary acute kidney injury. Human acute kidney injury most commonly arises as a complication of disorders (e.g., sepsis, advanced cardiac disease) that alone carry a poor prognosis. Therefore, when acute kidney injury does occur, the likelihood of a poor outcome is multiplied. In veterinary medicine, however, many dialysis candidates presented for acute kidney injury secondary to leptospirosis or select intoxications have no preexisting co-morbid conditions that may affect prognosis. Therefore, if the potential benefit of dialysis is recognized early, and these patients are treated with dialysis prior to the onset of severe complications, there is the potential for the veterinary community to significantly improve the current success rate for treatment of acute kidney injury.

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127

Micturition and Associated Disorders

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Physiology of Micturition

The primary purpose of the lower urinary tract is to store urine and facilitate its elimination at an appropriate time. The bladder is in storage phase 99% of the time and in emptying phase only 1% of the time. Coordination of both storage or filling and emptying requires a complex interaction between the somatic and autonomic nervous systems, as well as normal function of the tissues involved.

The three divisions of the peripheral nervous system innervate the urethra. The pudendal nerve carries somatic signals to the striated muscle that makes up the outer layer of the urethral muscles. The pelvic nerve, which is parasympathetic, and the hypogastric nerve, which is sympathetic, innervate the two smooth muscle layers that surround the urethra. Both the somatic and parasympathetic innervation arise from the sacral spinal cord segments, while the sympathetic innervation arises from the lumbar spinal cord. Local reflex arcs exist as well as central controls. Signals are processed in the pontine micturition center of the brainstem and the cerebral cortex to sense bladder distension and determine conscious control of voiding (Figure 127.1). The primary spinal segments involved in micturition are L1–L2, S1–S2 (storage phase), and S1–S3 (emptying phase).

During the normal storage phase, stretch receptors in the bladder wall send afferent signals along the pelvic nerve, which activate a reflex arc through the hypogastric nerve to the urethra. Norepinephrine (NE) is released by postganglionic neurons to activate beta-adrenergic receptors in the bladder wall, allowing for relaxation and continued filling. NE also stimulates alpha-1-adrenergic receptors in the urethra and causes contraction of the smooth muscle surrounding the urethra, thus preventing urine leakage.

An additional urethral reflex, called the guarding reflex in humans, is the somatic-mediated contraction of the striated muscle surrounding the urethra in response to a sudden increase in abdominal pressure, such as during a cough or sneeze. Afferent signals travel up the pelvic nerve and initiate efferent signals down the pudendal nerve, releasing acetylcholine (ACh) and activating nicotinic cholinergic receptors, causing contraction of the striated muscle.

In addition to normal neurologic mechanisms, several other factors are important for maintenance of urinary continence. The integrity of the smooth muscle of the urethra, normal urethral mucosa which creates a watertight seal, associated vasculature, and the support of connective tissues are also key. In females, estrogen appears to have a significant impact on these tissues. Its withdrawal after neutering appears to play a role in urethral sphincter mechanism incompetence seen in neutered female dogs.

During initiation of voiding, stretch receptors send afferent signals along the pelvic nerve to the pontine micturition center. Signals from the cerebral cortex and the hypothalamus are processed to determine if the situation is appropriate for initiation of micturition. If so, signals are sent down the pelvic nerve, leading to ACh release at the postganglionic parasympathetic neurons. ACh binds to receptors and stimulates bladder smooth muscle contraction. At the same time, inhibitory signals are sent to the hypogastric nerve and the urethra relaxes, allowing normal emptying.

Micturition disorders can be divided into those primarily related to storage and those related to emptying of urine.

Disorders of Storage

Storage disorders primarily result in the leakage of urine without intent by the animal. These may result from an anatomic or developmental abnormality or acquired

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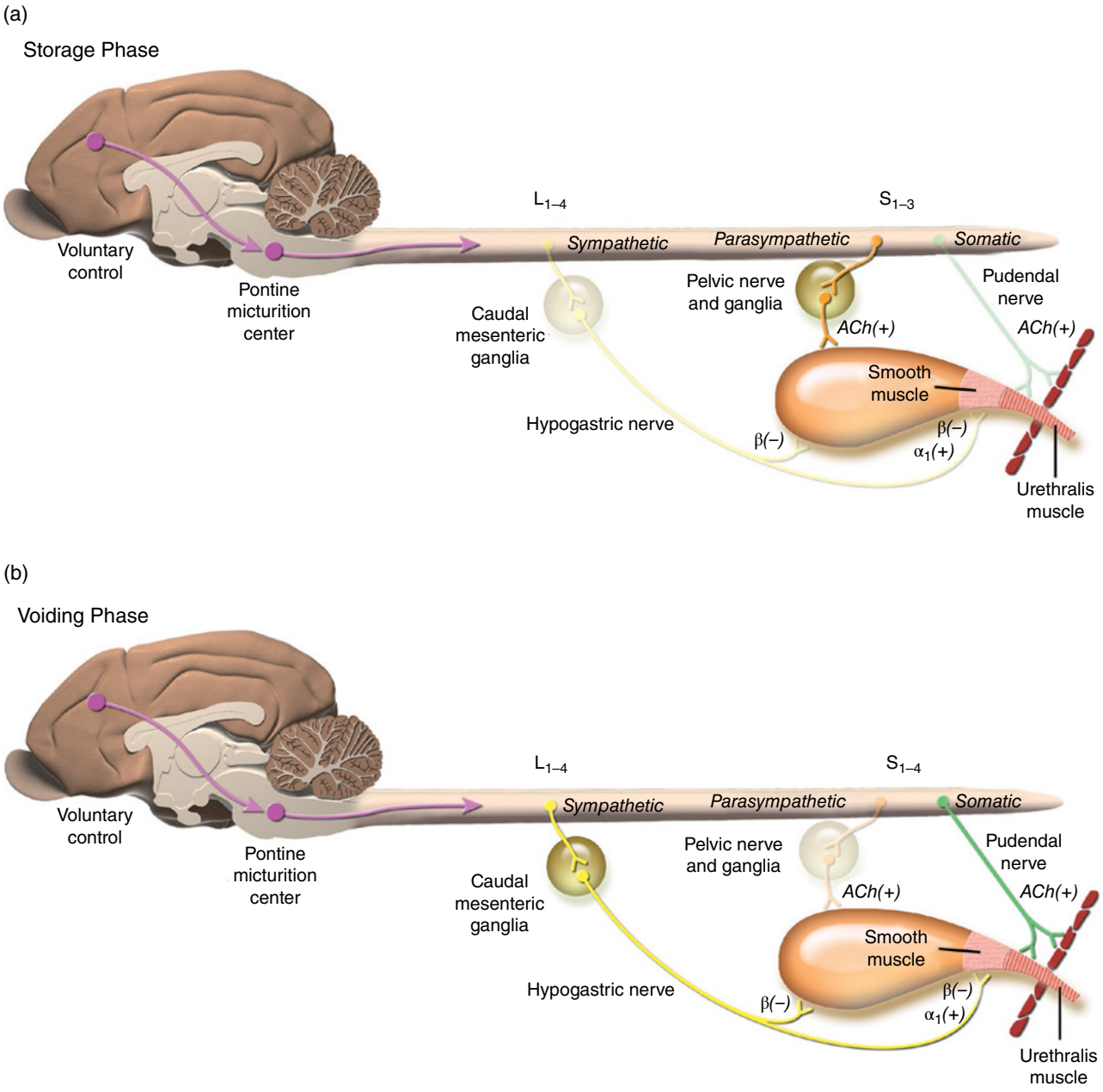


Figure 127.1 An overview of the neural control of micturition consisting of the storage phase (a) and the voiding phase (b).

dysfunction in the spinal cord, urinary bladder, or urethra and surrounding tissues.

Urethral Sphincter Mechanism Incompetence

Urethral sphincter mechanism incompetence (USMI) is the most common storage disorder in dogs. The urethral sphincter mechanism involves the smooth muscle of the urethra as well as the surrounding support tissues, submucosal vasculature, and urothelium. USMI is thought to result from a breakdown in this complex through reduced muscular responsiveness and tone, and structural changes in the periurethral tissues. In female dogs, these changes appear to be associated with a reduction in estrogen and alterations in follicle-stimulating hormone and luteinizing hormone after neutering – thus the term "hormone-responsive incontinence." Previously thought to be distinct processes, it is now understood that USMI and hormone-responsive incontinence are the same entity. The pathophysiology of its development in male dogs is poorly understood, but there may be a relationship to decreased testosterone

levels, and increased follicle-stimulating hormone and luteinizing hormone, since it appears more frequently in neutered than in intact males.

Urethral sphincter mechanism incompetence is most common among neutered female dogs. It is less common in neutered males and rare in cats. It appears to affect up to 20% of neutered females and up to 30% of large-breed dogs over 20 kg. Several breeds have been found to have increased risk including the Doberman pinscher, giant schnauzer, Old English sheepdog, Rottweiler, Weimaraner, and boxer, but any breed may be affected. Recent literature has demonstrated an increased risk of development of USMI in dogs neutered either before 3 months of age or after the first estrus. In addition, it appears that dogs over 15 kg have an increased risk of USMI the earlier they are neutered. It is possible that this is related to the development and sensitivity of the sphincter mechanism tissues to estrogen and other hormones, but the mechanism is incompletely understood. Predisposing factors such as a pelvic bladder, short urethra, or recessed vulva may also be associated with increased risk of developing USMI, but the presence of one of these does not necessarily lead to incontinence.

Signs of incontinence may begin at any time, but appear most often within a few years of neutering. Dogs with USMI usually have normal bladder capacity and are able to urinate normally with complete emptying of the bladder. While most of these dogs are otherwise healthy, clinical signs can worsen dramatically if co-morbidities develop, leading to polyuria or difficulty posturing to urinate. The increased volumes of urine in the bladder, and for longer periods of time, may lead to increased pressure on the already weakened sphincter mechanism and leakage. Lower urinary tract infection can also lead to increased frequency of clinical signs. It is suspected that USMI, and urinary incontinence of any cause, is associated with increased risk of urinary tract infection (UTI), but no studies have been conducted to fully evaluate this.

Owners often seek veterinary care when the frequency becomes bothersome, although on further questioning, it is apparent the signs have been occurring for months or years. It is essential to establish that the animal is passing urine unconsciously. Many owners will complain of "incontinence" when the animal is demonstrating submissive urination or is otherwise consciously urinating in inappropriate places. Dogs with USMI may leak urine when recumbent, sleeping, or after exertion. Although the passage of urine is involuntary, dogs may increase grooming of the perivulvar or preputial area to remove the urine. USMI is an acquired condition, so questioning of the owner regarding the onset of clinical signs is important. Animals that have been incontinent from birth or prior to neutering should be assessed for congenital malformations such as ectopic ureters, prior to making a diagnosis of USMI.

Physical examination of these animals is often normal, with the exception of perivulvar or preputial urine staining. As mentioned above, the conformation of the vulva should be noted, although its contribution to USMI is unclear. The presence of perivulvar dermatitis, regardless of conformation, may increase the risk of urinary tract infection. Rectal examination and palpation of the urethra are normal. Urination is observed to be normal and complete, with little or no residual volume. The assessment of residual urine is essential in male dogs to differentiate USMI from detrusor urethral dyssynergia, a disorder of incomplete bladder emptying (see later).

The presence of urinary incontinence in an otherwise healthy neutered female dog that was previously continent is often adequate for presumptive diagnosis of USMI and a trial of empiric therapy. Due to its lower incidence, intact females, males, and cats with similar histories and clinical signs require additional evaluation before making a diagnosis of USMI (Figure 127.2).

The animal should be observed urinating, if possible. Normal posturing and a full stream without stranguria should be noted. Assessment of residual urine volume may be made by bladder catheterization or estimated using abdominal ultrasound of the bladder. A urinalysis and urine culture should be performed. The presence of isosthenuria or hyposthenuria may contribute to severity of incontinence and may require additional evaluation for an underlying cause. Animals with polyuria may not respond to medical treatment as well as those making normal volumes of urine. As noted above, the risk of urinary tract infection in animals with USMI has not been evaluated, but its presence may lead to worsening signs. Therefore, screening for and treatment of an infection may increase therapeutic success. A complete blood count and serum biochemistry panel may be indicated but are not always necessary for diagnosis of USMI, although they may be helpful when making therapeutic choices, and are important in evaluating animals with polyuria.

If anatomic abnormalities are suspected, imaging such as contrast radiography, abdominal ultrasound, or contrast computed tomography is indicated. Cystoscopic evaluation of the lower urinary tract allows assessment of the entire urethra, ureter placement, and bladder mucosa. Advanced diagnostics, such as urodynamic studies, are designed to quantify the pressure produced along the urethra and the compliance and detrusor function of the urinary bladder. These are available at many referral institutions and are most often indicated in patients with equivocal signs and poor response to therapy, as well as in urologic research.

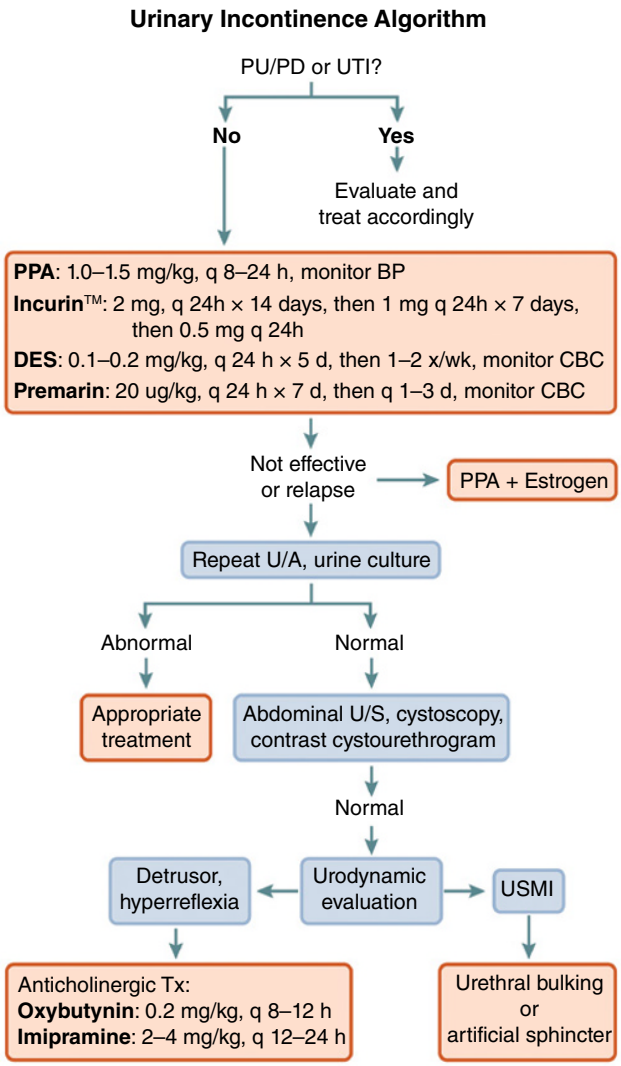


Figure 127.2 Diagnostic approach to the patient with urinary incontinence. The presence of urinary incontinence in an otherwise healthy neutered female dog that was previously continent is often adequate for presumptive diagnosis of USMI and a trial of empiric therapy before proceeding with additional diagnostics. BP, blood pressure; CBC, complete blood count; DES, diethylstilbestrol; PPA, phenylpropanolomine; PU/PD, polyuria/polydipsia; U/S, ultrasound; USMI, urethral sphincter mechanism incompetence; UTI, urinary tract infection.

Medical treatment of USMI in the neutered female dog consists of increasing number and sensitivity of alpha-receptors in the urethral sphincter with estrogen, or by stimulating those receptors with an alpha-agonist (Table 127.1).

The most commonly used estrogens are diethylstilbestrol (DES) and estriol (Incurin™). DES is not available commercially so it must be compounded. Adverse effects associated with estrogen use include mammary gland development, vulvar swelling, and attractiveness to males. These are usually dose related and subside with dose reduction. The more serious adverse event associated with estrogen use is irreversible bone marrow suppression, although the doses most associated with bone marrow suppression are much higher than those recommended to treat USMI.

Phenylpropanolamine (PPA, Proin™) is the alpha-agonist most widely used for the treatment of USMI. It is commercially available in sizes designed for use in dogs. The dose and frequency needed for each animal tend to vary widely and may need to be increased over time to maintain continence. Adverse effects associated with PPA include restlessness, aggression, changes in sleeping patterns, and gastrointestinal signs. These are also usually alleviated by a reduction in dose or frequency. Frequently, both an estrogen and PPA are used in the same patient for severe or refractory incontinence. There is little evidence supporting a synergistic increase in efficacy, but there are anecdotal reports of greater improvement than on a single medication regimen.

Phenylpropanolamine is also frequently used in male dogs and cats with USMI. In addition, neutered male dogs may be treated with testosterone cypionate as monthly injections, although its efficacy is not well documented. Although male dogs with USMI are most responsive to PPA, only 43% show good to excellent response, much lower than in female dogs. Estrogen compounds should not be used in males and are rarely used in cats. Care should be taken to monitor the mammary glands for neoplasia in cats receiving estrogens.

In patients that fail medical therapy, surgical options may be necessary. These are generally only pursued if the animal does not respond to, or cannot tolerate, medical treatment. A number of surgical procedures have been used to treat USMI, many based on the theory of increasing the transmission of abdominal pressure to the proximal urethra. These include colposuspension, transobturator vaginal tape, and urethropexy. These have had variable outcomes and are considered to have poor long-term efficacy. The most promising surgical procedure for USMI is placement of an artificial urethral sphincter which may be adjusted via a subcutaneous port. Recent studies have shown it to lead to a significant increase in continence in female dogs that had failed medical therapy for USMI. In addition, it has been successfully placed in male dogs and, recently, a female cat.

Lower Motor Neuron Bladder

Incontinence as a disorder of storage can also occur secondary to spinal cord injury or disease. Lesions in the S1–S2 region will lead to weakness of the striated muscular sphincter. Disruption of the local reflex arc at these segments leads to an easily expressible bladder which may empty with minor increases in abdominal pressure.

Table 127.1 Commonly used medical therapies for urethral sphincter mechanism incompetence

Drug	Class	Dose	Side-effects	Caution
Phenylpropanolamine (PPA) (Proin™)	Alpha-agonist	1.0–2 mg/kg PO q8–12h	Hypertension, aggression, restlessness, gastrointestinal upset, anxiety	Hypertension, Hyperadrenocorticism, renal disease
Diethylstilbestrol (DES)	Estrogen	0.1–1.0 mg/dog PO q24h for 5–7 days then weekly or as needed	Myelosuppression (rare at these doses), attractiveness to males, mammary/vulvar swelling, behavior changes	Males (can develop prostatic metaplasia)
Estriol (Incurin™)	Estrogen	2 mg/dog PO q24h × 14 days, then reduce to 1 mg q24h	Same as DES	Same as DES
Testosterone cypionate	Testosterone	2.2 mg/kg IM q4–8 weeks	Behavior change, aggression, perianal adenoma, prostatic hyperplasia	Cardiac disease, renal disease, hepatic disease, prostatic disease

IM, intramuscular; PO, by mouth (*per os*).

These animals are identified by decreased anal tone and a poor perineal reflex as well as their easily expressible bladder. Most of these animals are unable to voluntarily void and require intermittent catheterization or manual expression by the owner. Correction of the underlying cause may lead to some return to normal function. Because of the tendency to have incomplete emptying of the bladder with manual expression, these animals are at increased risk of developing urinary tract infection and appropriate monitoring must be in place.

Detrusor Hyperreflexia/Overactive Bladder

Detrusor hyperreflexia/overactive bladder (OAB) is the most common form of urinary incontinence in people, but it has been poorly characterized in domestic species. The true incidence of OAB and its importance as a cause of urinary incontinence in dogs and cats are unknown. In people, it is characterized by sudden urgency to urinate and involuntary loss of urine associated with bursts of detrusor contractions at bladder volumes far below capacity. In dogs, it may manifest as an animal that loses bladder compliance and capacity and thus may need to urinate more often than before without an increase in urine production or inflammation of the lower urinary tract. OAB may be a cause of treatment failure in some dogs treated for USMI, and should be considered in these cases.

Diagnosis of OAB in animals can be challenging and is only definitively made using urodynamic studies such as cystometrography. Response to therapy with antimuscarinic drugs is often used to presumptively diagnose OAB in veterinary species. The most commonly used include oxybutynin and imipramine, the latter of which also has alpha-agonist effects. Adverse effects of these medications include gastrointestinal abnormalities such as diarrhea and constipation, as well as parasympatholytic signs like tachycardia and hyposalivation.

Disorders of Emptying

The inability to completely empty the bladder during a normal void can result from either a functional or mechanical obstruction of the outflow tract and urethra, or an abnormality of the detrusor which impairs its complete contraction. Overflow incontinence can result from the lack of complete emptying, often when the animal is at rest. An owner may not be able to differentiate this from an animal with a storage disorder (e.g., USMI), and it is up to the clinician to determine the underlying process so that appropriate therapy can be instituted. Inability to completely empty the bladder is a risk factor for UTI, and these animals should be monitored for infection.

Detrusor Atony

Complete emptying of the urinary bladder is dependent on normal contraction of the detrusor muscle. In the normal animal, the bladder relaxes during filling with only small increases in intravesical pressure. As the bladder continues to fill, the pressure increases to a threshold which triggers a detrusor contraction and emptying. Loss of adequate detrusor contraction can result from neurogenic or nonneurogenic abnormalities. Injury to the sacral spinal cord S1–S3 or pelvic nerves can lead to bladder atony, and is often associated with weakened urethral tone. These animals often have decreased perineal reflexes and easily expressed bladders.

Treatment of the underlying lesion, if possible, may lead to improved voiding function. However, until normal function returns, careful management of urination must be followed. Male dogs are usually aseptically catheterized 2–4 times a day either in the hospital or at home, and cats and female dogs are often manually expressed. Parasympathomimetic drugs such as bethanechol are not useful in these animals as they require a functional pelvic nerve and associated spinal segments for clinical efficacy.

Direct damage to the detrusor muscle can occur from overdistension due to mechanical or functional outflow obstruction of acute or chronic nature. The muscle fibers of the detrusor transmit action potentials which initiate contraction via tight junctions. With overdistension, these tight junctions are interrupted, leading to an absent or ineffective contraction. The overdistension may be acute, as with obstructive feline idiopathic cystitis in a male cat, or chronic, as with a dog with a functional obstruction of the urethra. Relief of the obstruction and maintenance of a small bladder volume for up to two weeks may allow the junctions to reestablish and the return of coordinated detrusor function. This is usually managed by either indwelling or frequent sterile catheterization of the bladder. Bethanechol may be used in these patients to enhance stimulation of the detrusor contraction since the pelvic nerve is intact. Other medications that have been shown to enhance detrusor function are cisapride and metoclopramide. It is essential that relief of any urethral obstruction, functional or mechanical, be attained before starting medical therapy to enhance detrusor contraction.

Functional Obstruction – Detrusor Urethral Dyssynergy

Functional urethral obstruction, or detrusor urethral dyssynergy (DUD), arises from an abnormality in the reflex arc at the neurologic or muscular level which allows the urethral sphincter to relax at the initiation of

detrusor contraction and urination. It may affect the smooth muscle internal urethral sphincter, the striated external sphincter, or both. It is possible that the lesion is cranial to the associated spinal segments and involves the loss of inhibitory signals to the pudendal and hypogastric nerves, but may be a more local lesion to the nerves, the neuromuscular junction, or the sphincter itself. Unlike the "upper motor neuron bladder" seen in animals with thoracolumbar intervertebral disc disease and other spinal cord lesions, these animals typically have an otherwise normal neurologic examination.

The disorder affects primarily middle-aged, large- and giant-breed male dogs. One case series of 22 dogs reported a mean age of 4.9 years. Clinical signs are similar to those of mechanical obstruction. The animal often postures to urinate and is able to produce a urine stream that quickly becomes attenuated or stops completely. The animal may continue to posture to urinate or make several attempts without fully emptying the bladder. The presence of large amounts of residual urine typically leads to overflow incontinence and may be mistaken for USMI. This leakage can occur because the hypertonicity of the involved sphincter is often dynamic and is triggered by the act of voiding. In chronic cases, bladder overdistension and subsequent atony may develop. Unlike animals with mechanical obstruction, these dogs are typically easy to catheterize and usually do not show increases in urethral pressure on urodynamic evaluation unless actively voiding. Contrast urethrography may be normal or reveal areas of narrowing of the urethra (urethrospasm).

Presumptive diagnosis of DUD is often made by observing the dog urinate with a typical interrupted pattern, documentation of a large residual urine volume, easy passage of a urinary catheter, and ruling out of a mechanical obstruction. Normal residual urine volume in 48 normal dogs was reported to be 0.1–3.4 mL/kg body weight with a mean of 0.2 mL/kg. The author uses <0.5 mL/kg as a general guideline. Ultrasonography is recommended to assess the ureters and renal pelves for dilation secondary to chronic obstruction and ureterorenal reflux of urine. Additional diagnostics, including contrast urethrography, urethroscopy or urodynamic evaluation, may be necessary to verify the diagnosis in patients who fail to respond to medical therapy.

Treatment of the hypertonic urethral sphincter generally consists of alpha-adrenergic blockade with prazosin, an alpha-1-specific antagonist with demonstrated effects on both the internal and external urethral sphincter. Tamsulosin, which is specific for the alpha-1A subtype found in the internal urethral sphincter, has also been successful in these dogs. Some dogs will require additional therapy if the striated muscle is more significantly affected. Benzodiazepines, such as midazolam, or other skeletal muscle relaxants, including acepromazine and methocarbemol, may be more effective if the external urethral sphincter is involved. Midazolam or diazepam is typically administered 30 minutes before voiding to decrease external urethral sphincter pressure. Dantrolene and baclofen have been used in the past as skeletal muscle relaxants; however, the potential for adverse effects has decreased their use in veterinary patients. In severe and refractory cases, intermittent sterile catheterization by the owner at home may be necessary. Medical therapy of associated bladder atony should only be started after adequate relief of the functional urethral obstruction has been reached. Close monitoring of these patients for residual urine volume and UTI is needed to assess efficacy of treatment and prevent complications.

It is possible that patients with controlled DUD will experience relapse in times of stress such as hospitalization or boarding. These animals may need periodic additional therapy or catheterization even if usually able to urinate normally.

Prognosis for recovery of normal voiding is good, but most dogs will require life-long therapy for DUD. Attempts to taper medications to the lowest effective dose may be hampered by relapse of clinical signs after months of normal voiding. Prognosis appears to be worse in patients with bladder atony or UTI secondary to urine retention. Anecdotally, urethral stenting may improve clinical signs, but this is considered a salvage procedure with several potential complications, and indicated only in the most refractory of cases.

Functional Obstruction – Neurogenic

Neurogenic functional urethral obstruction is generally caused by spinal cord lesions cranial to the sacral segment. This leads to loss of inhibitory signals to the hypogastric and pudendal nerves which prevents sphincter relaxation upon voiding. This is the classic "upper motor neuron bladder" in which the patient is unable to urinate normally and is difficult to express manually. The most commonly affected patients are those with intervertebral disc disease and associated paresis. These animals typically have additional neurologic deficits, including paresis and nociceptive loss. Treatment of the underlying lesion typically leads to partial or complete return to normal voiding function after days to weeks. Until normal voiding resumes, the patients are managed as for DUD with alpha-adrenergic blockade, and manual expression or catheterization. Monitoring for overdistension and UTI is critical in these patients, as is nursing care, particularly since the overflow incontinence that can accompany this process may lead to skin breakdown in these recumbent patients.

Dysautonomia

Dysautonomia is a rare condition involving degeneration of the neurons of the autonomic nervous ganglia, leading to sympathetic and parasympathetic dysfunction. It has been most commonly reported in both dogs and cats in the UK and Scandinavia, but small clusters of cases in both species have been seen in the US. Its underlying cause is unknown, but neurotoxin exposure is strongly suspected.

In addition to the classic findings of unresponsive mydriasis and prolapsed nictitans, the abnormalities seen with dysautonomia can range from ileus and constipation to decreased systolic function of the heart. These dogs and cats often have significant voiding dysfunction and urine retention due to bladder atony and overflow incontinence secondary to urethral sphincter incompetence. There is no specific treatment for dysautonomia and spontaneous remission is uncommon.

The prognosis is related to the severity of the clinical signs and the specific organ functions affected. Management of the urinary complications is usually possible, involving bladder expression and/or urethral catheterization, along with parasympathomimetic agents. It is the challenging management of the gastrointestinal components of the disease which often leads to euthanasia.

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128

Urinary Tract Infections

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Etiology/Pathophysiology

The most common isolate from canine urine is *Escherichia coli* which accounts for one-third to half of all positive urine cultures. The next major group of uropathogens includes gram-positive cocci, *Staphlyococcus*, *Streptococcus*, and *Enterococcus*. Remaining uropathogens include *Proteus*, *Klebsiella*, *Pasteurella*, *Mycoplasma*, *Enterobacter*, and *Pseudomonas*. These 10 genera accounted for 95% and 97% of all urinary isolates in male and female dogs, respectively. A retrospective analysis of feline urine cultures submitted to a teaching hospital also found *E. coli* to be the most common pathogen (47%), followed by *Staphlyococcus* (18%), *Streptococcus* (13%), and *Klebsiella* (4%). In both dogs and cats with bacterial urinary tract infection (UTI), 75% of the time there is a single pathogen, in 20% of cases there are two pathogens and ≤5% of the time there are three species. Multiple organism infections are more commonly observed in female dogs.

Epidemiology/Signalment

Bacterial UTI is common; approximately 5–27% of dogs will experience infections of the urinary tract at some point during their lifetime. Female dogs are more commonly affected than males. In contrast to dogs, bacterial UTI is relatively rare in cats. In young, otherwise healthy cats with signs of lower urinary tract inflammation, bacterial UTI is rare (<2%). Incidence of bacterial UTI in cats increases with age and occurs more often in cats older than 10 years.

Urinary tract infections are common in dogs and cats with systemic diseases that may compromise normal antimicrobial defenses. In a retrospective study of 101 dogs with diabetes mellitus (DM) or hyperadrenocorticism or both, 42 (41.6%) had a UTI. Dogs receiving long-term glucocorticoids are also at risk with a reported incidence of 18–39%. Similarly, systemic disease can predispose cats to UTI. In retrospective studies evaluating known predisposing conditions in cats, positive urine cultures were found in 17–30% of cats with chronic kidney disease (CKD), 12–13% of cats with DM, and 12–22% of cats with hyperthyroidism. In one of these studies, decreasing urine specific gravity (USG) was not associated with positive urine culture; however, pyuria and hematuria were associated with positive urine cultures. In addition, Persian breed, females, increasing age, and decreasing body weight were associated with positive cultures.

History and Clinical Signs

Clinical signs associated with a UTI depend on bacterial virulence, status of the host immune system, duration of the infection, and site or sites of infection. The most common clinical signs associated with lower UTI include pollakiuria, stranguria, dysuria, hematuria, and inappropriate urination or periuria. If a UTI occurs secondary to a micturition disorder, such as an ectopic ureter, urethral sphincter mechanism incompetence (USMI), or urine retention, clinical signs associated with the primary condition may predominate. Similarly, in dogs and cats with systemic disease and compromised host defense mechanisms, clinical signs associated with the underlying disease may predominate and the UTI may be relatively asymptomatic.

Dogs with uncomplicated UTI often have unremarkable physical examination findings. Predisposing causes such as vulvar involution, severe perivulvular dermatitis, vaginal stenosis, cystic or urethral calculi, or urethral thickening may be identified in patients with a complicated UTI. Whenever possible, female dogs that present with a UTI should have a digital vaginal examination performed in order to identify an anatomic abnormality

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that may alter normal host defense mechanisms. For example, palpation of a persistent paramesonephric remnant may prompt further investigation for ectopic ureters and palpation of vaginal strictures may prompt further investigation for urine retention. Rectal examination may also identify abnormalities such as pelvic trauma, urethral stones, or urethral thickening associated with neoplasia or granulomatous urethritis.

Acute bacterial pyelonephritis, prostatitis, and metritis are often associated with systemic signs such as fever, an inflammatory leukogram, lethargy, and anorexia. In contrast, patients with chronic prostatitis and pyelonephritis may not exhibit systemic signs and therefore it may be more difficult to localize the infection.

Diagnosis

Urinalysis may be helpful in differentiating a UTI from other disorders causing lower urinary tract signs (e.g., bladder neoplasia), making initial antibiotic recommendations, and in some cases identifying potential predisposing disorders (e.g., glucosuria and crystalluria). Urine specific gravity can be variable in patients with a UTI. Dilute or minimally concentrated urine may be observed in patients with concurrent disease predisposing to UTI (e.g., DM or hyperadrenocorticism), or may be observed if the infection involves the upper urinary tract. With a UTI, hematuria and proteinuria are frequently observed on dipstick analysis. The dipstick analyses for nitrite (bacteria) and leukocyte esterase (white blood cells [WBCs]) are designed for use in people, and are not reliable tests for canine and feline patients.

A urine sediment examination should be performed to identify pyuria and bacteriuria. If urine is dilute or the patient is immunocompromised (e.g., suffers from hyperadrenocorticism, or is receiving exogenous corticosteroids), it may be difficult to identify WBCs or bacteria on urine sediment examination. Air-dried, stained sediment evaluations were more accurate than wet, unstained mounts for identification of bacteria when urine culture results were used as the gold standard. This air-dried, stained technique is easily performed in practice by placing one drop of sediment on a glass slide, allowing it to air dry without spreading, and then staining the sample with a commercially available modified Wright's stain. It is important to remember, however, that a culture is required for definitive diagnosis, and will provide additional information (e.g., bacterial identification, number of organisms/mL of urine, and antimicrobial susceptibility results).

Cystocentesis is the method of choice for collection of urine samples, especially if a urine culture is anticipated. In patients presenting with lower urinary tract signs (e.g., pollakiuria and stranguria), collection by cystocentesis may be difficult due to the small size of the urinary bladder. Alternative methods of urine collection may be acceptable if cystocentesis cannot be performed or is contraindicated (e.g., thrombocytopenia, suspected transitional cell carcinoma (TCC) of the urinary bladder or pyoderma of the ventral abdomen). Urethral catheterization provides a superior sample compared with a free-catch voided sample but requires more technical skill, especially in female patients. Care should be taken during catheterization to prevent contamination from external structures by clipping surrounding hair and cleansing the external genitalia prior to the procedure. Based on current recommendations, free-catch urine samples are not acceptable for culture. Urinalysis and urine culture results should always be interpreted in light of the urine collection method.

Although clinical signs and urinalysis findings may increase the index of suspicion for a UTI, a urine culture is the definitive diagnostic test. Ideally, the urine sample for culture should be obtained prior to starting treatment. In patients already receiving antimicrobial therapy, it may be necessary to discontinue treatment for 3–5 days before collection of urine culture. It is also important to consider storage and transport of samples for culture in practices where immediate culture processing is not possible. Sterile containers that do not contain additives or preservatives should be used. Commercially available urine collection kits may be acceptable for up to 72 hours if sample processing is delayed. Bacterial counts can increase in urine stored at room temperature within a few hours. In refrigerated samples, quantitative bacterial counts differed after six hours of storage; however, this was not associated with a change in interpretation of the clinical significance. It is recommended that urine samples be cultured immediately but it is acceptable for urine to be refrigerated in a closed container for up to six hours prior to culture.

Alternatives to sending a urine sample to a commercial laboratory for culture include using a calibrated bacterial loop (0.01 or 0.001 mL volume) to inoculate blood or MacConkey's agar plates in-house. Culture plates are then incubated for 24 hours and if significant numbers of colonies are produced in light of the urine collection method, the plate can be sealed and shipped to a microbiology laboratory for bacterial identification and antimicrobial sensitivity testing. Alternatively, products like UriCult® culture paddles may also be used. In most cases, a quantitative urine culture will aid interpretation of results. In addition to bacterial numbers/mL of urine, knowledge of the normal flora may also be helpful in determining contamination versus infection when methods other than cystocentesis are used.

Not all species of bacteria will induce clinical signs or cause disease.

Classification of Urinary Tract Infections

Asymptomatic Bacteriuria

Bacteriuria is expected in patients with UTI, but may also be observed in healthy dogs and cats if the urine sample has been contaminated with normal flora and/or pathogens from the distal urethra/urogenital tract (voided sample or during urethral catheterization) or if the sample contacts a contaminated surface (e.g., cage floor, examination table). It is important to differentiate urine contamination from a UTI since the former does not need to be treated. Certain organisms are known to be commensal within the lower urinary tract (Table 128.1). There is, however, overlap between normal flora and potential pathogens. Contamination can be ruled out by repeating a urinalysis with urine obtained via cystocentesis or by performing a quantitative urine culture on a voided or catheterized sample. Depending on the method of urine collection, the number of bacterial colony-forming units (cfu)/mL of urine will vary between contamination and UTI (Table 128.2).

Uncomplicated UTI

Uncomplicated UTI occurs in patients where no underlying structural, neurologic, or functional abnormalities exist. A UTI becomes complicated when host defense mechanisms are compromised (e.g., CKD, hyperadrenocorticism, DM, cystolithiasis, USMI). In addition, UTIs are often considered complicated if they occur in cats, male dogs, and intact female dogs, or if they involve the kidneys or prostate.

Recurrent or Reinfection

Recurrent UTIs can be defined as either relapses or reinfections. A relapse is an infection caused by the same bacteria that caused the original infection, and usually occurs within days of cessation of treatment. Relapses are most frequently associated with ineffective antimicrobial treatment. This may be due to improper antibiotic usage (inappropriate selection, dose, duration, or poor owner compliance), emergence of drug-resistant pathogens, or failure to eliminate predisposing causes

Table 128.1 Commensal bacterial genera in the urogenital tract of dogs

Genus	Distal urethra of males	Prepuce	Vagina
Acinetobacter		+	+
Bacteroides			+
Bacillus		+	+
Citrobacter			+
Corynebacterium	+	+	+
Enterococcus			+
Enterobacter			+
Escherichia	+	+	+
Flavobacterium	+	+	+
Haemophilus	+	+	+
Klebsiella	+	+	+
Micrococcus			+
Moraxella		+	+
Mycoplasma	+	+	+
Neisseria			+
Pasteurella		+	+
Proteus		+	+
Pseudomonas			+
Staphylococcus	+	+	+
Streptococcus	+	+	+
Ureaplasma	+	+	+

Source: Barsanti JA. Genitourinary infections. In: Greene CE, ed. *Infectious Diseases of the Dog and Cat*, 3rd edn. St Louis, MO: Saunders, 2006, pp. 935–61. Reproduced with permission of Elsevier.

Table 128.2 Quantitative urine cultures in dogs and cats[a]

	Significant		Suspicious		Contaminant	
Method of collection	**Dogs**	**Cats**	**Dogs**	**Cats**	**Dogs**	**Cats**
Cystocentesis	≥1000	≥1000	100–1000	100–1000	≤100	≤100
Catheterization	≥10 000	≥1000	1000–10 000	100–1000	≤1000	≤100
Midstream voiding	≥100 000[b]	≥10 000	10 000–90 000	1000–10 000	≤10 000	≤1000
Manual expression	≥100 000[b]	≥10 000	10 000–90 000	1000–10 000	≤10 000	≤1000

[a] Values are given in colony-forming units per milliliter of urine (cfu/mL). Data represent generalities. Occasionally bacterial UTI may be detected with fewer organisms (i.e., false-negative results).
[b] Because the contamination level of midstream samples may be 10 000 cfu/mL or higher (i.e., false-positive result), these samples should not be used for routine diagnostic culture.
Source: Pressler B, Barges JW. Urinary tract infections. In: Ettinger SJ, Feldman EC, eds. *Textbook of Small Animal Veterinary Internal Medicine*, 7th edn. St Louis, MO: Saunders, 2010, pp. 2036–47. Reproduced with permission of Elsevier.

that alter normal host defense mechanisms and allow the persistence of bacteria. Relapse UTIs may be associated with a higher degree of antimicrobial resistance compared to the original infection.

Reinfections occur when the initial infection was effectively treated (documented by negative culture after therapy and resolution of clinical signs) and repeat culture confirms another infection. Typically, the time between reinfections is greater than the time between relapses. Reinfections usually indicate that host defense mechanisms are compromised.

Therapy

Ideally, antimicrobial administration should be based on results from culture and susceptibility. Unnecessary or inappropriate usage of antibiotics can lead to antimicrobial resistance, or delay the diagnosis of noninfectious cause of lower urinary tract signs (e.g., like identification of underlying TCC). In addition to susceptibility results, the route and ease of administration, potential adverse effects, cost, and concentration in the urine (or other targeted tissues, e.g., prostate, kidney) should be considered when choosing an antibiotic.

To determine the minimum inhibitory concentration (MIC), serial dilutions of an antibiotic are used to discover the lowest concentration that will inhibit bacterial growth. This concentration is the MIC and although results are reported as susceptible, intermediate, and resistant, they usually also include the actual MIC followed by the breakpoints used to determine susceptibility. The goal of the breakpoint is to predict clinical outcome for an individual patient. Breakpoints are determined by a combination of information including the species, bacteria, disease, antibiotic, dose, route, and frequency. It is important to keep in mind that there are limited data available for veterinary medicine; therefore breakpoints are often determined by using information available from human breakpoints.

A result reported as "susceptible" indicates a high likelihood of treatment success (>80%) with most antibiotics; "intermediate" indicates possible success in treatment with potential alterations in normal dosing; and a "resistant" result indicates that a clinical cure is unlikely to occur with that antimicrobial. The result is considered susceptible if the MIC is in the breakpoint range or below, intermediate if it is at the high end of the breakpoint, and resistant if it is above the breakpoint.

Urine antibiotic concentrations are usually more important than plasma concentrations when treating a UTI. Minimum inhibitory antibiotic concentrations and the anticipated urine antibiotic concentration may be used to guide treatment choices. Clinical efficacy is expected if urine concentration is maintained at greater than four times the MIC of the pathogen between doses. For example, the MIC of ampicillin for a *Staphylococcus* organism is approximately 10 µg/mL. The expected serum and tissue concentrations of ampicillin are 1–2 µg/mL whereas the expected urine concentration of ampicillin is >300 µg/mL. Since the expected urine concentration is >4 times the MIC, sensitivity for a superficial UTI should exist. Minimum inhibitory antibiotic concentration testing based on anticipated urine concentrations is not appropriate for deeper tissue infections (e.g., pyelonephritis, thickened bladder wall) where serum and tissue antibiotic concentrations are expected.

Interpretation of Results

The Clinical and Laboratory Standards Institute (CLSI) is a committee of experts that examines pharmacokinetics, microbiology, pharmacodynamics, bacterial population, MIC distribution, and clinical trial results.

Recommendations from this committee are considered the gold standard for breakpoint determination. Veterinary laboratories (or human laboratories with appropriate susceptibility panels for commonly used veterinary antibiotics) that follow CLSI guidelines should be used for culture and sensitivity testing.

Depending on the laboratory, comparing antibiotics with similar susceptibility (e.g., cephalexin and cefazolin) may be necessary but requires making assumptions. For example, when comparing cefazolin with cephalexin, cefazolin is typically administered intravenously q6h whereas cephalexin is typically administered orally q8–12h. It is also important to remember that *in vitro* culture and sensitivity results may not correlate with *in vivo* efficacy. For example, regardless of the susceptibility results for *Enterococcus*, certain antibiotics including cephalosporins, trimethoprim-sulfamethoxazole, clindamycin, and aminoglycosides should always be considered resistant since they are not effective clinically and do not correlate with *in vitro* results.

In many cases, antibiotic sensitivity testing results provide a clear direction for treatment with an antibiotic that is orally administered, has few potential adverse effects, and reasonable cost. In some cases, sensitivity results demonstrate a high degree of bacterial resistance, and route of administration, high cost, or potential adverse effects of the potentially effective antibiotic may be a concern. Although MIC may be used as a guideline for antibiotic selection, veterinary breakpoints for most antibiotics in the urinary tract of dogs and cats have not been determined. When intermediate results are obtained, it may be possible to achieve a cure if no alternative antimicrobial exists. This would most likely be achieved by using a higher dose of an antimicrobial that is excreted in the urine. In resistant infections, requesting an expanded antimicrobial sensitivity profile (e.g., ceftazedime, carbenicillin) may suggest alternative treatment regimes. Most commercial bacteriology laboratories have a second and third tier of antibiotics for expanded sensitivity testing; however, high cost and parenteral administration may be trade-offs.

Inappropriate antibiotic dosages or unnecessary usage can lead to resistant organisms, affecting not only the individual patient but potentially bacterial resistance in other veterinary patients and owners. Antimicrobials that are excreted in the urine are the mainstay of UTI treatment and initial antibiotic considerations should include amoxicillin, cephalexin or trimethoprim-sulfadiazine. When host defense mechanisms are compromised, previous or current sensitivity results indicate potential resistance, or when the infection involves the prostate or kidneys, second tier antibiotic choices should be considered including potentiated beta-lactams (e.g., amoxicillin-clavulanic acid), fluoroquinolones, or extended-release cephalosporins (e.g., cefovecin). Second-tier antibiotics are not recommended as a first-line treatment for an uncomplicated UTI, without appropriate culture and sensitivity results. However, these may be considered when rapid treatment is necessary to return to function, prevent systemic spread of bacteria, or when penetration into a specific tissue, such as the prostate, is needed. For penetration into prostatic tissue, antibiotics should be lipid soluble, not highly protein bound, and ionize at the pH of the prostatic tissue. Good prostate gland penetration can usually be achieved with fluoroquinolones, trimethoprim-sulfa, and chloramphenicol.

Uncomplicated UTI

Dogs and cats with uncomplicated are typically treated with a 7–14-day course of antibiotics. It is reasonable to assume that shorter durations of appropriate antibiotics (≤7 days) may be effective but clinical trials are needed to further evaluate shorter duration treatments. It is always ideal to treat on the basis of urine culture and sensitivity results, although economic constraints may preclude this in first-time patients with suspected uncomplicated UTI. In these cases, antimicrobial selection should be based on bacterial characteristics observed in the urine sediment (e.g., gram positive vs gram negative, cocci vs rods). For example, if a gram-negative rod or bacillus is seen (e.g., *E. coli*, *Enterobacter*, *Klebsiella*, *Proteus*), cepalosporins would be a good option. With gram-positive cocci (e.g., *Staphylococcus*, *Streptococcus*, *Enterococcus*), amoxicillin and cephalosporin would be options. Clinical signs should resolve within 48 hours with appropriate treatment. Along with resolution of clinical signs, evidence of inflammation in urine sediment should also resolve in 3–5 days of antibiotic treatment.

When empiric antibiotic treatment is used, instructions to owners regarding what to expect as well as follow-up plans are critical. If presenting clinical signs do not resolve quickly, owners should be aware of the need for a follow-up urinalysis and culture and sensitivity. Owners should also be aware of the importance of completing the entire antibiotic regime, even if signs resolve early in the course of treatment. Finally, owners should be instructed to observe their pets closely for signs of UTI recurrence after the treatment regime is complete. Clear communication and understanding of the "game plan" will result in improved treatment outcome and increased client willingness to return in cases of empiric treatment failures.

Short-Course/High-Dose Protocol

Due to concerns with owner compliance during longer treatment protocols, short-course/high-dose protocols have been proposed for the treatment of uncomplicated

UTI in dogs. In a recent study in dogs, a short-course/high-dose protocol of enrofloxacin (18–20 mg/kg once daily for three days) was as effective as traditional-dose amoxicillin-clavulanate (13.75–25 mg/kg twice daily for 14 days) in treating uncomplicated UTI. Preliminary evidence suggests this may be an effective option but additional research may be necessary to incorporate this into routine clinical practice.

Complicated UTI

Antibiotic treatment of complicated UTIs should be prolonged (typically four weeks) and always based on urine culture and sensitivity results. It is possible that shorter duration of therapy may be effective in some or all clinical situations, but further studies are needed to provide more specific recommendations. One week into treatment and one week prior to discontinuing antimicrobials, reevaluation of the urine sediment can help determine response to therapy. When effective, no bacteria or white cells should be observed on sediment exam. Recheck urine culture is again recommended 5–7 days after completion of therapy to confirm successful resolution of the UTI. Prolonged treatment of a complicated UTI may be necessary to sterilize the urinary tract but "buying time" for correction of host defense mechanism abnormalities is another important consideration. If host defense mechanism abnormalities are not corrected, it may be difficult to clear the current infection or, more likely, the patient will experience reinfections.

Ancillary Therapies

Ancillary therapies designed to prevent recurrent UTI are considered in patients where breaches in host defenses are present but are not correctable or in cases where an underlying cause for reinfection is not identified. Care should be taken to treat any underlying infection prior to starting any prevention measures. Owners should watch closely for clinical signs and be advised that frequent rechecks will be necessary to detect and treat any breakthrough infections.

Urinary Antiseptics

The most commonly used urinary antiseptic is methenamine which is converted to formalin in an acidic environment. Methenamine may be considered in patients with recurrent infections or those with potentially untreatable or unresolved breaches in immunity. Just as with the use of cranberry extract, this prophylactic treatment is not recommended as a sole treatment for UTIs. Methenamine should only be used in conjunction with antibiotics for the treatment of current infections or as a preventive once the previous UTI has been cleared. Use should be avoided in patients on sulfonamides or medications that cause alkaline urine. Urine acidifiers added to methenamine cause acidic urine that can also decrease activity of fluoroquinolone and aminoglycoside antibiotics. High doses can cause irritation to bladder mucosa but this is more common in people than dogs.

Prophylactic Antimicrobial Protocols

Prophylactic antimicrobial treatment involves long-term daily administration of low-dose antimicrobials in order to inhibit or minimize uropathogen growth, thus decreasing the opportunity for bacterial adhesion and colonization of the uroepithelium. Unfortunately, there are no studies in dogs that have evaluated the efficacy and adverse effects of these protocols. Due to the risk of creating resistant infections, prophylactic, low-dose antibiotic administration should be reserved for refractory cases and then only after all attempts to resolve correctable problems have been exhausted.

Prophylactic, low-dose antibiotic treatment should only be initiated after standard-dose antibiotic treatment has been successful (negative urine culture). Best results are expected with drugs that are excreted in the urine. Other considerations should include potential side-effects of the drug and previous culture and sensitivity results. Commonly used protocols include fluoroquinolones, cephalosporins, or beta-lactam antimicrobials. The dose used should be one-half to one-third the therapeutic daily dose administered immediately after the last voiding before bedtime. This protocol is typically recommended for a minimum of six months and urinalysis and culture should be performed every 4–8 weeks. If at any point during the treatment a UTI occurs, it is treated as a complicated UTI. Prophylactic, low-dose therapy can be restarted after the reinfection has been resolved.

Cranberry Extract

Proanthrocyanidins, specifically A-type isoforms, found in cranberry juice inhibit *E. coli* attachment by blocking interaction of bacterial P-fimbriae with the surface of uroepithelial cells. Canine studies evaluating the efficacy of cranberry extract (CE) are limited, but some *in vitro* data show promising results. One study demonstrated that *E. coli* in urine from dogs receiving oral CE had decreased ability to agglutinate to human red blood cells. Similarly, a second study demonstrated that *E. coli* in urine from dogs receiving oral CE had decreased ability to adhere to Madin-Darby canine kidney (MDCK) cells. Based on these *in vitro* studies, oral administration of CE may help reduce *E. coli* reinfections in patients with compromised host defense mechanisms. Due to large variations of the active compound in over-the-counter products, it may be of benefit to use canine products dosed according to manufacturer recommendations.

Box 128.1 Ideal steps to follow in the management of UTIs in dogs and cats

1) Diagnosis should be determined on the basis of history, urine sediment, and, ideally, urine culture and sensitivity results. Rule out contamination in voided/catheterized samples with quantitative culture. Cystocentesis is the ideal way to collect urine for culture.
2) Select an antimicrobial agent based on culture and sensitivity. Without culture and sensitivity results, use air-dried sediment findings to guide antibiotic choice (e.g., cocci vs rods).
3) Reculture urine (or at least examine the urine sediment) in 3–5 days to ascertain effectiveness of selected antimicrobial agent. Urine culture should be negative and/or there should be no white blood cells in the urine sediment.
4) Examine urine sediment 3–4 days before discontinuing antibiotic treatment.
5) Repeat urinalysis and culture 5–7 days after cessation of antibiotic therapy. (Steps 4 and 5 are especially important for recurrent UTI.)
6) Patients with recurrent UTIs should undergo imaging studies (e.g., plain and/or contrast-enhanced radiography and/or ultrasonography), a complete blood count, and serum biochemistry profile to determine whether they have local/systemic underlying predisposing factors.
7) Frequent reinfections may need to be treated with low-dose nighttime antibiotic regimes or cranberry extract after the initial inflammation has been cleared up in response to standard-dose antibiotic treatment.

Box 128.2 Reasons for poor therapeutic response in dogs and cats with UTI

- Use of ineffective drugs or ineffective duration of therapy (relapse).
- Failure of owner to administer prescribed dose at proper intervals (relapse).
- Gastrointestinal tract disease, concurrent intake of food and drug resulting in decreased drug absorption, or impaired renal concentrating ability resulting in decreased antibiotic concentrations in the urine (relapse).
- Impaired action of drugs, either because bacteria are not multiplying or because they are sequestered in an inaccessible site (e.g., prostate, neoplasia, or uroliths) (relapse).
- Failure to recognize and eliminate predisposing causes (reinfection).
- Presence of mixed bacterial infections in which only one of the pathogens is eradicated by antimicrobial therapy (relapse).
- Iatrogenic reinfection caused by catheterization (reinfection)
- Development of drug resistance in bacteria (relapse).

Prognosis

Most UTIs are uncomplicated and appropriate antibiotic treatment rapidly clears the infection, resulting in a good prognosis. However, the prognosis for a complicated UTI may be guarded. It is of the utmost importance to correct underlying defects in host defenses whenever possible to achieve the best outcome with a complicated UTI. Following protocols for ideal UTI management and monitoring will improve treatment success and decrease the incidence of recurrent UTI (Boxes 128.1 and 128.2).

Further Reading

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Section 11

Oncologic Disease

129

Approach to the Cancer Patient

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The goal of this chapter is to present an overview of current cancer terminology, patient evaluation, diagnostic techniques, management strategies, and treatment options with emphasis on the application of radiation therapy.

Cancer is a group of diseases that are defined by the uninhibited growth and replication of cells. Cancer arises from an abnormal single cell that has suffered a disruption in its regulatory mechanism for proliferation and self-elimination. Cancer biology will be discussed in subsequent chapters.

Unregulated cellular proliferation is a characteristic of both benign and malignant tumors. Metastasis distinguishes a malignant from a benign tumor. Metastasis is the spread of cancer from one location to a regional or distant location. A tumor is named based on its cell of origin. A cancer that initiates from embryologically derived endoderm, more commonly termed skin or epithelium of the internal organs, is a carcinoma. Carcinoma will have a descriptor, a prefix, based on histology. An example of a carcinoma of the oral cavity is a squamous cell carcinoma. A benign mass within skin or epithelium may be an adenoma, cystadenoma or papilloma. A malignancy of mesoderm – bone, muscle, fat, cartilage, or other supportive structures – is termed a sarcoma. Benign examples include fibroma, lipoma, hemangioma, chondroma, and osteoma. Central nervous system cancers involve the brain and spinal cord and are named after the cells lining the interior and exterior of the brain (glial, meningeal, ependymal cells) or cells from vascular structures (choroid plexus). Lymphoma (lymphosarcoma) and multiple myeloma are malignancies involving immune regulatory cells.

Discrete cell tumor is a term applied to tumors that exfoliate as individual (discrete) cells, which are generally round in shape. This category includes mast cell tumor, plasmacytoma, transmissible venereal tumor, lymphoma, and histiocytic tumors, but is not limited to these tumors. Leukemia results from malignant blood-forming tissues of the bone marrow.

The terminology for some malignancies may be misleading. Examples include those used for lymphoma and melanoma. Lymphosarcoma and lymphoma are terms for the same malignant process. Melanoma may be benign or malignant depending on location, level of invasiveness, and species. A histopathologic description will state malignant melanoma versus melanocytoma (benign melanoma).

The overall mortality due to cancer in dogs is 20–30%, approximately one in four. The dog breed with the highest cancer prevalence in the United States is the golden retriever. Currently the Golden Retriever Lifetime Study is underway in the United States. The study's purpose is to identify the nutritional, environmental, lifestyle and genetic risk factors for cancer and other diseases in dogs (https://www.morrisanimalfoundation.org/golden-retriever-lifetime-study). In Sweden, a retrospective study found boxer and Bernese mountain dogs to be overrepresented in cancer deaths compared with other breeds, including the golden retriever. The selection of desired traits may lead to breed-specific risks for the development of cancer. Boxers, bulldogs, and retrievers are prone to cancer of the skin and subcutaneous tissues. The Siamese cat is predisposed to the development of cutaneous mast cell tumors. Osteosarcoma is historically a cancer of large and giant breeds. The power to identify hereditary influences lies in the pure-bred dog's reduced genetic complexity (diversity). Identification of pathway dysregulation(s) will elucidate potential upstream or downstream therapeutic targets. Current multiinstitutional consortium research is focused on the rapid identification and translation of novel therapies to benefit

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dogs and humans. (For more information see www.ccogc.net, www.vai.org, www.akcchf.org and for pet owners wishing to register their affected dogs, http://nationalveterinarycancerregistry.org/).

Initial Assessment

History

Pertinent information should be obtained through open-ended questions using reflective listening and confirming the information by paraphrasing important points. Taking a thorough history incorporates both nonverbal and verbal communication skills. This should include the onset of the current problem, the anatomic location of the problem or body system affected, descriptors of the nature of the problem such as quality, quantity, severity, onset, duration, timing of occurrence, frequency, as well as inciting factors that trigger the occurrence, alter the frequency and severity or improve the event. The duration of the presence of a mass and the rate of growth may facilitate differentiation between benign and malignant processes. Previous medical and surgical conditions, vaccination and administration location, allergies, exercise, travel history, housing, feeding practices, elimination details, administration of medications, vitamins, nutraceuticals, and supplements should also be investigated. This information is vital and may circumvent adverse events associated with polypharmacy. Once the information is obtained and organized, the organ system affected should become evident.

Patient Evaluation

The physical examination is an essential portion of every patient evaluation and should include all major organ systems. Leaving the affected body system for the final portion of the exam may permit minimal patient resistance. Attention should be paid to the demeanor and behavioral responses of the patient for pain assessment, location of primary and/or metastatic disease, site of surgical interventions, musculoskeletal conditions and mobility, neurologic function, and dermatologic conditions. Once the history and physical examination data have been integrated, the subsequent chapters will guide the reader through the most probable differential diagnoses. It is important to bear in mind that the presenting problem may not always reflect the origin of the tumor but rather be a consequence of a tumor-associated change(s) in function. For example, a dog may present for polyuria and polydipsia when the inciting factor is humoral hypercalcemia of malignancy (HHM), a paraneoplastic syndrome associated with particular tumors.

Diagnostic Testing

Based on the generated list of differentials, tailored diagnostic testing may be recommended to support or refute a diagnosis. Clinical features suggestive of a malignant tumor include rapid growth, invasion into deep tissues or overlying skin, fixation, ulceration, and poorly defined margins. If a tumor lacks these clinical features, it should not be assumed to be benign as malignant mesenchymal tumors may appear demarcated when surrounded by compressed normal tissue (pseudocapsule). Through the use of cytology or histopathology, sampling of a mass is required for differentiation.

An open dialogue is paramount when faced with evidence of a malignancy. The general public often has unrealistic expectations regarding the diagnosis and treatment of cancer. It is important to discuss the likelihood of a malignancy versus other diseases, as some families may not have the emotional or financial wherewithal to proceed. Once a diagnosis is made, the anticipated biologic behavior will influence further diagnostics to identify to what extent the body is affected locally, regionally, and distantly. This process is termed staging.

Staging

Staging is necessary prior to treatment for accurate assessment of overall condition, prognosis, and treatment response. The following chapters will illustrate the predicted biologic behavior for specific malignancies. Clinical staging using the World Health Organization (WHO) classification system of tumor-node-metastasis (TNM) has been applied to many canine and feline tumor types. This classification has proven useful in the prognostication of many but not all malignancies. Clinical stage of specific tumor types will include the size of the primary tumor (T), the identification of spread to regional lymph nodes (N), and the presence of metastasis (M). The subsequent chapters will reveal the tumor types for which stage has been shown to be predictive for prognosis. A few examples are canine oral melanoma, apocrine gland anal sac adenocarcinoma, and lymphoma.

Grading

Grading of a tumor is based on the histopathologic features, in particular mitotic index, percent necrosis, invasiveness, nuclear size, overall cellularity, and the presence of inflammation. Grading has also been shown to be predictive for particular tumors. The search for advanced prognostic markers and predictive factors is currently focused on molecular processes such as altered cell cycle progression, cellular proliferation, programmed cell

death (apoptosis), and angiogenesis (generation of blood vessels). Identification and understanding of the altered molecular tumor processes will ultimately reveal reliable markers for diagnosis, and predict the clinical behavior, prognosis, and response to therapy.

Diagnostics

Primary assessment should include evaluation of tumor extent, by clinical examination and appropriate diagnostic imaging or endoscopic techniques. Baseline blood testing and urinalysis rarely lead to a cancer diagnosis but may reveal any co-morbidity, and so revise the decision-making process or prognosis. Species differences must be taken into consideration. A dog with HHM may have lymphoma or an apocrine gland anal sac adenocarcinoma. In contrast, the inciting cause of feline hypercalcemia is more likely a direct action of tumor-induced bone destruction as in multiple myeloma or a carcinoma invading bone rather than HHM which is the result of cytokine- or hormone-induced hypercalcemia. The baseline blood testing for felines should always include retroviral testing. Cats with lymphoma and feline leukemia virus will likely have half the anticipated survival time.

Imaging

Tumor imaging concentrates on assessing the essential morphologic features. Radiography, sonography, computed tomography (CT), and magnetic resonance imaging (MRI) are applied routinely to identify local tumor extent and patient staging. When faced with a choice of diagnostic testing, the sensitivity and specificity should be considered. For instance, clinical examination of a limping Rottweiler with localization of pain to the proximal humerus may suggest a less extensive bone tumor where radiography may be adequate. However, radiography is less sensitive than CT, which is less sensitive than MRI. Be mindful that unless the owner is interested in a limb-sparing procedure, a radiograph may offer enough evidence to proceed with tissue sampling or surgery. Of note is that regional accessible lymph node sampling should be performed when malignant masses are suspected. Sampling completes staging and may assist in establishing a diagnosis.

When a tumor is expected to metastasize through the circulatory system to the pulmonary parenchyma, three-view thoracic radiographs are recommended. In tumors likely to metastasize through lymphatics such as mast cell tumors and lymphoma, ventral-dorsal and right lateral views will often suffice. The importance of clinical staging may be unintentionally disregarded, especially when exploratory surgery uncovers a mass. Any suspicious lesion should be sampled through biopsy or fine needle aspiration (FNA). As mentioned previously, sampling of the regional lymph nodes should also be performed. Any instruments contaminated with tumor or intestinal contents should be discarded. Fresh tissue should be cultured if granulomatous disease is anticipated.

Advanced Diagnostics

Recent advancement in veterinary oncology has provided us with insight into disease processes and an evolution toward targeted treatments. Prognostic information regarding survival time and disease-free interval in canine osteosarcoma was identified through monitoring of serum alkaline phosphatase (ALP) and bone ALP. Diagnostic tests for specific tumors are available: PetScreen® test for lymphoma, CADET® BRAF, CADET® BRAF Plus and V-BTA™ (urine test for bladder tumor analytes/mutations) for bladder cancer diagnosis and monitoring. CADET® HM is a diagnostic test utilizing cytological preparations or formalin fixed parrafin embedded tissue to identify histiocytic diseases. Tests evaluating antibodies for thymidine kinase and serum levels of the protein lactate dehydrogenase can identify an ongoing malignant process. Once sufficient data are accrued, mainstream implementation such as screening, diagnostic, prognostic and as treatment management tools may become possible. Polymerase chain reaction (PCR) and flow cytometry have yielded prognostic information, and guided our treatment choices in lymphoreticular cancers and mast cell tumors. Please refer to these specific chapters for more detail.

Therapy

Curative techniques are treatments that are intended to induce remission of the cancer and may include various therapeutic options such as chemotherapy, surgical extirpation, radiation therapy, and immunotherapy, all with the goal of long-term tumor control. Definitive therapy will both accomplish tumor control and result in alleviation or elimination of pain, whereas palliative therapy is an important tool for control of oncologic pain and improved function, generally with minimal control over the tumor itself.

Ultimately, the treatment choice should be based on several factors that will be individual to each family: time available for hospital visits, feasibility of administering in-home medications, anticipated survival time with and without treatment, acceptable side-effect profile, emotional and financial wherewithal to tolerate treatment, and disease-related side-effects.

Chemotherapy

Fundamentally, local disease requires a treatment to be directed to a specific area, typically surgery or radiation therapy. Chemotherapy is often indispensable when presented with widely disseminated but chemoresponsive disease (lymphoma) or when the development of metastatic disease is highly anticipated (canine osteosarcoma). The application, administration, and response rates achievable through the use of chemotherapy are addressed in their respective chapters.

Treatment Advances

Recent treatment advances have provided the veterinarian with orally administered targeted treatments for mast cell tumors (Palladia™ and Kinavet-CA1®). TANOVEA®-CA1 (rabacfosadine) is the first FDA conditionally approved drug for the treatment of lymphoma in dogs. This drug is delivered intravenously and has been found to inhibit the proliferation of lymphoma cells in vivo. Interventional radiology utilizes fluoroscopy and endoscopy, placing expandable metallic stents in the urethra of dogs with neoplasia, resulting in increased urine flow with tumor obstruction or near-obstruction. Chemoembolization refers to the angiography guided administration of a vascular occluding substance and chemotherapy through a catheter into a pinpointed vessel within the tumor. This technique has shown promise for the treatment of unresectable liver tumors. Hematopoietic stem cell transplantation (HCT) is available for dogs with hematopoietic malignancies. Immunotherapy research collaboration has provided the first USDA-approved canine melanoma vaccine (Oncept®) indicated for aiding in extending survival of dogs with stage II or stage III oral canine melanoma. Other available conditionally licensed vaccines include; Canine Lymphoma Vaccine, a xenogeneic murine CD20 DNA therapeutic vaccine for use in dogs with B-cell lymphoma upon achieving remission through chemotherapy. Canine Osteosarcoma Vaccine for the treatment of dogs one year or older diagnosed with appendicular osteosarcoma. The vaccine is a lyophilized formulation of a modified-live,attenuated, recombinant HER2/neu–expressing strain of *Listeria* that activates cytotoxic T cells. Lastly for our felines, Feline Interleukin-2 (IL-2) Immunomodulator Vaccine may delay postsurgical recurrence of feline fibrosarcoma in adult cats with stage I disease.

We have also had advancements in treatment-related side-effects, with reports revealing protection from tissue necrosis associated with administration of dexrazoxane in patients with chemotherapy extravasation. Entyce®, capromorelin is an orally active small molecule that mimics the action of ghrelin, which causes growth hormone secretion and appetite stimulation. This has significant potential to treat inappetence related to chemotherapy and/or underlying cancer in dogs and possibly cats. Maropitant citrate (Cerenia®) offers an economical addition to the armament for the prevention and treatment of chemotherapy-induced nausea and vomiting. In an effort to avoid chemotherapy related toxicity primarily found in herding breeds an assay is available. These breeds have a higher risk of toxicity from chemotherapeutic agents that are actively transported by the p-glycoprotein pump (e.g., vinca alkaloids, doxorubicin, dactinomycin, taxanes). The assay is noninvasive, and is simply performed through either a blood sample or cheek swab. For more information visit www.vetmed.wsu.edu/depts-vcpl/.

Surgery

Surgical intervention is the backbone of localized cancer treatment and is often used adjunctively in metastatic cancers. Surgical oncology will be addressed in the respective chapters for which is applies.

Interestingly, perioperative anesthetic and analgesic practices, including administration of opioid analgesics and nonsteroidal antiinflammatory drugs (NSAIDs), use of local anesthetic techniques, precipitation of the neuroendocrine stress response, temperature regulation, and transfusion of blood products may influence long-term outcomes such as recurrence and metastasis.

Radiation Therapy

Radiation therapy (RT) utilizes the delivery of radiation from a distance. The delivery of radiation therapy in veterinary medicine is through the use of three machine types: orthovoltage (infrequently employed), cobalt-60 (widely used), and linear accelerators (most common). Pedestal machines are limited to up-and-down movement while isocentric machines rotate around the patient. The advantage permits treatment from a variety of angles. The prescribed radiation dose is expressed as tissue absorbed dose in units of gray (Gy). The total prescribed radiation is delivered in small defined doses called fractions. Radiation therapy is often employed when surgical resection of a tumor is limited by normal surrounding structures, and it is not possible to eliminate microscopic cells. In select cases when normal tissue structures preclude adequate surgical removal, radiation may be performed prior to surgery (preoperative). The majority of radiation therapy is performed 10–14 days postoperatively.

It is important that the radiation oncologist be aware of the original tumor site, including the dimensions and extent of invasion, so as to include all the affected tissue in the planned radiation field. When microscopic

residual disease is outside the treatment field, it is left untreated and recurrence is likely; this is referred to as a geographic miss. The risk increases with multiple surgeries by means of distortion of normal tissue structures. Placement of hemoclips (radiopaque clips) at the margins of the resected tissue benefits treatment planning, decreasing the likelihood of a geographic miss. The majority of radiation-induced adverse effects are often mild and self-limiting. Advanced imaging developments have enhanced our ability to delineate tumor tissue extent and have led to improved treatment outcomes and fewer patient side-effects.

Intensity-Modulated Radiation Therapy (IMRT)

The majority of radiation treatments in veterinary oncology are delivered with radiation beams of uniform intensity in a static field. Collimators are used to limit the treatment beam and provide a rectangular treatment field. Further development has led to the more complex multileaf collimator (MLC) which is made of many metal slats capable of independent movement to shape the field. IMRT has the ability to specifically modulate the weights of small segments within an individual radiation beam. This is referred to as intensity distribution, and allows the beam to conform to the three-dimensional shape of complex tumor target volumes. This technique of RT delivers a nonuniform fluence (beam intensity) to the patient, allowing optimization of dose distribution to the target volume while sparing critical tissues. The MLC uses the superimposition of many subfields that deliver the prescribed dose. The use of IMRT has permitted the radiation oncologist to treat tumors (nasal and prostate) that would otherwise be difficult to control without significant patient side-effects.

Stereotactic Radiation Therapy

Stereotactic radiosurgery (SRS) involves precision delivery of one or several high doses of radiation to the target (tumor) by means of a linear accelerator with a sophisticated treatment planning system, delivery, and positioning device (frame). The conformal nature of SRS permits avoidance of toxicity to normal surrounding tissues. The CyberKnife® Radiosurgery System delivers radiation through a manipulated robot-mounted linear accelerator. At present, SRS is primarily utilized in select canine osteosarcoma patients and veterinary patients with central and peripheral nervous system tumors. Stereotactic radiation therapy (SRT) involves precision delivery of one or several high doses of radiation therapy delivered to the target (tumor) by means of a linear accelerator with a sophisticated treatment planning system, delivery, and positioning device(s). Most linear accelerators are floor mounted and revolve 360 degrees around the patient. The conformal nature of SRT permits avoidance of toxicity to normal surrounding tissues. There are several terms under the umbrella term SRT. SRS (stereotactic radiosurgery) treats the CNS, brain and spine. Despite having surgery in the name, the procedure is noninvasive,and no surgery is involved. SBRT (stereotactic body radiation therapy) treats all other structures than the brain and spine. SRT is used to treat tumors that would otherwise be considered inoperable and classically it is not used to address microscopic disease. At present, SRT use in veterinary patients is expanding beyond the initially treated bone tumors, central and peripheral nervous system tumors.

Radiopharmaceuticals

Radiopharmaceuticals are radioactive substances used to image and/or treat particular cancers. One example is iodine-131, a frequently employed treatment of thyroid adenoma/carcinoma in the cat. Samarium-153 and related compounds have been used for treatment of multilobular osteochondrosarcoma, and osteosarcoma.

Palliative Medical Care

Metronomic Chemotherapy

Metronomic chemotherapy, which is intended to prevent tumor angiogenesis, is based on frequent, low-dose, continuous cytotoxic drug administration lacking the rest period included with conventional chemotherapy. It results in minimal toxicity, is often cost-effective, and convenient. In veterinary medicine, metronomic therapy has become an affiliate to many protocols and usually combines an orally administered cytotoxic chemotherapeutic agent with an NSAID. It is most frequently applied in the treatment of visceral hemangiosarcoma (HSA), transitional cell carcinoma of the urinary bladder, nasal tumors, and metastatic cancers.

Pain Management

It is often difficult for clients to recognize the signs of pain or discomfort in their pets. Unrelieved pain is a major cause of suffering in patients with cancer. Veterinarians managing cancer patients must be vigilant about monitoring for and providing relief from pain, whether caused by the neoplastic process itself or coincidental in nature. Providing adequate management of pain is central to oncologic care and will improve the quality of life of the animal patient.

Palliative Radiation Therapy

Palliative radiation therapy (PRT) is the administration of a radiotherapy dose in a smaller number of treatments (fractions) than would be used in the delivery of curative intent RT (CRT); however, the fraction dose is higher and less percise than SRT. The appeal of PRT lies in

improved quality of life through symptom relief and when compared to CRT, the cost incurred is minimal. The mechanism of radiation-induced pain amelioration is currently undefined. Reduction of inflammatory cells through irradiation inhibits the release of chemical pain mediators and is probably responsible for the rapid reduction in pain seen in some patients. Decreased activity of osteoclasts in the bone microenvironment reduces bone destruction and predicts the relief of pain through irradiation.

Most patients treated with PRT will not be afforded long-term survival. Symptom relief may last 1–3 months. The common early side-effects associated with RT are often easily ameliorated and patient tolerated. While uncommon, late reactions associated with PRT may be undesirable and life-threatening. Tumor reirradiation may be possible but continued treatment will increase the likelihood of deleterious late effects. Aside from the successful alleviation of discomfort in bone tumors, PRT may offer relief for a variety of tumor types especially in patients with tumor-induced pain and limited function.

Adjunctive Techniques

Complementary techniques including acupuncture, massage, and herbal remedies are being evaluated. The actual practice of acupuncture incorporates many forms, including dry needling, laser acupuncture, and electroacupuncture, and may incorporate acupressure or herbal medicine. Specific considerations for acupuncture in the presence of cancer include avoidance of insertion of needles into or near tumors, and attention to the risk of infection in patients who are immunocompromised.

End-of-Life Management

The hospice movement originated in the late 1960s when Dame Cicely Saunders established the first medical hospice that focused on palliative care of the whole patient in an attempt to control distressing symptomatology while also managing the psychosocial aspects of dying for the patient and the patient's family. These ideas are quite applicable to veterinary medicine. The American Veterinary Medical Association's established guidelines for hospice care are available at: www.avma.org/public/PetCare/Pages/hospice-care.aspx

Euthanasia is a valid therapeutic tool in the management of progressive and intractable pain or disease in veterinary patients but it is not one that is applied easily in most situations. Many owners have questions about timing and fear making the wrong decision. The veterinarian managing a terminal patient must be prepared to handle a wide range of physical, financial, and emotional issues. The grieving process is an individual experience, making it essential to be supportive, permitting clients to grieve in a manner we may not understand. Clients may also need encouragement to speak openly with children.

Veterinarians must perform many functions during the course of treatment and palliative care of the oncology patient:

- listening to the goals, fears, and contextual experience of the owners
- demonstrating awareness of the difficult nature of the situation; reflective listening and empathy can help build trust between the client and the veterinarian
- guiding the owners through the expected course of the disease and helping them define an appropriate quality of life for the patient
- providing a peaceful and dignified release from suffering through appropriate methods of euthanasia.

Veterinarians have an inordinate amount of pressure to provide for patients, especially those under protracted care. Attention should be given to the internal struggles that may ensue should compassion fatigue arise.

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130

Biology of Cancer and Cancer Genetics

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Veterinary patients develop cancer in all tissues of the body, and these neoplasms are characterized according to their cell type of origin: carcinoma – epithelial; sarcoma – mesenchymal; round cell tumor – typically of the hematopoietic system. Cells can transition from a normal phenotype to malignancy through acquisition of mutations of certain types of genes. Oncogenes are defined as those which code for proteins that allow dysregulated tumor cell growth and proliferation, while tumor suppressor genes, which normally restrain cell growth, allow cancer cells to grow and divide indefinitely when absent or inactivated by mutation. The abnormal characteristics and behaviors of cancerous cells and tissues share commonalities, such that the neoplastic transformations and progression pathways have been defined according to various hallmarks of cancer.

In their 2011 review, Hanahan and Weinberg revised and expanded upon their initially described hallmarks. The original six hallmarks are:

- enabling replicative immortality
- evading growth suppressors
- resisting cell death
- sustaining proliferative signaling
- inducing angiogenesis
- activating invasion and metastasis.

As new developments in cancer biology were discovered, emerging hallmarks that involve the complex tumor microenvironment were added:

- avoiding immune destruction
- deregulating cellular energetics and enabling characteristics crucial to the acquisition of the original hallmark capabilities
- genome instability and mutation
- tumor promoting inflammation.

This chapter on the biology of cancer and cancer genetics is organized in accordance with the hallmarks of cancer. Each section will review the cancer biology and genetics underlying the particular neoplastic characteristic being discussed, followed by examples of the relevance of the abnormality in clinical small animal oncology today. Topics were assigned to a particular hallmark, and although it is recognized that overlaps in content exist, this organization allowed a concise but in no way comprehensive account of how the biology and genetics of veterinary cancer may be conceptualized. Further, the hallmarks are organized in an order that allows the topics to progress from cellular to microenvironmental effects. Clinical aspects of each category will be highlighted; however, for more detailed discussions, see chapters devoted to specific tumor types.

Enabling Replicative Immortality

Cancer cells require the ability to replicate unlimitedly, uninhibited by normal space restrictions, to form a macroscopic tumor. Normal cells will progress through a tightly regulated, limited number of cell divisions; thereupon, they face either senescence, which is an irreversible, nonproliferative, viable state, or crisis (cell death). Cancer cells do not respect the bounds of senescence or crisis, and attain a state of immortality.

The classic *in vitro* demonstration of unlimited replication is the ability to continuously grow and passage tumor cells in cell culture in the laboratory setting. The development and maintenance of cancer cell lines *in vitro* have allowed for molecular characterization of specific tumor types and evaluation of therapeutic responses through experimental manipulations at the cellular level. Recent research utilizing veterinary cancer cell lines includes

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studies of canine osteosarcoma, B cell lymphoma, mammary carcinoma, prostate carcinoma, and mast cell tumors, as well as feline vaccine-associated fibrosarcomas.

There are several fields of study devoted to understanding the uncontrolled nature of tumor cell replication. An underlying mechanism by which a cell regulates the number of divisions tolerable over time is through the integrity of chromosomal telomeres. Telomeres are specialized nucleoprotein complexes that "cap" and protect the end of every eukaryotic chromosome against chromosomal fusion, recombination, and terminal DNA degradation. Telomeres become progressively shorter with each doubling until they reach a critically short length and induce replicative senescence. The enzyme telomerase maintains telomeres by synthesizing and replenishing telomeric DNA. Cancer cells exploit this function by expressing telomerase and perpetually replace their telomeres. It is through this mechanism that most cancer cells gain replicative immortality. It has been shown in dogs that telomerase activity is upregulated in a majority of cancers and is absent in normal adult tissue. In fact, according to veterinary oncologic studies, telomerase is present in greater than 90% of canine cancers and is absent from most normal tissues, with the exception of germ cells. Further, it has been suggested that a different form of telomere maintenance, known as alternative lengthening of telomeres (ALT) via homologous recombination, may occur in canine osteosarcoma cells.

Important to the concept of replicative immortality, there has been great interest in studying cancer stem cells. The basis of the cancer stem cell model is that tumor development relies on a subset of stem cells that have the ability to self-renew and generate the diverse cells that comprise the tumor through differentiation. As such, the tumor exists as a heterogenous structure, maintained by cancer stem cells, which are inherently resistant to traditional chemotherapy and radiotherapy. Recently, cancer stem cells have been identified, isolated, and characterized from canine osteosarcoma cells *in vitro*.

Evading Growth Suppressors

The cell cycle is an organized balance of signals promoting and restricting replication and division; however, neoplastic cells exist with dysfunctional growth control mechanisms. The basic phases of the cell cycle have been defined as S phase (DNA synthesis), M phase (mitosis), and gaps, G_1 (between M and S), G_2 (between S and M), G_0 (senescence).

When cells are exposed to damaging agents, such as ionizing radiation or certain chemotherapy drugs, the therapeutic efficacy varies with respect to the phase of the cell cycle. For example, irradiated cells are most sensitive to the treatment during mitosis and most resistant when in the S phase. If treated in or prior to G_1 or G_2 phase, a temporary arrest or "block" in the cell cycle occurs. It is felt that the G_1 and G_2 blocks are necessary in order to repair damage done to fragile DNA prior to duplication of a faulty template or distribution of defective genes to a daughter cell in mitosis. These transient delays are also known as checkpoints. These checkpoints exist as safety mechanisms to limit the propagation of heritable errors and promote the survival of the cell. A well-known tumor suppressor protein, p53, plays a critical role in the G_1 checkpoint and controlling the fate of injured cells. It has been determined that a majority of cancers are affected with mutated p53, which allows cells that have been damaged to proceed through the cell cycle and replicate, creating daughter cells with flawed genetic content.

Chemotherapy drugs can be defined as cell cycle phase specific or cell cycle phase nonspecific. Examples of chemotherapeutics that are cell cycle phase specific include antimetabolites (i.e., gemcitabine, cytosine arabinoside, 5-fluorouracil), which are S phase specific, interfering with the incorporation of nucleotides during DNA synthesis, and vinca alkaloids (i.e., vincristine, vinblastine) which are M phase specific, as they disrupt the assembly of tubulin into microtubules and inhibit cell division.

Understanding these interactions, combination treatment plans, in which chemotherapy and radiation therapy are administered concurrently, can exploit the sensitive phases of the cell cycle, with the goal of improving therapeutic efficacy. A clinical illustration of this practice is the combination of gemcitabine, which kills cells specifically in S phase, with radiation therapy, where cells in S phase are the most resistant. The chemotherapy dose must be reduced with this approach to limit the severity of normal tissue toxicity; however, the combination has been reported for treatment of canine sinonasal carcinoma and feline oral squamous cell carcinoma.

Resisting Cell Death

Conventional cancer therapeutics may kill cells by inducing a lethal, cellular division, known as mitotic catastrophe, or triggering an organized, controlled cell death, known as apoptosis.

Playing a dual role, the p53 tumor suppressor gene, which was described in the previous section as controlling the G_1 checkpoint in managing the cell cycle, is also critical in activating the apoptotic response following cellular damage. As it is very common for malignancies to exist with mutant p53, cancer cells are adept at avoiding death by apoptosis. For example, the incidence of p53 mutations in canine osteosarcoma varies from 24% to 47%.

An alternative mechanism of resisting cell death by cancer cells is through manipulating antiapoptotic pathways. These antiapoptotic pathways are intended to maintain the natural homeostasis of cellular proliferation and deletion within tissues. Widely studied inhibitors of apoptosis include members of the Bcl-2 family and survivin. The distribution of Bcl-2 protein in normal and neoplastic feline tissues has been studied, as well as the expression of survivin in canine urinary bladder transitional cell carcinoma.

In general, mitotic catastrophe is the primary method of cellular killing by radiation exposure and a significant component of cell death by certain chemotherapy agents. A major mode of action of chemotherapy-induced death is the activation of apoptosis. To provide a clinical example, a class of drugs incorporated in cancer therapy protocols which induces apoptosis in a specific cellular population are the bisphosphonates. Bisphosphonate drugs used in veterinary oncology include pamidronate and zoledronate, and these are prescribed for patients that have developed malignancies which involve the destruction of bone. Bone undergoes constant turnover. Homeostasis of the tissue is maintained by the activity of osteoblasts, which create bone, and osteoclasts, which destroy bone. Bisphosphonates inhibit the destruction of bone by reducing osteoclast activities and stimulating these cells to undergo apoptosis. The therapeutic effect of osteoclast inhibition is to slow the malignant destruction of the affected bone, which results in alleviation of pain and improvement of quality of life. Recent examples of clinical research utilizing bisphosphonate drugs for the treatment of veterinary cancer patients include the use of pamidronate in the management of canine appendicular osteosarcoma and zoledronate for treatment of oral squamous cell carcinoma in cats.

Genome Instability and Mutation

In an established neoplasm, mutations have evolved to circumvent effective cell cycle checkpoints and DNA repair mechanisms. This allows the tumor to reproduce in a state of genetic instability, further driving an aggressive phenotype. In veterinary oncology, such genetic instability has recently been studied in canine mammary tumors, where variable rates of microsatellite sequence aberrations were documented among the mammary cancer samples.

A given population of tumor cells is heterogenous by nature, with variable distributions of genetic mutations and phenotypic manifestations of these abnormalities. Genetic and pathologic evaluations of tumors with the same clinical diagnosis exhibit intertumoral heterogeneity due to multiple mutations in oncogenes and tumor suppressor genes, varying environmental conditions, and inherited germline variations. The combination of these factors leads to immense natural heterogeneity in tumor phenotypes, disease outcomes, and response to therapies. The development of new molecular biological tools has expanded the understanding of genetics and the pathophysiology of tumorigenesis.

Gene expression profiling with the use of microarray technology has greatly improved our ability to classify tumors by generating unique molecular fingerprints that have delineated tumor subtypes. DNA microarray technology allows the study of gene activity and gene function at the genome level as a means to analyze the molecular phenotypes and clinical heterogeneity of tumors. The emergence of genome sequences for a variety of veterinary species has allowed for the development of new microarray-based technologies that facilitate whole genome, or gene-targeted, profiling to be performed at a considerably higher resolution and throughput.

The use of microarray-based technology in the veterinary field has become more prevalent. Recently, the utility of gene expression analysis using a cDNA microarray to differentiate metastatic and nonmetastatic soft tissue sarcomas in dogs was investigated. Further, microarray technology was used to characterize the gene expression profile of tumors in a population of dogs with soft tissue sarcomas being treated with radiation therapy and hyperthermia to predict therapeutic response. Comparisons were made between the gene changes that occurred, tumor volume, and functional MRI parameters. Significant correlations were identified between tumor responses and genes involved in telomerase activity, DNA repair, inflammation, and growth factor signaling. In this cohort of canine sarcomas, the gene expression of tumors was affected significantly, but not uniformly, by the combination of radiation and hyperthermia.

Tumor Promoting Inflammation

While it is important to understand the cellular characteristics of a tumor, we must consider that the cells exist in a complex microenvironment. Tumor cells are intimately associated with supporting stromal cells, immune cells, and microvasculature. Solid tumors exist in a state of active inflammation, and conventional cancer therapy can both promote and reduce inflammation. Tumor tissue reacts as a unit to therapeutic interventions; however, responses to treatments are not limited to the neoplasm. There are unique localized and systemic responses to chemotherapy, radiation therapy, and other

treatments that can result in transient or chronic effects. Clinical examples of local and systemic inflammatory reactions to oncologic treatments in veterinary medicine would include localized oral mucositis within the radiation field and generalized intestinal inflammation with certain chemotherapeutic agents, respectively.

The association between chronic inflammation and neoplasia is well established. Some recent interesting examples of chronic inflammatory lesions that progress to cancer in veterinary medicine include biliary tract trematode infection leading to cholangiocarcinoma in cats, superficial corneal squamous cell carcinoma occurring in dogs with chronic keratitis, and traumatic or surgical fracture-associated osteosarcoma development in dogs.

A nonspecific and complex host response to inflammation that has been investigated for its potential use as a prognostic and monitoring tool is the formation of acute phase proteins (APP). APPs are induced by proinflammatory cytokines, and tumor cells produce large amounts of transforming growth factor beta, cytokines including interleukins 6 and 10, and prostaglandin E2. Veterinary studies evaluating the use of APPs include trials with canine and feline lymphoma, canine mammary carcinoma, mast cell tumors, soft tissue sarcoma, and combinations of tumor-bearing dogs and cats.

A targeted approach to inhibiting the inflammatory component of cancer that is commonly used in veterinary oncology is the use of cyclooxygenase (COX) inhibitors, specifically those that inhibit the enzyme COX-2. Overexpression of COX-2 in tumors drives many cancer-associated mechanisms and COX-2 inhibitors are prescribed to prevent or reduce the neoplastic proinflammatory state. The effects of the COX-inhibitor piroxicam have been evaluated in the treatment of canine urinary bladder transitional cell carcinoma, as well as canine oral malignant melanoma, inflammatory mammary carcinoma, prostatic carcinoma, and oral squamous cell carcinoma.

Avoiding Immune Destruction

Cancer develops in the host through deception of the immune system. The roles of the immune cells are defined by their involvement in either innate or adaptive immunity. Cells of the innate pathway include phagocytic, antigen-presenting cells (APC), such as macrophages and dendritic cells, and those of the adaptive pathway consisting of cells with randomly generated antigen receptors, like B and T lymphocytes. Generally, APCs are activated by immunogenic stimuli, migrate to lymphoid organs to present antigen to T cells, and stimulate the adaptive immune response.

The function of effector T cells and APCs can be disrupted by a T lymphocyte type, known as regulatory T cell (Treg). Treg cells are important for immune tolerance through downregulation of self-reactive lymphocytes; however, suppression of antitumor immune responses by Tregs can promote tumor progression and development. Large populations of Tregs have been shown to be present in various human cancers and to correlate with poor prognosis. The involvement of Tregs in veterinary oncology has been investigated in a number of different canine tumor types. In these studies, the numbers of Treg cells in the peripheral blood and tumor-draining lymph nodes were increased in dogs with cancer compared to healthy dogs. Further, Treg cell infiltration was statistically correlated with high histologic grade in canine mammary carcinoma.

Many therapeutic approaches have been developed that utilize the immune system to target and treat cancer, and these techniques have been explored in veterinary oncology. Nonspecific tumor immunotherapies, including biologic response modifiers, such as bacterial strains, oncolytic viruses, and recombinant cytokines, growth factors, and hormones, have been used to treat several veterinary malignancies. Also, specific targeted immunotherapies, such as cancer vaccines, where the immune system detects tumors through tumor-associated antigens, have been utilized for veterinary patients. Clinical examples of veterinary cancer vaccines include the xenogeneic DNA vaccine for canine melanoma and the autologous tumor RNA-loaded, activated B cell vaccine for canine lymphoma.

Inducing Angiogenesis

Tumor vasculature is unique and abnormal. In order for a developing solid tumor to grow into a macroscopic mass, it must induce the surrounding normal tissue to either share its oxygen and nutrient supply or create its own vascular network. The processes by which a tumor forms new blood vessels, known as vasculogenesis, and/or remodels existing vasculature, known as angiogenesis, involve highly integrated signaling and communication between cells of the microenvironment. Tumors stimulate persistent angiogenesis through expression of many factors, one of the most important being the family of vascular endothelial growth factor (VEGF) proteins.

Vascular endothelial growth factor is a growth factor and its signal is transmitted through the tyrosine kinase activity of transmembrane VEGF receptors. Most cancer cells and certain tumor stromal cells express VEGF, and stimulation of VEGF leads to endothelial cell proliferation, migration, and survival. In veterinary oncology, VEGF expression has been recognized as a negative

prognostic marker for a number of tumors, such as canine intracranial meningiomas, osteosarcoma, lymphoma, oral malignant melanoma, and feline invasive mammary carcinoma.

Abnormal tumor vessel morphology includes aberrant architecture and function of blood vessels which often leads to low oxygenation within the tumor, known as intratumoral hypoxia. Tumor hypoxia may stimulate angiogenesis through expression of the transcription factor hypoxia inducible factor-1 (HIF-1). HIF-1 induces several proangiogenic factors such as VEGF. Hypoxic regions within tumors are a significant issue in radiation therapy because hypoxic cells are more resistant than oxygenated cells to treatment. Hypoxic cells are also more resistant to chemotherapy as hypoxic cells are farther from the vasculature and may not be exposed to lethal drug concentrations. Importantly, hypoxia may increase the biologic aggressiveness of a tumor by HIF-1 activation of several neoplastic pathways.

Targeted therapeutic approaches have been developed recently which are intended to disrupt tumor angiogenesis. The use of continuous, low-dose chemotherapy is commonly referred to as "metronomic chemotherapy." Three aspects of angiogenesis that are affected by metronomic chemotherapy are direct cytotoxic effects on the endothelial cells of the tumor blood vessels indirect effect of tipping the influence from proangiogeneic growth factors to inhibitors, thus preventing further vessel expansion, and reducing the recruitment of bone marrow-derived endothelial progenitor cells. The efficacy of metronomic chemotherapy protocols has been studied in veterinary oncology through clinical trials with canine patients treated for splenic hemangiosarcoma and soft tissue sarcoma with the drug combination of cyclophosphamide and piroxicam.

Sustaining Proliferative Signaling

In normal tissues, growth factors regulate cellular proliferation and differentiation. Cancer cells, however, develop a reduced requirement for exogenous growth factors as they become capable of autonomous activation of autocrine and paracrine growth pathways. As the goals for cancer therapy include tumor regression and eradication, this aberrant proliferation must be inhibited to prevent resistance and recurrence.

Some of the key proteins regulating cell survival and proliferation are the transmembrane epidermal growth factor receptor (EGFR) and ligand epidermal growth factor (EGF). EGFR is overexpressed in many tumor types and is associated with aggressiveness and resistance to therapies. EGFR and EGF have been studied in veterinary medicine as potential prognostic indicators and possible therapeutic targets in canine mammary cancer, glial brain tumors, nasal carcinomas, and feline oral squamous cell carcinoma.

Epidermal growth factor receptor belongs to a group of proteins that form the receptor tyrosine kinase (RTK) superfamily. Tyrosine kinases are transmembrane receptors that regulate normal cell signal transduction and maintain cell growth and differentiation. Additional examples of receptor tyrosine kinases include Kit, Met, VEGFR, PDGFR, and FGFR. RTKs are commonly abnormally activated and dysregulated in human and veterinary cancer. For instance, Kit is a receptor found on mast cells, and mutations to Kit in canine mast cell tumors (MCTs) have been shown to drive unregulated proliferative signaling. Up to 30% of all canine MCTs are affected with Kit mutations, and these have been shown to be significantly associated with tumor grade, as the more malignant tumors are more likely to have abnormal Kit receptors. Further, canine gastrointestinal stromal tumors (GIST) have also been characterized as carrying Kit mutations.

Recently, a variety of small molecule inhibitors that target tyrosine kinases, known as tyrosine kinase inhibitors (TKIs), have been approved for the treatment of human cancer. The use of these inhibitors has resulted in significant clinical efficacy, being used as sole therapeutics or in combination therapy protocols. Importantly, TKIs have now been incorporated into veterinary oncology care. Examples of these drugs include Palladia™ (toceranib), and Gleevec® (imatinib). Gleevec has been used to treat cancers in dogs and cats, and Palladia has undergone registrational studies in dogs with MCTs. The molecular targets inhibited by these drugs consist of Kit, VEGF, and PDGFR and they have been used to treat MCTs and sarcomas in dogs and cats, as well as carcinomas, melanoma, and myeloma in dogs.

Deregulating Cellular Energetics

It has been discussed with the preceding hallmarks that tumors adapt and proliferate despite harsh conditions of inflammatory stress and disorganized, ineffective microcirculation. The tumor microenvironment is not only characterized by varying degrees of hypoxia, but also nutrient deprivation and low extracellular pH. The unusual metabolism of cancer cells is intimately involved in creating such an abnormal physiologic state.

Normal tissues are able to sustain routine cellular functions through the oxidation of nutrients to provide energy in the form of adenosine triphosphate (ATP). Glucose metabolism is regulated in response to changes in cellular oxygen levels. Initially, glucose is converted to

pyruvate by glycolytic enzymes. Under well-oxygenated conditions, pyruvate is oxidized in the tricarboxylic acid cycle to form water and a substantial amount of ATP (oxidative phosphorylation); however, under hypoxic conditions, lactate dehydrogenase A converts pyruvate to lactate and generates very little ATP (glycolysis).

It has been shown that glycolysis, under aerobic conditions, is particularly high in aggressive tumors when compared with benign tumors and normal tissues. This discovery of tumor-specific, oxygen-independent glycolysis was labeled the Warburg effect. This peculiar metabolic preference of tumor cells drives a significantly inefficient breakdown of glucose for ATP and creates an acidic microenvironment through the build-up of the byproduct lactic acid.

The increased dependence of cancer cells on the glycolytic pathway provides a biochemical basis for the functional imaging technique positron emission tomography (PET). PET imaging has become increasingly invaluable in human and veterinary oncology. Using the glucose analog fluorine-18-fluorodeoxyglucose (^{18}FDG), the detection of glucose metabolism with PET is associated with the presence of malignant tissue before anatomic evidence occurs. While traditional methods for determining response to therapy in veterinary oncology centers on anatomic changes in measurable target lesions, ^{18}FDG-PET combined with a CT scan can be used as a sensitive marker of tumor response to anticancer therapies via interrogation of cellular glucose metabolism.

Positron emission tomography plays an important role in the diagnosis, staging, image-guided treatment planning, and monitoring of malignant diseases. A recent preliminary study described the use of serial ^{18}FDG-PET/CT to assess the response to toceranib therapy in canine cancer. Multiple types of canine tumors have been evaluated for their avidity for FDG, including mast cell tumor, lymphoma, mammary carcinoma, and hemangiosarcoma. FDG-PET has identified the involvement of metastatic sites not detected on physical examination and has been reported to provide more accurate disease detection for improved diagnosis, staging, and restaging with treatment of companion animals with cancer.

Activating Invasion and Metastasis

The final hallmark to be reviewed is invasion and metastasis, the processes of which are incredibly convoluted and intricate. The properties required to attain the phenotype of an invasive and metastatic neoplasm involve the multistep, coordinated foundation of the previously discussed hallmarks.

Experimental molecular oncology studies suggest that the progression of a solid tumor to a metastatic phenotype is not simply the result of dysregulated signal transduction pathways, but instead is achieved through a stepwise selection process. The adaptation of populations of neoplastic cells to their harsh microenvironment facilitates cancer cell dissemination through the up- or downregulation of critical metastasis-associated genes, such as E-/N-cadherin for epithelial-mesenchymal transition (EMT), uPAR for degradation of the basement membrane and extracellular matrix, HGF/MET for cell motility, and VEGF for stromal interactions, intra/extravasation, and angiogenesis. The systematic alteration of these phenotypic regulators allows cells to escape the hostile microenvironment of the primary tumor and colonize a secondary location.

The role of E-cadherin in metastasis of veterinary cancer has been investigated. E-cadherin is a transmembrane glycoprotein involved in cell-to-cell adhesions of two adjacent cells and is typically expressed by epithelial cells. Metastatic epithelial malignancies are associated with loss of E-cadherin expression and connectivity with their neighboring cells; this leads to EMT, where epithelial tumor cells obtain mesenchymal characteristics, as well as invasive and metastatic properties. In veterinary medicine, studies that have investigated E-cadherin expression have evaluated canine mammary carcinoma and anal sac gland adenocarcinoma for associations with clinical malignancy.

Dissemination of primary tumor cells to a secondary location may result in colonization of any number of anatomic locations. One of the most common metastatic sites is the first regional lymph node or nodes to which the lymphatics from the primary tumor drain; therefore, the disease status of what is known as this sentinel lymph node (SNL) is important in cancer screening. Lymphoscintigraphy, the injection of a radioactive tracer at the tumor site to identify lymphatic drainage, and intratumoral/peritumoral blue dye injection have been used to locate SNLs in veterinary oncology. The SNL can then be evaluated via histopathology for the presence of metastatic disease. In veterinary practice, lymph nodes are generally aspirated or biopsied if palpably enlarged; however, since metastases occur in lymph nodes of normal clinical appearance and in lymph nodes other than those routinely assessed according to the anatomic location of the primary tumor, this advanced technique for metastasis identification has been recommended. Reports describing SNL identification in veterinary medicine include studies investigating canine head and neck tumors and mammary carcinoma.

Conclusion

Hanahan and Weinberg's hallmarks of cancer provides an incredibly useful conceptual framework for understanding the complex biology of cancer, and it is evident that intimate associations link each. The categorical focus of these cancer principles allows the specialized refinement of molecular mechanisms; however, the appreciation that each hallmark operates as part of a greater circuit will promote discoveries that further advance the study of veterinary cancer and clinical oncology. The advancements made by veterinary researchers and clinician scientists featured in this chapter have contributed to a greater understanding of translational oncologic concepts between human and companion animal cancer patients.

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131

Endocrine Manifestations of Cancer

Ectopic Hormone Production

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Ectopic hormone production of endocrine origin from nonendocrine tumors is a particular type of paraneoplastic syndrome. Some of the more common manifestations, such as hypoglycemia and hypercalcemia, are covered in Chapter 132. Those more particular to the endocrine system are covered in this chapter.

Cushing Syndrome

Etiology/Pathophysiology

Corticotropin (also known as adrenocorticotropic hormone – ACTH) is produced by the anterior pituitary and stimulates cortisol production by the adrenal cortex. Corticotropin has been demonstrated to be produced by a variety of tumors in human medicine, resulting in a Cushing-like syndrome. Although primarily reported with small cell lung carcinoma, other tumor types include carcinoid tumors of the thymus, gastrointestinal tract, thyroid, pancreas, and adrenal medulla. Ectopic production of corticotropin is not well described in veterinary medicine, although sporadic case reports exist. It is theorized by some that ectopic corticotropin production is underestimated in animals due to diagnostic limitations. Routine pituitary imaging is not typically pursued in dogs diagnosed with Cushing disease. Therefore, dogs with ectopic production of the hormone may be assumed to be pituitary dependent and treated accordingly. Based on this assumption, ectopic corticotropin production may be more prevalent than is currently reported in the veterinary literature.

Diagnosis and Treatment

At a minimum, ectopic corticotropin production should be considered in dogs with neoplastic disorders that show concurrent symptoms of hyperadrenocorticism. The diagnosis of ectopic ACTH production is based on hormonal evidence of pituitary-dependent hyperadrenocorticism (PDH), normal to high endogenous ACTH levels, and normal pituitary imaging. Therapy for ectopic corticotropin production has not been well defined in animals, although treatment of the primary tumor should be attempted. Treatment with trilostane, an adrenal enzyme blocker, resulted in adequate resolution of symptoms in one dog.

Recently, production of sex hormone steroid precursors from adrenal cortical tumors has been identified as a source of Cushing symptoms. These animals may demonstrate typical signs of Cushing disease, including polyuria/polydipsia, polyphagia, weight gain, potbellied appearance, thin skin, and alopecia. Despite the clinical findings consistent with hyperadrenocorticism, these animals test negative for hyperadrenocorticism by conventional screening methods (ACTH stimulation, low-dose dexamethasone suppression test). However, an assay for particular cortisol precursors (such as progesterone and 17-OH-progesterone) may reveal elevated concentrations. Although this condition is classically related to the presence of an adrenal cortical tumor, cortisol precursors may be noted with pituitary-dependent disease as well. This is considered eutopic hormone production as opposed to ectopic, as the hormone produced by the tumor is a product of the tumor itself. However, as the particular hormone being produced is atypical for expected forms of hyperadrenocorticism, it is worthy of mention.

In the presence of a cortical tumor, surgical excision is generally recommended if presurgical staging allows. Abdominal ultrasonography is particularly useful to identify a tumor, local vascular invasion, and metastases. Approximately 50% of adrenal cortical tumors are malignant, and presurgical screening may identify local vascular invasion, metastatic disease to distant organs (particularly the liver), and irregularity of the affected

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gland. If surgery cannot be performed, clinical symptoms may be managed with trilostane (Vetoryl®) or op-DDD (Lysodren®). Trilostane is a competitive inhibitor of 3-beta-hydroxysteroid dehydrogenase, thereby reducing cortisol synthesis from the adrenal gland. The inhibition of steroid production is rapidly reversible and dose dependent. Effects on cortisol production will wane within 10–20 hours after cessation of the drug. Lysodren is directly cytotoxic to the cells of the zona fasciculata and zona reticularis of the adrenal cortex. As approximately 50% of cortical adrenal tumors are malignant, op-DDD is the theoretical medical therapy of choice though studies evaluating survival and disease-free interval of dogs with adrenocortical carcinoma treated with trilostane vs op-DDD are lacking.

Management of symptoms may be made easier by the use of trilostane, as the side-effects are generally found to be less severe. Lysodren may be difficult to administer in a clinically ill animal, as it causes nonselective adrenal cortical necrosis and could result in a relative hypoadrenocortical state. This could be difficult to manage in the ill patient due to the length of time needed to recover from excessive adrenal gland destruction. Trilostane, however, will have no effect on delaying the progression of metastatic disease.

Therefore, in the case of nonsurgical metastatic disease, Lysodren may be more effective at prolonging survival due to the cytotoxic effects on metastatic tissue. Trilostane has been used successfully to control clinical symptoms of Cushing disease caused by an adrenal tumor in the absence of metastases. The use of trilostane or op-DDD for the medical management of an adrenal tumor should be carefully considered by the clinician if surgery is not feasible.

Syndrome of Inappropriate Antidiuretic Hormone Secretion

Etiology/Pathophysiology

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is commonly discussed but rarely diagnosed in the small animal patient. Much more common in human medicine, SIADH is frequently diagnosed in patients with pulmonary cancer (oat cell carcinoma). Excessive production of ADH by the tumor cells results in inappropriate free water retention. This leads to one of the hallmark signs of the disorder, hyponatremia. Due to excessive volume expansion, many elements within the blood may undergo dilutional effects, such as urea nitrogen and potassium. Serum osmolality is also low, but urine osmolality may be higher than that of serum as free water is being retained by the kidneys.

Diagnosis and Treatment

The finding of a urine osmolality higher than that of serum in the face of hyponatremia is suggestive of SIADH. Careful water restriction will improve clinical symptoms while the cause is elucidated. Water restriction must be monitored closely to avoid rapid fluctuations in serum sodium concentrations. SIADH has been described rarely with tumors in dogs (such as salivary carcinoma). This condition is more common with systemic diseases, such as cholangiohepatitis, congenital hydrocephalus, and meningitis. Therefore, water restriction could lead to dehydration if the patient is clinically ill. With chronic hyponatremia, the serum sodium concentrations should not increase at a rate greater than 0.5 mEq/L/h or 8–10 mEq/day to avoid cerebral fluid shifts. Due to the paucity of reports of this disease in the veterinary literature, the prognosis is unpredictable and dependent on the underlying condition.

Erythrocytosis

Etiology/Pathophysiology

Erythrocytosis is defined as an increase in red blood cell parameters (hematocrit, red blood cell count, hemoglobin). It may also be referred to as polycythemia. This condition may be classified as relative or absolute.

A relative polycythemia is an apparent increase in red blood cell mass that is actually due to a decrease in plasma volume. This is commonly noted with dehydration and may be treated with fluid therapy to offset the reduction in plasma volume. A relative polycythemia would be expected to be associated with normal (or low) erythropoietin levels.

An absolute polycythemia may be subclassified as primary or secondary. Primary polycythemia is independent of erythropoietin influence and arises from progenitor cells within the bone marrow. The expanded red blood cell mass appears morphologically normal, and bone marrow aspiration suggests erythroid hyperplasia. Primary polycythemia is classified as a myeloproliferative disease, and is often referred to as polycythemia vera. It may rarely progress to leukemia.

An absolute polycythemia that is classified as secondary is dependent on erythropoietin influence. This may be an appropriate response, as seen with altitude changes, right-to-left cardiac shunting disorders and hereditary methemoglobin reductase deficiency. An inappropriate polycythemic response may be seen with certain tumors, especially of the kidney.

These tumors may produce erythropoietin ectopically, resulting in a paraneoplastic syndrome of erythrocytosis. Several other mechanisms have been proposed to

explain the rise in hematocrit, including decreased metabolism of erythropoietin and production of erythropoietin-stimulating hormones. Renal hypoxia due to thrombosis or tumor mass may also play a role. This condition is rarely reported with other tumors, but has been described in a dog with cecal leiomyosarcoma.

Diagnosis and Treatment

Erythrocytosis may be approached first by physical examination to assess hydration status, cardiac auscultation, abdominal palpation to screen for abdominal masses, and complete blood count (CBC)/serum chemistry. If the examination and bloodwork suggest dehydration, a fluid therapy trial should result in resolution of the polycythemia. If dehydration is not present, or if fluid therapy does not result in resolution, an absolute polycythemia is present.

In the absence of obvious causes of a secondary absolute polycythemia (including appropriate responses such as right-to-left shunting disorders and altitude changes), evaluation of serum erythropoietin levels will help to differentiate erythrocytosis secondary to a renal (or other) tumor from polycythemia vera (absolute primary polycythemia). In the latter condition, the erythrocytosis is independent of erythropoietin, and erythropoietin levels may be low to normal. The diagnosis of primary erythrocytosis (polycythemia vera) is often performed by ruling out all other causes of secondary absolute polycythemia, as erythropoietin measurements are not often available and the assay is not species specific. Bone marrow evaluation should be considered if an absolute primary erythrocytosis is suspected to rule out marrow neoplasia.

Erythrocytosis secondary to production of erythropoietin from a renal tumor or other neoplasm will demonstrate marked elevations of serum erythropoietin levels. Abdominal radiology or, preferably, ultrasonography will help to detect a neoplasm of the gastrointestinal tract or renal system. Treatment for an absolute erythrocytosis that arises as a manifestation of cancer involves identifying and removing the causative neoplasm (i.e., renal tumor, cecal tumor, etc.). Removal of the tumor will result in resolution of the polycythemia. Phlebotomy may be necessary prior to surgery to relieve symptoms of hyperviscosity and reduce risk for a vascular accident. No more than 20 mL/kg of blood or 25% of blood volume should be removed at a time. A more exact volume to be removed may be calculated by the following formula:

$$\begin{aligned}&\text{Blood to be removed}\,(\text{mL})\\&=\text{body weight}\,(\text{kg})\times\text{blood volume}\,(\text{mL/kg})\\&\times\frac{\text{actual PCV}-\text{desired PCV}}{\text{actual PCV}}\end{aligned}$$

where PCV is packed cell volume. Blood volume for dogs and cats is considered to be 90 and 70 mL/kg respectively.

If tumor removal is not feasible, periodic phlebotomy may control signs of hyperviscosity. In the case of renal tumors, surgical removal alone affects survival, and without surgical intervention the prognosis is poor. In one study evaluating surgical intervention, median survival for dogs with renal carcinoma was 16 months (range 0–59 months), for dogs with sarcomas nine months (range 0–70 months), and for dogs with nephroblastoma six months (range 0–6 months). In the same study, dogs that did not undergo surgery had a median survival of <1 month (range 0–32 months). Additionally, removal of a renal tumor results in resolution of the paraneoplastic polycythemia. For a dog with a reported cecal leiomyosarcoma, phlebotomy helped control clinical symptoms for over two years. It is important to note that fluid replacement is not generally recommended post phlebotomy. In the presence of right-to-left cardiac shunting disorders, volume replacement may be poorly tolerated by the cardiovascular system. In the presence of polycythemia vera, the animal is volume replete prior to phlebotomy.

Treatment for primary polycythemia or absolute secondary polycythemia related to an uncorrectable cause (such as a right-to-left shunt) involves a combination of phlebotomy and hydroxyurea, covered elsewhere.

Zollinger–Ellison Syndrome

Etiology/Pathophysiology

Secretion of excessive gastrin by neoplastic delta cells of the pancreas has been described (gastrinoma). Gastrin is also produced by G cells of the gastric antrum and duodenum, and continued secretion results in hyperacidity. Clinical symptoms are related to excessive production of gastric acid from the continued stimulation of gastric parietal cells. The findings of melena with a microcytic, hypochromic anemia should lead to suspicion for gastrointestinal hemorrhage. This may be accompanied by weight loss, anorexia, and/or vomiting. Dogs may present late in the course of disease, and as such cancer cachexia may be present. Additionally, gastric ulceration may be severe and may predispose to gastric perforation. Endoscopic evaluation of the stomach may reveal an ulcer, which typically is located along the lesser curvature. Although gastrinomas tend to be slow growing, approximately 85% demonstrate metastasis at the time of diagnosis.

Diagnosis

Diagnosis of a gastrinoma can be challenging. Serum gastrin levels may be evaluated, and samples should be

obtained prior to administration of gastroprotectants. Antacids such as famotidine, ranitidine, and omeprazole will artifactually raise serum gastrin levels. Abdominal ultrasonography may identify a pancreatic mass, but as is the case with insulinomas, gastrinomas are often too small to detect. Ultrasonography can be useful to screen for metastatic disease, due to the relatively high rate of metastasis with this tumor. Radioactive scanning with pentetreotide may be useful but has limited availability. Surgical exploration with or without abdominal CT may be necessary if presurgical screening does not identify a mass or obvious metastatic disease. Histopathology is required for an accurate diagnosis.

Treatment

Medical therapy alone may be employed if a patient is a poor surgical candidate. Aggressive antacid therapy is indicated. Often, the author will combine a proton pump inhibitor (such as omeprazole) with an H2 blocker (such as famotidine). In addition, sucralfate may be administered with antacids, preferably 30 minutes to an hour apart. Sucralfate should be administered first, as it reacts with hydrochloric acid to create a protective complex. Administration of an antacid prior to sucralfate may reduce its efficacy.

Motility modifiers may be necessary to control reflux and vomiting. Metoclopramide should be used with caution if a stomach ulcer is present, as it may enhance the potential for perforation. Centrally acting antiemetics, such as ondansetron or maropitant, are preferred. Finally, streptozocin has been advocated as adjunctive chemotherapy to surgical intervention, but should be used with caution due to its toxicity. The prognosis with gastrinoma is typically guarded. Paraneoplastic effects, such as gastric perforation and peritonitis, adversely affect prognosis. However, with aggressive treatment, including surgery, survival times have ranged from 4.5 to 18 months.

These above conditions are particular to ectopic hormone production resulting in endocrine manifestations. Further paraneoplastic syndromes are described elsewhere in this text.

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132

Paraneoplastic Syndromes

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Many tumors produce effects on the body that are not related to direct invasion or compression. These effects have become widely recognized as paraneoplastic syndromes. Recognition and treatment of these conditions may allow early detection of occult neoplasia, reduction of morbidity, and prolonged survival. The effects of paraneoplastic syndromes are due to the production and excretion of peptides and hormones as well as immune cross-reaction between tumor and normal cells. This chapter describes the most commonly recognized paraneoplastic syndromes and their treatment. It is important to recognize that the most effective treatment for all paraneoplastic syndromes is removal of the underlying tumor.

Hypercalcemia

Etiology/Pathophysiology

Hypercalcemia remains one of the most commonly encountered paraneoplastic syndromes in the dog and cat. Commonly termed "humoral hypercalcemia of malignancy," this condition must be differentiated from other common causes of hypercalcemia. Although it is often noted with lymphoma (particularly mediastinal lymphoma), multiple myeloma and anal sac adenocarcinoma, it may be observed with a variety of tumors. The most common mechanism resulting in hypercalcemia is release of a peptide by the tumor cells closely resembling parathyroid hormone (PTH), called parathyroid hormone-related protein (PTH-rp). PTH-rp mimics the activity of PTH by binding to PTH receptors within the renal tubule and bone. This leads to decreased calcium excretion from the kidney and increased bone resorption. Other factors involved in hypercalcemia not related to humoral hypercalcemia of malignancy include direct bone invasion resulting in increased osteolysis and production of osteoclast-activating factor by tumor cells.

Diagnosis

Initial investigation should include a thorough physical and rectal examination. Further diagnostic evaluation should include thoracic radiographs and abdominal radiographs or ultrasonography. Ultrasonography is preferred to evaluate for diffuse infiltration of abdominal organs as well as abdominal lymphadenomegaly, as these may be difficult to appreciate radiographically. Aspiration of peripheral lymph nodes may be useful, even when the lymph nodes are not clinically enlarged. Bone marrow aspiration may be considered, especially in the face of peripheral cytopenias, and additional radiographs or bone scintigraphy may be carried out based on the presence of lameness or discomfort encountered during palpation of long bones. Confirmation of an elevated calcium secondary to malignancy may be attempted by evaluating PTH, PTH-rp, and ionized calcium levels in the serum. It is important to note that the ionized calcium level is increased in patients with humoral hypercalcemia of malignancy, and this may be monitored for a more accurate assessment of bioactive calcium levels. Evaluation of PTH-rp with ionized calcium and PTH can also help differentiate humoral hypercalcemia of malignancy from other causes of hypercalcemia (i.e., renal disease, hyperparathyroidism).

Treatment

Common symptoms of hypercalcemia include polyuria/polydipsia, muscle tremors, neurologic abnormalities (including coma), renal dysfunction, and inappetence. Treatment is aimed at reducing the ionized calcium level

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as cancer therapy is ongoing. Mildly elevated total calcium levels are generally left untreated as cancer therapy is ongoing, but all treatment decisions should take into account the patient's neurologic and renal status. Total calcium levels that approach or exceed 13.5 mg/dL may benefit from saline diuresis and administration of a loop diuretic such as furosemide. Furosemide should only be administered in the volume-replete patient. Therefore, subcutaneous or intravenous saline administration may be necessary if clinical dehydration is appreciated. Glucocorticoids may reduce intestinal absorption of calcium but should only be used once a diagnosis is obtained, as they are directly cytotoxic to lymphoma and myeloma cells. Use of the drug prior to establishing a diagnosis may preclude an accurate diagnosis or require more invasive procedures to obtain an accurate diagnosis.

Finally, total calcium levels that are markedly elevated (>17 mg/dL) constitute a medical emergency and warrant hospitalization for diuresis. Administration of calcitonin may be attempted, although the effects are short-lived. Administration of calcitonin subcutaneously may be considered for a longer acting effect. Bisphosphonates (pamidronate and zoledronate) may be used for persistent hypercalcemia and bone pain. The author generally prefers pamidronate given as an intravenous infusion every 2–4 weeks. In select cases of lymphoma, a chemotherapy trial may be necessary if a diagnosis is elusive or if patient status dictates rapid intervention as laboratory tests are pending. This should be supported by clinical suspicion and after exhaustion of all available diagnostic methods. Serum should be drawn and saved prior to a chemotherapeutic trial. The author prefers L-asparaginase when this approach is necessary.

In all cases, successful treatment of the underlying neoplasm will result in resolution of the hypercalcemia, and the prognosis is dependent on the tumor type and stage. The decline in calcium can be rapid with successful treatment of lymphoma. Calcium levels may then be used as an additional tool to monitor for recurrence of the neoplasm.

Hypoglycemia

Etiology/Pathophysiology

Hypoglycemia as a paraneoplastic syndrome may be related to excessive production of insulin-like substances, direct consumption of glucose by tumor cells and decreased gluconeogenesis due to hepatic parenchymal involvement. Production of IGF-2 (acting as an insulin-like substance) has been implicated as a source of hypoglycemia in nonpancreatic neoplasms. Paraneoplastic hypoglycemia has been associated with tumors such as lymphoma, hepatocellular carcinoma and leiomyosarcoma, as well as renal tumors, mammary carcinoma, oral melanoma, multiple myeloma, splenic hemangiosarcoma, pulmonary carcinoma, and others. Glucose levels may be severely and persistently decreased (20–40 mg/dL) in many cases, and clinical symptoms are related directly to the neurologic effects of the hypoglycemia as well as the concurrent release of counterregulatory hormones such as catecholamines. Many times, the symptoms of hypoglycemia are severe and may predate the diagnosis of the causative tumor.

Common symptoms of paraneoplastic hypoglycemia include ataxia, lethargy, weakness (polyneuropathy), nervousness or collapse, hunger or anorexia, focal neurologic abnormalities, seizures, and/or coma.

Diagnosis

Discovery of a persistent hypoglycemia should lead to investigation for underlying neoplasia. Other etiologies of hypoglycemia, including hypoadrenocorticism, sepsis, congenital and acquired hepatic disorders, insulinoma, malnutrition and toxicity (such as xylitol), should also be investigated. Serum insulin levels should be evaluated in the face of hypoglycemia to assess for an insulin-secreting neoplasm. Normal or elevated insulin levels in the face of hypoglycemia is not a normal finding. Secretion of an insulin-like substance (such as IGF-2) will not be detected when measuring serum insulin levels. Therefore, insulin levels are most often useful in the diagnosis of pancreatic beta-cell neoplasia (insulinoma). Insulin concentrations should be determined on the same sample documenting hypoglycemia. Thoracic radiographs and abdominal ultrasonography are indicated to screen for a pancreatic islet cell tumor as well as intestinal, hepatic, and round cell neoplasia. Abdominal radiographs may be able to identify large intestinal or hepatic tumors. Often, islet cell neoplasms cannot be identified via ultrasonography due to their small size. In these instances, surgical exploration or contrast CT may be required.

Treatment

Treatment of this paraneoplastic syndrome involves controlling clinical symptoms of hypoglycemia as the underlying neoplasm is addressed. Often, it is difficult to obtain euglycemia in the face of extensive or metastatic neoplasia. In this situation, controlling the clinical manifestations of hypoglycemia becomes more important. Management strategies for neoplasia-related hypoglycemia are covered elsewhere.

Anemia/Thrombocytopenia

Etiology/Pathophysiology

Anemia and thrombocytopenia can be grouped together as hematologic paraneoplastic syndromes as they may occur together due to a common pathophysiology. Immune-mediated destruction due to mimicry of cell membrane-associated receptors or other immune cross-reactions tends to be the most widely accepted etiology of secondary immune-mediated hemolytic anemia (IMHA) and thrombocytopenia. Symptoms of anemia and thrombocytopenia are nonspecific to the cause and are covered elsewhere.

Diagnosis

When anemia is considered individually, it must first be determined to be regenerative or nonregenerative. A nonregenerative anemia may suggest bone marrow involvement, especially in conjunction with other cytopenias. Bone marrow disease must be differentiated from an acute anemia in which a regenerative response has not yet had time to develop. Typically, it will take an average of 3–5 days to develop a moderate regenerative response, depending on how suddenly the anemia developed and the degree of anemia. Additionally, clinical signs of anemia tend to be more severe the more acute the onset, as the body has time to adapt to a chronically developing anemia.

A bone marrow biopsy and/or aspirate should be considered in the face of a chronic, nonregenerative anemia. The author prefers to begin with a bone marrow aspirate. If the aspirate is productive, a slide may be reviewed to assess for cellularity. Bone marrow infiltration due to lymphoma or myeloma tends to be highly cellular, and assuming bone marrow elements are observed in a cellular sample, an aspirate may suffice. If the aspirate is nonproductive (i.e., a "dry" tap), a bone marrow biopsy may be obtained. A biopsy may be necessary to obtain a diagnosis of myelofibrosis or other chronically progressive bone marrow disorders. With these chronic conditions, bone marrow elements are replaced by fibrosis and the aspirate may be hemodilute or completely nonproductive.

As most animals present with a moderate to severe anemia, these procedures are generally performed shortly after a component blood transfusion to improve the candidacy for anesthesia. It is important to remember that if a bone marrow aspirate or biopsy is deemed necessary, it should be obtained before or within 12 hours of beginning steroid therapy. Steroids, including prednisone and dexamethasone, are directly cytotoxic to lymphoma and myeloma cells. These are two of the more common cancers that may infiltrate the bone marrow. Thrombocytopenia is not a contraindication to bone marrow sampling, as the associated hemorrhage typically results in an autotransfusion into the marrow, thereby remaining clinically silent. Prolonged external pressure to the incision site within the skin may be necessary, however.

Classically, pancytopenia will develop with a leukopenia followed by thrombocytopenia. Anemia will develop last due to the longer half-life of red blood cells in relation to platelets and white blood cells. This may not be the case in clinical practice, as multiple factors affect the production and destruction of all bone marrow elements. It is not uncommon to encounter myelophthisis in the face of thrombocytopenia alone, and any combination of cytopenias should raise suspicion for bone marrow involvement.

If the anemia is determined to be regenerative, bone marrow sampling is typically not necessary. Red blood cell morphology may identify clues as to the source of the anemia. A morphology review by an experienced pathologist or lab technician should be obtained. Specifically, immune-mediated disease may be confirmed by the presence of a moderate to large amount of spherocytes. Spherocytes are red blood cells that have undergone a loss of membrane due to removal of antigen–antibody complexes by the phagocytic portion of the immune system. This results in a loss of surface area with retention of volume. The consequence of this is the red blood cell changing its morphology from a biconcave disc to a sphere, resulting in the term "spherocyte." Immune-mediated hemolytic anemia may also be diagnosed by identifying gross or microscopic autoagglutination. In the absence of a significant number of spherocytes or detectable autoagglutination, a Coombs test may be performed to identify an immune component to the anemia. In the presence of visibly detectable autoagglutination, a Coombs test is not necessary.

A schistocyte is a red blood cell fragment that may develop due to shearing forces. These fragments do not have a central pallor and are irregular. Schistocytes may be noted in IMHA, but they are most commonly recognized as a consequence of hemangiosarcoma. Red blood cells may be damaged as they travel through the smaller blood vessels and fibrin strands of the tumor, and as such schistocytes should prompt evaluation for an underlying vascular neoplasm. Anemia due to damage to red blood cells as they travel through the smaller capillary beds is often termed microangiopathic anemia. Microangiopathic anemia may be seen with any hypercoagulable disease, and should also alert the clinician to the potential for thrombosis. Fibrin strands and smaller blood clots may be noted with hyperadrenocorticism, pancreatitis and other nonneoplastic disorders, and these may all result in a microangiopathic anemia.

Anemia may result from nonparaneoplastic disorders, such as gastrointestinal blood loss, iron sequestration, and medication. Thrombocytopenia may also be present due to increased utilization, poor bone marrow production and immune-mediated destruction that is unrelated to a neoplastic disorder. The presence of these hematologic disorders should prompt the evaluation of a paraneoplastic disease if the clinical history, signalment, and physical examination are suggestive. As a paraneoplastic syndrome, thrombocytopenia tends to develop due to immune-mediated destruction from mechanisms similar to the development of IMHA, or increased consumption due to large tumors such as hemangiosarcoma.

Treatment

Treatment of secondary IMHA and immune-mediated thrombocytopenia (ITP) is similar to that of primary IMHA, with attention to dealing with the underlying cause. Immune suppression with prednisone is indicated once a diagnosis is established, and may be effective at controlling the anemia as cancer therapy is ongoing. A wide dose range is reported for these disorders (1–4 mg/kg/day), and the author prefers 0.5–1 mg/kg of prednisone twice daily, or 0.3 mg/kg dexamethasone sodium phosphate IV twice daily. A higher dose may be used if steroids are to be employed as sole therapy. Antithrombotic therapy may be initiated with low-dose aspirin, unfractionated heparin or clopidrogel. It should be noted that the use of low-dose aspirin (0.5 mg/kg by mouth once daily) in the dog is considered safe in conjunction with immune suppressive doses of prednisone or dexamethasone. This is the author's treatment of choice in the dog. For cats, the author recommends one-quarter of a 75 mg tablet (18.75 mg) of clopidrogel by mouth once daily. The use of heparin is considered more effective at preventing thrombi, versus preventing the progression of a clot as with aspirin. However, monitoring of heparin therapy is difficult and often expensive. Heparin use should be considered if monitoring is available and feasible. Component blood therapy may be necessary with either disorder, and should be tailored to the patient. Platelet transfusions have typically been found to be ineffective at long-term management of ITP, but they may play a role in preventing active bleeding. This may be important if intracranial hemorrhage is suspected.

Gastrointestinal hemorrhage may result in significant and refractory anemia, especially in the face of thrombocytopenia. This is an unfortunate negative prognostic indicator with ITP and should be differentiated from gastrointestinal ulceration. In the latter scenario, gastroprotectants should be instituted, and any medication that may result in ulceration should be reduced or discontinued if possible. The majority of gastric ulcers will develop due to medication or neoplasia, so if the clinical history does not identify an offending medication, cancer should become a primary differential. More specific therapy for primary IMHA and ITP is covered elsewhere.

Hypertrophic Osteopathy

Etiology/Pathophysiology

Hypertrophic osteopathy (HO) is an uncommon paraneoplastic syndrome. The pathophysiology is unclear, but afferent neurologic stimulation may alter blood flow to long bones. This is supported by case reports demonstrating resolution of lesions following vagotomy. HO is most commonly noted with pulmonary lesions including heartworm disease, but has been reported with nonthoracic neoplasia as well, including transitional cell carcinoma and adrenocortical carcinoma. Typical findings include periostosis and subperiosteal new bone formation along the shafts of long bones. This condition is frequently painful. Affected limbs may be warm and swollen, and radiographs will typically demonstrate the common features of the disorder. Finding radiographic evidence of HO should prompt radiographic evaluation of the thorax. Abdominal ultrasonography may be considered if pulmonary lesions are not identified.

Treatment and Prognosis

Treatment is directed at removal of the underlying neoplasm. Vagotomy has been described but is not typically performed as the primary treatment is to address the underlying etiology. If the neoplasm cannot be treated, pain management must be addressed. Opiates, nonsteroidal medication, steroids, and bisphosphonates have been used alone or in combination to control discomfort. Localized palliative radiation has been described but is not typically recommended due to lack of supportive evidence. If tumor removal is successful, HO lesions may persist for several weeks and require continued pain management during this time. The lesions should resolve given time if a thoracic neoplasm is successfully removed.

Myasthenia Gravis

Etiology/Pathophysiology

Myasthenia gravis is an immune-mediated condition that develops from production of antibodies to nicotinic acetylcholine receptors located on the postsynaptic neuromuscular junction. This prevents neurogenic signal transduction, leading to the hallmark signs of episodic weakness, exercise intolerance, megaesophagus,

and regurgitation. Aspiration pneumonia is a common complication of frequent regurgitation and may result in respiratory symptoms. This paraneoplastic syndrome is most commonly related to the presence of thymoma.

Myasthenia gravis may be focal, generalized or fulminant. As a paraneoplastic syndrome, a generalized form is typically encountered. This type of myasthenia affects skeletal muscle of the limbs, resulting in the aforementioned clinical signs. Ocular muscles may be affected, resulting in a fatigue to repeated palpebral reflexes. Myasthenia may be suspected based on clinical symptoms, and confirmed by evaluated serum levels of anticholinergic receptor antibodies. Administration of edrophonium chloride ("Tensilon test") may provide presumptive support for myasthenia gravis as serum titers are pending. Both focal myasthenia and generalized myasthenia result in megaesophagus, which is easily demonstrated radiographically.

Treatment

Treatment of thymoma can result in resolution of myasthenia, but at times the megaesophagus may be persistent. The reason for this is not known. Anticholinesterase medication, such as oral pyridostigmine or injectable neostigmine, may help ameliorate clinical symptoms. It is important to note that injectable medication may be necessary if severe megaesophagus with frequent regurgitation is present. Alternatively, many dogs may be managed well with a supplemental gastrostomy tube. This can allow delivery of medication and supplemental nutrition into the stomach, thereby circumventing the esophagus altogether. Gastrostomy tubes do not reduce the overall frequency of regurgitation or the risk for aspiration pneumonia, however. Food should be delivered in a standing position, and consistency of the food should be experimented with. Some dogs will tolerate food in a meatball, some as a slurry, and others in a gelatin. Use of a Bailey chair, which encourages an upright position during feeding, may be considered as well. If possible, the dog should be taken for a short walk after each feeding.

Superficial Necrolytic Dermatitis

Etiology/Pathophysiology

Superficial necrolytic dermatitis (SND, or hepatocutaneous syndrome) is a condition characterized by erythema, alopecia, and crusts involving the eyes, nose/muzzle, and extremities. A typical feature of this disorder is hyperkeratosis of the footpads with central necrosis affecting one or multiple pads. Often, the footpads may be so painful that the animal will refuse to walk. The disease has been noted commonly with chronic hepatic disorders as well as chronic administration of large doses of phenobarbital. As a paraneoplastic syndrome, SND may be noted with glucagonoma. In the author's experience, chronic and fibrotic liver disease is the most common disorder associated with SND.

Diagnosis

The finding of footpad hyperkeratosis with or without concurrent clinical findings should prompt abdominal ultrasonography to evaluate the pancreas and liver. An experienced ultrasonographer should be used to evaluate the pancreas for a mass. The liver may have a typical "Swiss cheese" appearance. A liver biopsy may be diagnostic but may need to be obtained via laparoscopy or laparotomy due to hemorrhage risk. Animals with a glucagonoma may have symptoms of diabetes, including polyuria/polydipsia and weight loss (for further information refer to Chapter 144). A poor appetite is often associated with chronic liver disease. Measurement of glucagon levels may be undertaken but the test is not always available, and glucagon levels are not always elevated in the face of a glucagonoma. SND is often associated with a hypercatabolic state which may be manifested with a hypoalbuminemia and/or hypoproteinemia. An amino acid profile may reveal significant reductions in serum amino acids, helping to confirm the diagnosis. Skin biopsy may be characteristic if lesions are present.

Treatment

Treatment is aimed at the underlying cause. Surgical resection of a glucagonoma is best if feasible. With chronic liver disease or nonresectable neoplasia, administration of intravenous amino acids will often help skin lesions to resolve. This may help to reduce discomfort. 10% Aminosyn® (or an equivalent solution) must be administered via a central catheter and over 8–12 hours due to its hypertonicity. It is typically administered weekly until skin lesions resolve.

Skin and footpad lesions should be kept clean and dry. A high-protein diet may be prescribed with supplementation of egg whites or protein powder. Broad-spectrum antibiotics may be administered to control secondary infections, and analgesics may be necessary if discomfort is present. Zinc, omega-3 fatty acids, and niacin have all been suggested as adjunct therapies. These may be difficult to administer in the face of a poor appetite and are considered supplemental therapy.

Paraneoplastic Alopecia

Paraneoplastic alopecia is described in cats affected by pancreatic carcinoma. It may occasionally be seen with hepatic or biliary carcinomas, and is characterized by a

noninflammatory alopecia. Hair may be epilated in clumps, and the underlying skin is often thin and glistening. Affected areas may include the ventral abdomen, thorax, limbs, pinnae, and periorbital region. The cause is unknown, but theorized to be secondary to cytokine production by the tumor resulting in follicular atrophy. Most cats present systemically ill, as the skin lesions typically develop at a later stage of the disease process. Metastases may be present within the liver and/or lungs, and diagnosis may be achieved through imaging (including abdominal ultrasound, abdominal/thoracic CT, and/or thoracic radiographs) and appropriate tissue sampling.

Conclusion

Paraneoplastic syndromes are diverse in their presentation and severity. In fact, many other paraneoplastic conditions exist that are beyond the scope of this text. These include thymoma-related exfoliative dermatitis, peripheral neuropathies, nodular dermatofibrosis, and paraneoplastic pemphigus. Other conditions, such as fever and cachexia, are often considered paraneoplastic but are not specific or unique in their presentation. Prompt identification and treatment of these conditions will aid the clinician in additional diagnoses, maintain patient comfort, and prevent life-threatening sequelae as cancer therapy is ongoing.

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133

Lymphoid Leukemias, Myeloid Neoplasia, and Myelodysplastic Syndrome

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Lymphoid Leukemias

Etiology/Pathophysiology

Lymphoid leukemias are differentiated as either chronic lymphocytic leukemia (CLL) or acute lymphoblastic leukemia (ALL). CLL is a clonal, neoplastic proliferation of small, mature-looking lymphocytes that manifests as a persistent, often severe lymphocytosis. Three subsets have been recognized based on immunophenotyping. The most common is granular T-CLL which consists of proliferations of cytotoxic (CD8+) T cells. Despite conventional thinking that CLL is always a primary bone marrow disease, granular T-CLL is considered a primary splenic disease which can be verified by expression of a marker for splenic red pulp (CD11d). The second is B-CLL (CD21+, CD79a+) and the third is nongranular/atypical T-CLL (CD3+) in which no consistent pattern of concurrent CD4 or CD8 expression is found. ALL is defined by proliferation of immature lymphoblasts in the bone marrow or peripheral blood. The immunophenotype of ALL is typically B cell (CD21+, CD3-, CD4-, CD8-) with an acute, immature lineage based on expression of CD34, a stem cell marker.

Classification of lymphocytes involves assessment of cell surface antigen (marker) expression that pertains to both lineage and function. This classification is usually performed by immunophenotyping. Immunophenotyping consists of the application of antibodies specific for differentiation antigens of lymphocytes and other immune cells to identify lineages of these cells present in neoplastic or reactive diseases. Immunophenotyping can be performed on cytology smears, blood smears, fluids (blood or bone marrow), formalin-fixed paraffin sections or snap-frozen tissue sections. Immunophenotyping tests include immunohistochemistry (on tissue samples), immunocytochemistry (on cytologic or fluid samples), and flow cytometry in which cell suspensions are stained with specific fluorochromes, analyzed by a focused laser beam and sorted by size and DNA content (ploidy of cells). Immunophenotyping can identify the presence of different blood cell lineages but cannot predict clonality (whether a population arises from a single cell).

It is important to know normal percentages of lymphocyte subsets found in the peripheral blood of dogs and cats to be able to distinguish a benign or reactive process from a malignant one. In general, peripheral lymphocytes of dogs consist of ~80% T cells (CD3+ or CD5+) with 45% being helper T cells (CD4+), 25% being cytotoxic T cells (CD8+) and the remainder being double-negative T cells (CD4-, CD8-). Approximately 15% are B lymphocytes (CD21+) and the remaining lymphocytes are natural killer (NK) cells. Cats are very similar but have slightly fewer T cells (~75%) and a greater percentage of B cells (~25%) in the peripheral blood.

The etiology of lymphoid leukemias is largely unknown. In people, there is no known association with radiation, chemicals or alkylating agents and no viral cause. Genetic factors are suspected in both humans and dogs but immunophenotype of the neoplastic cells in these species is different in that most human lymphoid leukemias are B cell in origin. Therefore, it is unwise to try to make direct correlations between species since different causative factors may be involved. In cats, retroviruses such as feline leukemia virus (FeLV) play a role since ~60–80% of cats with ALL are FeLV+. There is no known association between FeLV and CLL in cats and no evidence of a retroviral cause in dogs.

Epidemiology

In people, CLL is an indolent disease of older adults (>60 years of age) and accounts for 25–30% of all adult leukemias among white populations in North America and

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Western Europe. Ninety-five percent of CLL in people are B cell in origin. ALL is most common in young children (peak between 2 and 5 years) with a second peak in aged populations and is most commonly B cell. The true incidence of lymphocytic leukemias in animals is unknown. CLL is thought to be less common than ALL but more common than myeloproliferative disorders.

Signalment

In the dog, both ALL and CLL are most commonly seen in middle-aged to older animals with a median age of 10 years. No sex predilection has been found. Golden retrievers and German shepherds are overrepresented in CLL. CLL is rare in cats but seems to occur in elderly cats with a mean age of 14 years. Cats with ALL are usually young and FeLV positive.

History and Clinical Signs

Most CLL animals are asymptomatic and the diagnosis is incidental. When clinical signs are present, they are generally attributable to the degree of lymphocytosis, bone marrow involvement or other organ involvement and may include lethargy, inappetence, and weight loss. Physical exam may show hepatosplenomegaly and mildly enlarged peripheral lymph nodes. Clinical signs of ALL patients are similar to CLL although they are typically more severe. On physical exam, splenomegaly is the most common finding but hepatomegaly and lymphadenopathy can also be present. Signs of life-threatening cytopenias such as pale mucous membranes, pyrexia, and/or petechial hemorrhages are also possible.

Diagnosis

Diagnosis of CLL is commonly made by examination of the peripheral blood and bone marrow by a clinical pathologist. A complete blood count (CBC) generally reveals an absolute mild to marked lymphocytosis (6000 to >100 000 lymphocytes/μL) and cytologically the nuclei appear small and mature with condensed chromatin (Figure 133.1).

Other common hematologic findings include a mild normochromic, normocytic, nonregenerative anemia, a mild thrombocytopenia (>100 000/μL), and rarely neutropenia. The hematologic abnormalities associated with feline CLL have not been well characterized although they are thought to be similar to dogs. A monoclonal gammopathy or hyperglobulinemia in cats has been reported but is uncommon since most CLL are T cell in origin. Bone marrow aspirates show a significant proliferation of small mature lymphocytes (usually >30%) except in granular T-CLL which demonstrates a marked splenic proliferation or infiltration of granular lymphocytes with minimal bone marrow involvement. Other staging tests commonly recommended include thoracic radiographs, abdominal ultrasound, and subsequent aspirate and cytology of any enlarged organ. Immunophenotyping of blood, bone marrow or cytology samples generally reveals the presence of a T cell lymphocyte population with no evidence of CD34 expression (early hematopoietic stem cell marker), confirming the maturity of the lymphocytes in question. The presence of 30% or more lymphoblasts in the bone marrow is considered diagnostic for ALL. Lymphoblasts are intermediate-to-large sized lymphocytes with moderate amounts of basophilic cytoplasm. Lymphoblasts are larger than neutrophils, have a condensed nuclear chromatin pattern, and have a high nuclear to cytoplasmic ratio (Figure 133.2).

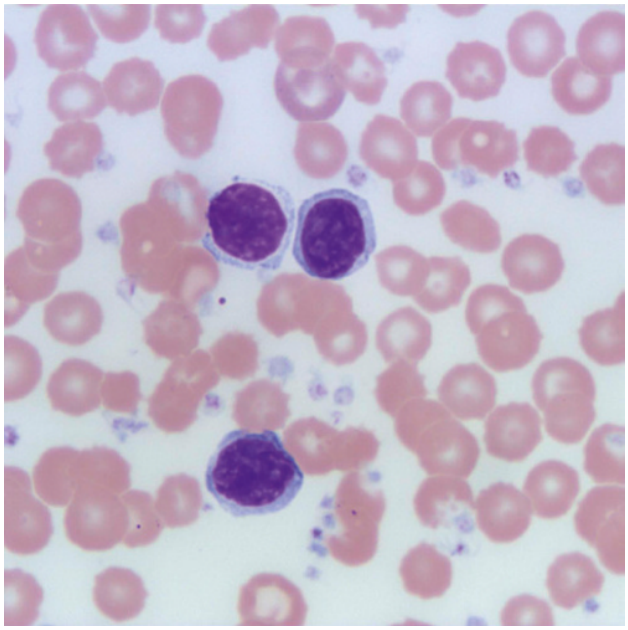


Figure 133.1 Photomicrograph of lymphocytes in the peripheral blood of a dog that has CLL. The lymphoid morphology is predominantly small and well differentiated. Wright Giemsa stain, 1000× magnification. *Source:* Courtesy of Dr Jan Andrews, Antech Diagnostics.

Staging tests recommended for ALL are similar to CLL; however, one of the principal goals is to differentiate ALL from stage V lymphoma by degree of blood and bone marrow involvement, lack of significant lymphadenopathy and, most importantly, its immunophenotypic characteristics. Patients with stage V lymphoma can have a better prognosis since their disease does not originate in the bone marrow. Immunophenotyping, especially flow cytometry, can be very useful in these cases because ALL patients will be CD34+, confirming an early hematopoietic origin. Both stage V lymphoma and CLL patients will be negative for this marker.

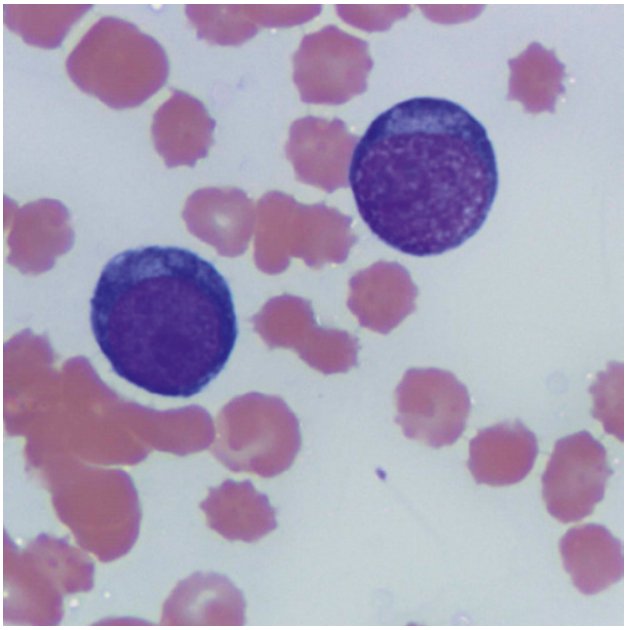


Figure 133.2 Photomicrograph of lymphoblasts in the peripheral blood of a dog with ALL. The cells are characterized by large size with prominent nucleoli. Wright Giemsa stain, 1000× magnification. *Source:* Courtesy of Dr Jan Andrews, Antech Diagnostics.

Other causes of a lymphocytosis (chronic ehrlichiosis, Rocky Mountain spotted fever, and severe babesiosis in dogs; feline immunodeficiency virus [FIV], *Toxoplasma gondii*, and chronic inflammatory bowel disease in cats) should be ruled out if lymphocytic leukemia is not an obvious conclusion.

Therapy

Chronic lymphocytic leukemia can have a protracted clinical course and treatment is not usually instituted until specific criteria are met: the presence of peripheral cytopenias (anemia, thrombocytopenia and/or neutropenia), clinical signs associated with the disease, peripheral lymphadenopathy, organomegaly, and/or a peripheral lymphocytosis of >60 000 (although this is not standardized). The standard treatment for CLL is a combination of the oral alkylating agent chlorambucil and prednisone. The dose and frequency of chlorambucil can vary. In dogs it is typically given orally at 0.2 mg/kg or 6 mg/m^2 orally once daily for 7–14 days, then reduced to 0.1 mg/kg or 3 mg/m^2 every other day thereafter. In cats, 2 mg/cat every 48 hours is commonly used. Oral prednisone is used concurrently with chlorambucil at 1 mg/kg daily for 1–2 weeks, then 0.5 mg/kg every other day thereafter. In cats, 10 mg/cat every 24 hours is commonly used. The addition of vincristine or the substitution of cyclophosphamide for chlorambucil has been used in nonresponsive patients. Treatment of ALL requires aggressive chemotherapy; CHOP-based therapies like those used in lymphoma are the most common protocols. Remission rates of 25% have been reported but remission times tend to be short.

Prognosis

Chronic lymphocytic leukemia is a slowly progressive disease and many patients are monitored for months before any therapy is instituted. Remission rates with treatment are ~70–75% with overall survival times of >1 year. Immunophenotype has been shown to be predictive with survival times for dogs with granular T-CLL, B-CLL, and atypical CLL of 930, 480, and 22 days respectively. Although the prognosis is good in the short term, ultimately, CLL patients can experience an acute blast crisis in which lymphoblasts replace mature lymphocytes (ALL) and response to aggressive treatment is poor. Prognosis for dogs and cats with ALL is very poor. Median survival times of 3–128 days have been reported in ALL dogs with a CD34+ phenotype treated with CHOP-based treatment protocols.

Hematopoietic peripheral blood stem cell transplantation (HSCT) is presently a viable treatment option for dogs with leukemias. Although not widely available, improved survival and cure are possible with this advanced form of therapy.

Myeloid Neoplasia

Myeloid neoplasms arise from clonally proliferating cells in the bone marrow and manifest as either accumulation of neoplastic cells in the blood or lack of normal blood cells. Myeloid neoplasms are divided into acute myeloid leukemia (AML) and myeloproliferative neoplasms (MPNs) which include chronic myelogenous leukemia (CML), polycythemia vera (PV), basophilic/eosinophilic leukemia, and essential thrombocytosis. (Box 133.1).

Acute Myeloid Leukemia

Etiology/Pathophysiology

Acute myeloid leukemia is defined by an abnormal proliferation of clonal cells in the bone marrow and peripheral blood that arise from a single immature blast cell. AML is divided into several subcategories based on the Animal Leukemia Study Group's 1991 proposal which was modeled after the human leukemia French-American-British (FAB) Cooperative Group classifications (see Box 133.1). In this system, myeloid leukemias are divided into phenotypic subtypes based on morphology and cytochemistry profiling using an alphanumeric

Box 133.1 Classification of leukemias in animals as proposed by the Animal Leukemia Study Group

Lymphoid leukemias

Chronic lymphocytic leukemia (CLL)
Acute lymphoblastic leukemia (ALL)

Myeloid neoplasia

Acute myeloid leukemias (AML)
Acute myeloblastic leukemia with minimal differentiation (LMA-M0)
Acute myeloblastic leukemia without differentiation (LMA-M1)
Acute myeloblastic leukemia with maturation (LMA-M2)
Acute promyelocytic leukemia (LMA-M3) (not recognized in animals)
Acute myelomonocytic leukemia (LMA-M4)
Acute monocytic leukemia (LMA-M5)
Acute erythroleukemia (LMA-M6)
Acute erythroleukemia with erythroid predominance (LMA-M6Er)
Megakaryoblastic leukemia (LMA-M7)

Chronic myeloid leukemia (CML)

Chronic myelomonocytic leukemia
Chronic monocytic leukemia
Eosinophilic leukemia
Basophilic leukemia
Polycythemia vera
Essential thrombocythemia

Myelodysplastic syndromes (MDSs)

Myelodysplastic syndrome with excessive blasts (MDS-EB)
Myelodysplastic syndrome with refractory cytopenia (MDS-RC)
Myelodysplastic syndrome with erythroid predominance (MDS-ER)

code of M-#, with the M standing for myeloid. The most commonly reported forms in the dog are acute myeloblastic leukemia (M1 and M2) and acute myelomonocytic leukemia (M4). Monocytic leukemia (M5), erythroleukemia (M6), and megakaryoblastic leukemia (M7) are also recognized in dogs but promyelocytic leukemia (M3) has not been reported.

In dogs, the etiology of AML along with the other myeloid neoplasms is unknown. Genetic and environmental factors such as exposure to radiation, drugs or toxic chemicals are thought to play a role. Defining genetic factors in dogs is difficult because canine karyotyping is an arduous process due to the large number and morphologic similarities of chromosomes and their resistance to banding. Recently, however, advancements in molecular cytogenetic analysis have aided in the discovery of canine chromosomal abnormalities that are similar to human AML which may serve not only as diagnostic and prognostic factors but also as therapeutic targets.

Epidemiology

A lack of veterinary studies examining myeloid neoplasms has led to a deficiency of uniform diagnostic criteria, nomenclature, and ultimately accurate diagnosis. Because of this, correct information regarding incidence and other epidemiologic information cannot be verified until a more uniform classification system is standardized.

Signalment

Acute myeloid leukemia is rare with a variable patient age at diagnosis. Males are more commonly affected than females and large-breed dogs seem to be predisposed. Retrospective studies suggest an increased incidence in German shepherds, golden retrievers, and Labrador retrievers. Small-breed dogs have been represented in single-case reports. The majority of feline AML patients are FeLV positive.

History and Clinical Signs

The clinical course of AML is rapid. Common clinical signs include extreme lethargy, secondary infection, and hemorrhage. Hematologic abnormalities can be severe with a WBC count as high as 150,000 μ/L. Anemia, neutropenia, and thrombocytopenia are also common. Spleen, lymph nodes, and liver are frequently involved but other sites such as heart, kidney or central nervous system (CNS) may be infiltrated as well.

Diagnosis

It is important to understand that AML is a disorder resulting from uncontrolled proliferation or decreased apoptosis of cells incapable of maturation, leading to the accumulation of poorly differentiated or "blast" cells. This is different from other myeloid neoplasms which result from unregulated proliferation of cells that exhibit incomplete/defective maturation, leading to the accumulation of well differentiated cells. The diagnosis of AML is generally made by evaluation of peripheral blood or bone marrow. Confirmation of AML should include consistent hematologic and morphologic criteria, positive staining for myeloperoxidase which is a heme protein synthesized during myeloid differentiation that constitutes the major component of neutrophil azurophilic granules, a consistent pattern of beta-2 integrin expression and absence of lymphoid antigens by immunocytochemistry or flow cytometry (Figure 133.3).

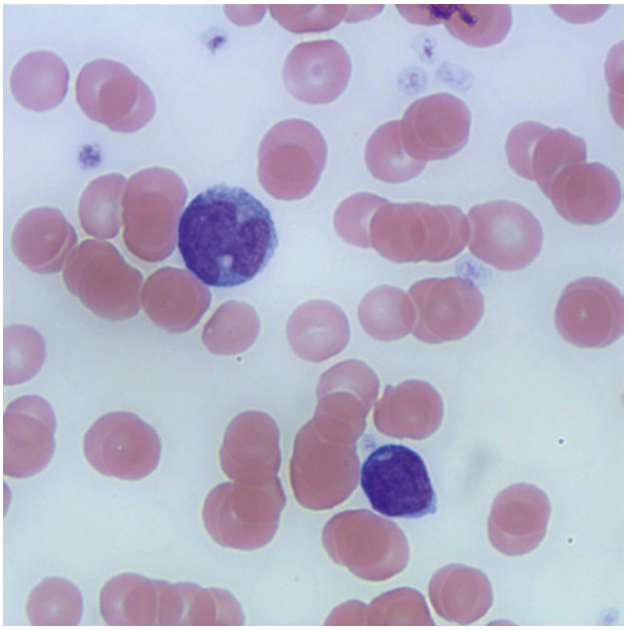


Figure 133.3 Photomicrograph of poorly differentiated blast cells in the peripheral blood of a dog that has myelomonocytic leukemia diagnosed via flow cytometry. The neoplastic cells are large with pleomorphic nucleoli and prominent nucleoli. Wright Giemsa stain, 1000× magnification. *Source:* Courtesy of Dr Jan Andrews, Antech Diagnostics.

Table 133.1 lists immunophenotypic markers for uncharacterized leukemias in animals recommended by the ACVP Oncology Committee.

Therapy

The course of the disease is short, usually only days to weeks, and animals quickly succumb or are euthanized soon after diagnosis. Traditional chemotherapy alone is largely unrewarding due to inadequate or short-term responses. As with other forms of leukemia, HSCT is becoming a viable treatment option for dogs with leukemia. However, owing to limited availability and rapid progression of the malignancy, treatment is often limited to palliative cytoreductive chemotherapy with such drugs as cytosine arabinoside, doxorubicin, vincristine, and cyclophosphamide. Intensive supportive care is commonly necessary and may include blood and/or platelet-rich plasma infusion along with aggressive antibiotic therapy for infection.

Table 133.1 Recommended immunophenotyping markers to differentiate animal leukemias as proposed by the Myeloid Neoplasm Subcommittee of the American College of Veterinary Pathologists

Cell type	Immunophenotypic marker(s)
B lymphocytes	CD79a
T lymphocytes	CD3
Myeloid	MPO, CD11b
Megakaryoblastic	CD41
Dendritic cells	CD1c
Acute leukemia	CD34

Source: McManus PM. Classification of myeloid neoplasms: a comparative review. *Vet Clin Pathol* 2005; **34**: 189–212. Reproduced with permission of John Wiley & Sons.

Prognosis

The prognosis for AML is considered poor. In one study of 16 dogs with confirmed AML, median and mean survival after diagnosis were 7 days and 20 days respectively with a range of 2–138 days. Most of the dogs in the study were treated with chemotherapy. However, protocols were not consistent and some dogs were euthanized before any treatment could be instituted due to rapidly progressive clinical signs. There is one case report of a dog with megakaryoblastic leukemia that demonstrated a lengthy survival of 24 months with treatment so all AML is not necessarily rapidly fatal. For some dogs, HSCT may be feasible. For those animals, HSCT offers the possibility of prolonged survival and cure.

Myeloproliferative Neoplasms

Myeloproliferative neoplasms (MPNs) are defined as overproduction of differentiated bone marrow cells which results in the accumulation of the affected cell (granulocytes and/or monocytes, erythrocytes or platelets).

Chronic Myelogenous Leukemia

Etiology/Pathophysiology

Chronic myelogenous leukemia (CML) in dogs is characterized by a neoplastic proliferation of the neutrophil series and is more similar to human chronic neutrophilic leukemia than human CML. Human CML is associated with the proliferation of several hematopoietic cell lineages due to the presence of a BCR-ABL translocation (Philadelphia chromosome) between chromosomes 9 and 22. The regions of human chromosomes 9 and 22 are evolutionarily related to regions on canine chromosomes 9 and 26 and a canine equivalent to the BCR-ABL mutation (Raleigh chromosome) has been identified in three cases of canine CML. The etiology of most canine and feline CML is unknown.

Signalment

There is no known age, sex, or breed predilection in canine CML. FeLV infection has been associated with CML in cats.

History/Clinical Signs

Many patients have no clinical signs until significant organ infiltration or myelophthisis of the bone marrow

occurs. If clinical signs are present, they are often nonspecific and may include lethargy, inappetence, organomegaly, pale mucous membranes, and hemorrhage caused by severe thrombocytopenia.

Diagnosis

At diagnosis, the peripheral white blood cell count (WBC) count is commonly >100 000/μL. Neutrophils and neutrophilic precursors accumulate in bone marrow, peripheral blood and other organs such as the spleen, liver, and lymph nodes. Eosinophils and basophils may also be increased. CML must be distinguished from a leukemoid reaction caused by inflammation, immune-mediated diseases, and/or a paraneoplastic syndrome. Staging tests such as three-view thoracic radiographs, abdominal ultrasound, and bone marrow cytology can be helpful in making this distinction. Biopsy of the liver or spleen may also be helpful in distinguishing CML from a leukemoid reaction due to its invasiveness.

Therapy

Treatment of CML consists of the chemotherapy agent hydroxyurea at 20–25 mg/kg PO twice daily until the leukocyte count drops to 15 000–20 000 cells/μL. The dosage of hydroxyurea can then be reduced by 50% on a daily basis or to 50 mg/kg given biweekly or triweekly.

Prognosis

Although responders can be managed for several months with chemotherapy, most CML patients will enter a terminal phase of their disease. HSCT offers the only possibility of cure for dogs but may not be feasible or practical. Death is either due to infection or hemorrhage caused by neutrophil dysfunction and thrombocytopenia or secondary to a "blast crisis." Response rates in patients in a blast crisis are low and the prognosis is very poor. It is unknown whether the subset of canine CML patients that have a BCR-ABL chromosome will respond to BCR-ABL kinase inhibitors which have become the standard of care for human CML patients.

Polycythemia Vera

Etiology/Pathophysiology

Polycythemia vera (PV) is a clonal disorder of erythroid precursors in the bone marrow, which leads to the overproduction of red blood cells independent of erythropoietin. PV is rare in the dog and must be differentiated from more common causes of polycythemia such as relative polycythemia which is a result of hemoconcentration or secondary polycythemia which is driven by erythropoietin. Conditions associated with secondary polycythemia include chronic pulmonary disease, congestive heart failure, renal disease, renal neoplasia, and/or right-to-left cardiac shunts.

Signalment

Polycythemia vera generally affects middle-aged dogs and cats with no breed or sex predilection.

History and Clinical Signs

The majority of clinical signs occur secondary to hyperviscosity syndrome which is the sludging of blood due to increased red blood cell mass. These signs may include hemorrhage, exercise intolerance, neurologic signs such as seizures or ataxia, splenomegaly, hyperemic mucous membranes, injected sclera/retinal vessels, and weakness. Cardiac or renal disease may also occur.

Diagnosis

Recommended diagnostic tests to rule out relative or secondary polycythemia include thoracic radiographs, abdominal ultrasound, bone marrow aspiration, arterial blood gas measurements, and serum EP levels if possible. The diagnosis of PV is made by the demonstration of significant erythrocytosis (hematocrit of 60–75%) with normal to decreased serum EP levels. Bone marrow cytology in PV is consistent with erythroid hyperplasia with normal patterns of maturation.

Therapy

Treatment of PV consists of decreasing the red blood cell (RBC) volume and, ideally, suppression of erythroid production in the bone marrow. Phlebotomy with reinfusion of the patient's plasma after removal of the RBCs or administering colloid and crystalloid solutions to replace lost electrolytes is recommended. The PCV should be reduced to 50–60% or by one-sixth of its starting value (15–20 mL/kg body weight can be removed at one time). The drug of choice to suppress erythroid production is hydroxyurea which works by inhibiting DNA synthesis. Hydroxyurea is instituted at 20–25 mg/kg PO given twice daily in dogs (10–15 mg/kg in cats orally once daily). Once the hematocrit is below 60%, hydroxyurea is maintained at every other day dosing with the goal of maintaining a normal or close to normal packed cell volume (PCV).

Prognosis

The prognosis of PV is good with a high response rate and survival times of longer than a year for responders.

Basophilic and Eosinophilic Leukemia and Essential Thrombocythemia

Etiology/Pathophysiology

Basophilic leukemia has rarely been reported in dogs and is diagnosed by an increased WBC count with a high proportion of basophils in bone marrow and/or peripheral blood. The etiology is unknown. It is unclear whether dogs and cats develop eosinophilic leukemia. At this

time, due to lack of useful clonality assays, eosinophilic leukemia and hypereosinophilic syndrome are difficult to differentiate. Essential thrombocythemia has been described in the dog and is characterized by persistent thrombocytosis of >600 000/μL without evidence of circulating blast cells.

Signalment

There is no known age, breed, or sex predilection in any of these disorders.

History and Clinical Signs

A history of lethargy, inappetence, and/or weight loss is common with any of the myeloid neoplasms. Clinical signs are generally vague and may include fever, pale mucous membranes, petechiation, hepatosplenomegaly, and lymphadenopathy.

Diagnosis

Basophilic leukemia must be differentiated from mastocytosis based on morphology. Although these cells are usually easily distinguished from each other, changes in morphology of the nucleus and granules in basophilic leukemia can make this distinction more difficult. Infiltration into other organs is possible, including the liver, spleen and lymph nodes, so evaluation of these organs by abdominal ultrasound and/or cytology can aid in the diagnosis. To make a diagnosis of eosinophilic leukemia, disorders associated with eosinophilia such as skin diseases, respiratory, and/or gastrointestinal tract diseases and parasitism need to be ruled out before considering a neoplastic leukemic etiology. Dogs with essential thrombocythemia can present with hepatosplenomegaly, nonregenerative anemia, and neutrophilia. On examination of bone marrow, megakaryocytic hyperplasia is the most common feature. Diseases that are known to cause secondary thrombocytosis such as chronic inflammatory diseases, rebound from severe hemorrhage and iron deficiency anemia need to be ruled out before making a diagnosis of essential thrombocythemia.

Treatment/Prognosis

Treatment for basophilic leukemia with hydroxyurea has provided complete or partial remissions for several months in case reports. The effective treatment of eosinophilic leukemia is unknown but in one case report, treatment with corticosteroids was effective. Information on treatment for essential thrombocythemia is lacking but in one case report, a dog was successfully treated with a chemotherapy protocol consisting of vincristine, cyclophosphamide, Ara-C, and prednisone. As with all forms of leukemia, HSCT can be considered for suitable dogs if feasible.

Myelodysplastic Syndromes

Myelodysplastic syndromes (MDS) are a heterogeneous group of acquired alterations of hematopoietic stem cells that have been described in humans, dogs, and cats. MDS can be primary or secondary/acquired. Primary MDS result from clonal expansion of a defective pluripotent stem cell and therefore are considered neoplastic. Some refer to myelodysplasia as preleukemia since it can progress to acute leukemia in some cases.

Etiology/Pathophysiology

Several different aberrations can result from a dysfunctional hematopoietic system constituting MDS. In dogs, there are usually cytopenias in 2–3 cell lines in the peripheral blood due to cell death caused by ineffective hematopoiesis. Other blood abnormalities may include dysplastic changes in several cell lines, metarubricytosis, and macrocytic erythrocytes. The bone marrow is usually normocellular or hypercellular. Blast cells in bone marrow make up <30% of all nucleated cells but in people this threshold has been changed to <20%.

Three subtypes of primary MDS have been proposed for dogs and cats: MDS with excessive blasts (MDS-EB), in which blast percentages are >5% and less than 20%, MDS with refractory cytopenia (MDS-RC) with blast percentages <5% and cytopenias in one or more lineages, and MDS with erythroid predominance (MDS-ER) in which the myeloid:erythroid (M:E) ratio is <1. Cases of canine secondary MDS consistently have <5% myeloblasts in the bone marrow. Secondary MDS in dogs has been associated with several conditions including myelofibrosis, neoplasia (lymphoma and multiple myeloma), immune-mediated thrombocytopenia, immune-mediated hemolytic anemia, drugs, and ionizing radiation. In cats, secondary MDS can be associated with FeLV.

Epidemiology

Genetic abnormalities in hematopoietic cells such as mutations in oncogenes and tumor suppressor genes along with chromosomal deletions have been discovered in human MDS patients and are thought to play a role in veterinary patients.

Signalment

MDS-EB is the most common type of primary MDS and occurs most frequently in middle-aged to older dogs. Both MDS-RC and MDS-ER occur in older dogs. No breed or sex predilection is known in any of the subtypes.

History and Clinical Signs

The clinical signs of both MDS-RC and MDS-ER are vague and commonly include lethargy and exercise intolerance. Physical exam generally reveals pale mucous membranes and an anemia-related heart murmur. Clinical signs of MDS-EB tend to be more severe and include depression, anorexia, fever, and diarrhea. These patients commonly have a history of illness that progresses over several months.

Diagnosis

Evaluation of blood and/or bone marrow is needed for diagnosis of MDS. Because primary and secondary MDS cannot be consistently differentiated cytologically, a diagnosis of primary MDS should be made only if secondary causes have been ruled out. The most common hematologic abnormalities in MDS-RC and MDS-ER are nonregenerative anemias without any evidence of thrombocytopenia or leukopenia. MDS-ER differs from MDS-RC by characterization of marked erythroid hyperplasia and the presence of >5% rubriblasts in the bone marrow. Patients with MDS-EB have moderate to severe nonregenerative anemia with evidence of neutropenia and thrombocytopenia. Dysplastic features in all cell lines are commonly found and a hallmark feature of MDS-EB is the presence of increased numbers of myeloblasts (between 5% and 20% of total nucleated erythroid and myeloid cells).

Therapy/Prognosis

There is no standard treatment for primary MDS. In humans, patients commonly receive no treatment because they often do not have clinical signs. Supportive care such as blood transfusions and antibiotics for infections is used as necessary. Growth factors can also be used. In one case report of a dog with MDS-ER, human recombinant erythropoietin was used to treat profound anemia to promote terminal differentiation of dysplastic erythrocytes. The hematocrit increased and that patient remained in remission for >30 months. Dogs with MDS-RC and MDS-ER can have prolonged survivals when treated with chemotherapy (cyclophosphamide or cytosine arabinoside is most common) and supportive care. Patients with MDS-EB can progress to AML and treatment has been less rewarding, with survival times of days to months. For suitable dogs, allogeneic HSCT can be considered. The treatment and prognosis of secondary/acquired MDS are dependent on the underlying cause.

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134

Lymphomas

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Canine Lymphoma

Etiology/Pathophysiology

Canine lymphoma is one of the most commonly encountered neoplasms in the dog and is most analogous to non-Hodgkin lymphoma in people. It includes multiple disorders of the lymphoid system, which are characterized by a monoclonal expansion of lymphoid cells. The etiology of lymphoma is currently unknown and is likely to be multifactorial.

Recent advances in molecular cytogenetics have demonstrated various chromosomal aberrations associated with diagnosis and prognosis in canine lymphoma. These results, while in the early phase of research, are similar to those seen in human non-Hodgkin lymphoma with dysregulation of certain molecular pathways.

Environmental Influences

A number of case–control studies have evaluated environmental influences on the development of lymphoma. These studies demonstrated that exposure to 2,4-D herbicides increases the risk of developing lymphoma. Other studies have suggested that exposure to strong magnetic fields or proximity to environmental waste may be risk factors.

Certain viruses have been associated with the development of lymphoma in humans (e.g., Epstein–Barr virus, HIV). No viruses have been identified as a causative agent for the development of canine lymphoma.

Various immune-mediated disorders (immune-mediated hemolytic anemia or thrombocytopenia), organ transplantation or a history of atopic dermatitis have been implicated in the development of canine lymphoma.

Epidemiology

The incidence of canine lymphoma has steadily increased, with approximately 84 per 10 000 dogs diagnosed each year. Certain breeds are considered to have a higher overall lifetime risk of developing lymphoma, suggesting a heritable genetic component. These include boxers, golden retrievers, basset hounds, and bulldogs. Likewise, certain breeds of dogs are considered to be at much lower risk, including dachshunds and Pomeranians.

Signalment

Average age at diagnosis is between 5 and 10 years old with no apparent sex predilection.

History and Clinical Signs

Clinical presentation of multicentric lymphoma is highly variable and will depend on the anatomic location and extent of the disease. An established World Health Organization (WHO) staging scheme for domestic animals assigns patients into five categories based on disease dissemination and anatomic site (Table 134.1). This staging system is used for accurate planning of therapy, provides prognostic information, and allows for comparisons between patients for the purposes of clinical research.

The WHO substage (a/b) is another system used for prognostication and is defined as the presence/absence of constitutional signs at the time of presentation. Constitutional signs of illness include anorexia, vomiting, diarrhea, weight loss, cachexia, fever, etc. Although these signs are somewhat subjective, this system consistently proves to be very prognostic.

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Table 134.1 World Heath Organization clinical staging scheme for lymphoma in domestic animals

	Remarks
Anatomic location	
A	Generalized
B	Alimentary
C	Thymic
D	Skin
E	Leukemia
F	Other
Stage	
I	Involvement of single lymph node or lymphoid tissue in a single organ
II	Multiple involved lymph nodes in a single region
III	Generalized lymph node involvement
IV	Involvement of the liver and/or spleen (+/- stage III)
V	Presence of lymphoma in the blood/bone marrow and/or involvement of other organ systems (+/- stage I–IV)
Substage	
a	No systemic signs of illness
b	With systemic signs of illness

The most common presentation is that of an asymptomatic dog with nonpainful but markedly enlarged peripheral lymph nodes which would be classified as stage III, substage a (see Table 134.1).

In general, dogs with stage V lymphoma will present with clinical signs related to the anatomic location of the disease. For example, dogs with bone marrow infiltration may present with cytopenias, fever, sepsis or hemorrhage. Dogs with marked pulmonary involvement may present in respiratory distress.

As lymphoma has the potential to cause a wide array of clinical syndromes, it should be considered as a potential cause of any unexplained disorder in high-risk breeds until proven otherwise.

Diagnosis/Clinical Staging

A diagnosis of canine lymphoma can be achieved via fine needle aspiration (FNA) and cytologic evaluation of an enlarged peripheral lymph node or tumor tissue. Cytology supportive of lymphoma will demonstrate a population of large or intermediate-sized lymphocytes comprising the majority (>50%) of cells. Small cell lymphoma is an exception, as it may not appear cytologically malignant.

It is important to note that the presence of an inflammatory process within enlarged lymph nodes may confound a diagnosis since reactive lymphoid hyperplasia can be difficult to distinguish from lymphoma. This occurs commonly in the mandibular lymph nodes (due to dental disease or ear infections), and evaluation of these nodes should be avoided if possible.

A definitive diagnosis of lymphoma may require further analysis to determine if a clonal population of lymphocytes is present. This can be accomplished via polymerase chain reaction-based assay evaluating antigen receptor rearrangements (PARR). The presence of a clonally expanded population of cells strongly supports a diagnosis of lymphoma as it is uncommon in a reactive process. It should be noted, however, that this test can result in a high percentage (upwards to 25%) of false negatives. An alternative to PARR is a diagnostic test called flow cytometry. This assay relies on monoclonal antibodies and fluorescent markers to help confirm a diagnosis of lymphoma by evaluating for aberrancies and determining the phenotype of leukocytes within a fresh sample of blood or tissue (e.g., lymph node, effusions). Because flow cytometry requires living cells to complete the assay, an abundance of dead or dying cells will confound a definitive result.

Ideally, cytology should be used as a first-line test followed by confirmation with histology. A biopsy of lymph node or other affected tissue can be obtained surgically or via needle core biopsy. An excisional biopsy is preferred, as it allows for a more thorough classification of the type of lymphoma by preserving the architecture of the affected tissue. Biopsy samples also provide adequate tissue to perform immunohistochemical phenotyping for prognostic information by distinguishing between B and T cell forms.

Histologic Classification

Lymphomas are a complex group of diseases that vary clinically from indolent to aggressive, and from poorly controlled to manageable with treatment.

Indolent forms of lymphoma are uncommon and poorly understood. These low-grade forms of lymphoma are relatively slow growing and are associated with long survival times with limited or no therapy. Examples include marginal zone lymphoma, follicular lymphoma, B or T cell small cell lymphoma, and T zone lymphoma.

The majority of dogs have a multicentric intermediate or high-grade variety, with diffuse large lymphoblastic B cell being the most common. While higher-grade lymphomas tend to be more responsive to chemotherapy, the duration of tumor control is short when compared to animals with low-grade lymphoma, in which long survival is often achieved with minimal to no treatment.

Immunophenotype

Immunophenotyping is commonly used to distinguish the population of lymphoid cells that make up the tumor. Cell surface markers, such as CD3 and CD79a, aid in differentiating T cell from B cell lymphomas. It is well established that dogs with a B cell form of lymphoma have better response rates and prognosis compared to those with a T cell phenotype.

Staging

Minimum database including a complete blood count (CBC) with differential blood cell count, serum biochemistry profile, and urinalysis should be completed to evaluate for the presence of paraneoplastic conditions and rule out co-morbid disease.

Potential abnormalities related to lymphoma noted on a CBC include blood dyscrasias such as a nonregenerative anemia, thrombocytopenia, lymphocytosis or presence of circulating lymphoblasts. Bone marrow aspiration is indicated in dogs with blood dyscrasias to confirm lymphoma and rule out an unrelated blood disorder. This may also help to differentiate between multicentric stage V lymphoma and a primary lymphoblastic leukemia, which carries a worse prognosis.

A chemistry profile that includes a serum ionized calcium level is recommended to evaluate for the presence of hypercalcemia of malignancy and to assess liver and kidney function.

A urinalysis is helpful in evaluating renal function and can rule out a subclinical urinary tract infection. It is important to note that dogs with hypercalcemia of malignancy may present with azotemia and isosthenuria, which may not represent primary renal disease but instead is a consequence of the effects of hypercalcemia on renal tubules.

Thoracic and/or abdominal radiographs or abdominal ultrasound are recommended to determine the presence and extent of disease within visceral organs. When present, pulmonary infiltrates typically appear radiographically as diffuse interstitial and/or alveolar patterns. Rarely are there nodules or bronchial changes. Widening of the cranial mediastinum may indicate the presence of mediastinal lymphoma.

Because of the potential for cardiotoxic effects of certain chemotherapy drugs, thoracic radiographs are also important for assessment of cardiac changes.

Therapy

After establishing a diagnosis of lymphoma, a comprehensive discussion with the owner should encompass goals, prognosis, associated costs, and potential complications. It is important to note that many owners have a preconceived notion of cancer and its treatment. Therefore it should be made clear that the majority of dogs who receive chemotherapy will respond to treatment and can achieve a remission in which they are free of clinical signs related to lymphoma. In the author's experience, most owners who decide to proceed with chemotherapy are cooperative, realistic, and appreciative of the efforts made to help their pets.

Treatment options range from multiagent protocols to single-agent prednisone and will be determined by the location of the disease, the overall health of the pet, and the emotional/financial commitment of the owner.

A primary veterinarian can easily manage many dogs with multicentric lymphoma. However, consultation with an oncologist may be helpful in establishing a treatment protocol. Referral to an oncology center may be indicated for atypical cases or for patients that are refractory to treatment.

Multiagent Chemotherapy Protocols

Drugs with established activity include cyclophosphamide (C), doxorubicin (H, hydroxydaunorubicin or doxorubicin), vincristine (O, Oncovin®), and prednisone (P). Protocols incorporating these drugs are called CHOP-based protocols. All CHOP-based multiagent chemotherapy protocols are believed to be superior to any single-agent protocol with respect to remission duration and overall survival time. Multiple studies have demonstrated that approximately 80–90% of all dogs receiving a CHOP-based chemotherapy protocol will experience a clinical remission with an overall median survival time of 10–12 months. While success of treatment is highly variable, the majority of multiagent protocols induce a first remission of >6 months after chemotherapy induction.

Multiagent protocols are typically discontinued 15–19 weeks after the start of therapy. Long-term maintenance chemotherapy has not demonstrated benefit with respect to remission duration or progression-free survival.

A commonly used and well-studied chemotherapy protocol for dogs with newly diagnosed or naive multicentric lymphoma is the University of Wisconsin 19-week discontinuous (short) CHOP protocol. This protocol is simple to administer since it relies on single-agent treatment at each visit, allowing for an assessment of tolerability and efficacy of each drug. At week 19, chemotherapy is discontinued if the dog is in complete remission (Table 134.2).

Single-Agent Chemotherapy Protocols

As noted earlier, multiagent protocol drugs work best when given in combination at the onset of therapy.

Table 134.2 UW-Madison short CHOP lymphoma protocol

Treatment week		Drug, dosage, and route
1	Baseline CBC/chemistry profile/UA	Vincristine (0.5–0.7 mg/M^2) IV Prednisone 2 mg/kg once per day for 7 days
2	Pretreatment CBC/plt	Cyclophosphamide (250 mg/M^2) IV or PO[a] Prednisone 1.5 mg/kg once per day for 7 days
3	Pretreatment CBC/plt	Vincristine (0.5–0.7 mg/M^2) IV Prednisone 1 mg/kg once per day for 7 days
4	Pretreatment CBC/plt	Doxorubicin (30 mg/M^2) IV + Prednisone 0.5 mg/kg once per day for 7 days then discontinue
5		No treatment: consider restaging to assess for response to treatment[b]
6	Pretreatment CBC/plt	Vincristine (0.5–0.7 mg/M^2) IV
7	Pretreatment CBC/plt	Cyclophosphamide (250 mg/M^2) IV or PO[a]
8	Pretreatment CBC/plt	Vincristine (0.5–0.7 mg/M^2) IV
9	Pretreatment CBC/plt	Doxorubicin (30 mg/M^2) IV
10		No treatment
11	Pretreatment CBC/plt	Vincristine (0.5–0.7 mg/M^2) IV
12	Pretreatment CBC/plt	Cyclophosphamide (250 mg/M^2) IV or PO[a]
13	Pretreatment CBC/plt	Vincristine (0.5–0.7 mg/M^2) IV
14	Pretreatment CBC/plt	Doxorubicin (30 mg/M^2) IV[c]
15		No treatment
16	Pretreatment CBC/plt	Vincristine (0.5–0.7 mg/M^2) IV
17	Pretreatment CBC/plt	Cyclophosphamide (250 mg/M^2) IV or PO[a]
18	Pretreatment CBC/plt	Vincristine (0.5–0.7 mg/M^2) IV
19	Pretreatment CBC/plt	Doxorubicin (30 mg/M^2) IV[d]

[a] Administer with furosemide 2 mg/kg SC to prevent sterile hemorrhagic cystitis (SHC). Substitute with chlorambucil at 1.4 mg/kg if SHC develops.
[b] Reduce dose to 1 mg/kg for dogs <15 kg.
[c] Do not exceed 180 mg/M^2 maximum cumulative dose.
[d] If progressive disease is noted at any point in the treatment protocol, rescue chemotherapy should be considered.
CBC, complete blood count; IV, intravenous; plt, platelets; PO, by mouth (per os); UA, urine analysis.

If multiagent therapy is not an option, it is reasonable to incorporate any number of the CHOP drugs and create an individual protocol that suits the dog and the owner. Doxorubicin as a single agent, administered every 2–3 weeks (up to five total treatments), can induce a remission in 50–75% of dogs for a median of 6–8 months. Care must be taken to monitor for cumulative cardiotoxic effects of this drug in the dog, which can result in dilated cardiomyopathy (DCM). It is advisable to avoid this drug in dogs with a preexisting heart condition or breeds that are considered high risk for DCM (e.g., boxer, Doberman pinscher, Great Dane, etc.). Other protocols with similar success include cyclophosphamide, vincristine, and prednisone (referred to as COP).

Dogs which are treated with a palliative protocol of prednisone as a sole therapy can achieve a short-lived remission of approximately 1–2 months. It is important to note that these dogs, when compared to dogs given multiagent therapy from the outset, are more likely to develop multidrug resistance and experience shorter remission and survival times if any subsequent chemotherapy is administered.

Reinduction Chemotherapy Protocols

Reinduction with CHOP-based drugs is recommended provided that the recurrence is temporally far enough from the conclusion of the initial protocol (i.e., ≥ 2 months). Typically, a second or even third remission is achievable with a variable duration of response.

Rescue Chemotherapy

Inevitably, resistance to the CHOP-based chemotherapy drugs will develop, and it is unlikely that continued use of the same drugs will provide a significant benefit. At that point, drugs not used in the initial CHOP protocols are recommended and are referred to as rescue

chemotherapy agents/protocols. Successful induction of an additional remission with rescue protocols varies between 50% and 90% but the length of remission is decreased, at 1.5–2.5 months.

A novel chemotherapy agent, rabacfosadine (Tanovea®), has been conditionally approved for use in dogs with naive or relapse lymphoma. This compound as a single agent has demonstrated excellent efficacy for dogs with B cell form of lymphoma and may be variably successsful for dogs with a T cell variant. Other second-line drugs often used for rescue therapy include lomustine (CCNU), mechlorethamine (Mustargen®), vinblastine (Velban®), dacarbazine (DTIC), and cytosine arabinoside (Cytosar-U®). While each of these drugs has a variable degree of efficacy against lymphoma, the duration of response is considerably lower when compared to standard multiagent protocols.

Complications of Chemotherapy

A majority of dogs tolerate chemotherapy well. Potential adverse effects include mild to moderate nausea, vomiting, or diarrhea, all of which are easily treated with supportive care or symptom management. In rare instances, life-threatening complications related to chemotherapy-induced myelosuppression can develop, requiring hospitalization and aggressive supportive care.

A CBC must be performed prior to every treatment to ensure an adequate white blood cell count. It is generally accepted that an absolute neutrophil count of >2000 cells/μL and >50 000 platelets/μL be present prior to chemotherapy administration to minimize the risk of sepsis or other complications.

Extranodal Forms of Lymphoma

There are instances where a dog will present with lymphoma isolated to a solitary site, such as the alimentary tract, skin, central nervous system (CNS) or nasal cavity. On rare occasions, local therapies such as surgery or radiation therapy may be employed. Careful staging, including bloodwork, thoracic radiographs, +/- abdominal ultrasound, +/- bone marrow aspiration, is essential to ensure multicentric involvement is not present before considering local therapy.

Alimentary Lymphoma

Alimentary lymphoma is an uncommon extranodal lymphoma. Dogs will present with nonspecific clinical signs consistent with gastrointestinal (GI) disease, including weight loss, anorexia, diarrhea, and vomiting. Limited information in the veterinary literature suggests this form of lymphoma is poorly responsive to chemotherapy. In the author's experience, a chemotherapy protocol that incorporates CCNU can be more effective than a multidrug CHOP-based chemotherapy protocol alone.

Cutaneous Lymphoma

A primary cutaneous form of lymphoma can develop within the skin and/or the oral cavity (mucocutaneous). Dogs may present with pruritus, scaling of the skin, and alopecia that will progress to areas of ulceration, nodules, and proliferative plaques. Lesions can be solitary or can involve multiple skin sites. Oral involvement appears as plaque-like lesions or nodules associated with the gums and lips. Multiple punch biopsies of the affected areas are necessary to establish a diagnosis of lymphoma. There are two types of cutaneous lymphoma distinguished histologically and phenotypically: epitheliotropic (T cell) lymphoma (also called mycosis fungoides) and nonepitheliotropic (B or T cell) lymphoma.

Treatment of cutaneous lymphoma depends on the extent and location of disease. Single lesions may be appropriately treated with local therapy consisting of surgery or radiation therapy. Diffuse cutaneous lymphoma is best treated with chemotherapy. B cell cutaneous lymphomas often respond better than T cell, but the response rate with chemotherapy is less than that seen with other forms of lymphoma.

CCNU or multiagent chemotherapy is the treatment of choice, although a recent study has also supported the use of Tanovea when treating dogs for cutaneous forms of lymphoma. While many dogs have an initial response to chemotherapy, the lesions often return or new lesions develop within a short period of time (3–5 months). Many dogs are euthanized within six months of diagnosis due to the discomfort associated with progressive ulceration, bleeding, and pruritus.

Prognosis

Response rates and remission duration for dogs with newly diagnosed lymphoma will vary depending on the clinical picture, biologic behavior, histologic classification, immunophenotype, and treatment protocol. In general, dogs with large B cell lymphoma have better response rates to a CHOP-based chemotherapy protocol than dogs with T cell lymphoma. In fact, due to the variable success in the treatment of dogs with T cell lymphoma, many oncologists are now relying on a modified chemotherapy protocol that incorporates more alkylating agents (e.g., cyclophosphamide or lomustine). This modification is based on the presumption that these agents may be more effective agents for dogs with a T cell form of lymphoma.

Additional Treatment Strategies

Because most dogs ultimately will develop chemotherapy resistance, other methods of lengthening a clinical remission may be employed. These include total and half-body radiation therapy, hematopoietic stem cell

transplantation (bone marrow transplant), and immunotherapy. These treatment strategies have variable success and continue to be an active area of investigation.

Feline Lymphoma

Etiology/Pathophysiology

Lymphoma (LSA) is one of the most common neoplasms in the cat and can present in a variety of ways, depending on the organ(s) affected. An association with retroviral infection has been firmly established, with approximately 25% of feline leukemia virus (FeLV)-positive cats developing lymphoma during their lifetime. Feline immunodeficiency virus (FIV) has also been implicated in the development of lymphoma, although its true contribution has been difficult to determine since it often occurs in conjunction with FeLV. Chronic immunosuppression secondary to retroviral infection is thought to play a role in this association. This correlates with the increased incidence of lymphoma in cats receiving chronic immunosuppressive drugs after renal transplantation. Collectively, these findings parallel an increased incidence of lymphoproliferative cancers in humans with human immunodeficiency virus (HIV) or those receiving chronic immunosuppressive therapy.

The underlying cause of nonretroviral-induced feline lymphoma is not completely understood. It is likely that chronic inflammation plays a role given that feline lymphomas frequently arise in organs or sites affected by chronic inflammation. For example, a correlation between chronic inflammatory bowel disease and alimentary lymphoma has been proposed. Comparatively, humans with celiac disease have a similar predisposition towards lymphoproliferative disorders and cancer.

Recent studies have also demonstrated that chronic exposure to environmental tobacco smoke is associated with an elevated risk for gastrointestinal lymphoma in cats.

Epidemiology

Lymphoma is the most common neoplasm of the hematopoietic system of cats, with an estimated incidence of 200 per 100 000 cats.

Studies have demonstrated that FeLV-positive cats have a 60-fold or greater relative risk of the cancer. FIV infection also increases the relative risk of lymphoma 5–6-fold.

While the incidence of feline lymphoma has not changed with the development of effective antiviral vaccines, the most common presentation of lymphoma is now in older retrovirus-negative cats.

Signalment

There is a bimodal distribution for feline lymphoma in which retroviral-positive cats present with lymphoma at a young age (1–3 years) and virus-negative cats present at an older age (10–13 years). Currently, the median age at presentation is approximately 11 years. There is no sex predilection and any breed of cat can be affected, although Siamese cats are overrepresented, suggesting a genetic susceptibility to the disease.

History and Clinical Signs

Location of the tumor appears to be the determinant of clinical signs and prognosis in feline lymphoma. Consequently, the WHO staging system is not used. Instead, lymphoma is generally divided into different anatomic classifications: mediastinal, gastrointestinal, multicentric, and miscellaneous sites (such as nasal and renal).

Mediastinal Lymphoma

Young cats typically present with a mediastinal form of lymphoma with acute-onset dyspnea, which rapidly progresses as the tumor begins to occlude lymphatics, leading to pleural effusion. Physical examination may reveal a noncompressible cranial thorax and muffled or caudodorsal displacement of cardiac sounds.

Alimentary Lymphoma

Alimentary lymphomas usually involve the stomach and intestines of older cats. Gastrointestinal tumors may be discrete or diffuse. The primary clinical signs are anorexia and weight loss, although some cats may also present with vomiting and/or diarrhea. With these clinical signs, it is important, though often difficult, to differentiate lymphoma from inflammatory bowel disease.

Extranodal Lymphoma

Cats with other forms of lymphoma (e.g., nasal, renal, CNS, laryngeal) will present with clinical signs reflecting the anatomic location.

Diagnosis

As described in dogs, a diagnosis of lymphoma can be achieved via fine needle aspiration or surgical, endoscopic or needle biopsy of affected tissue. As noted previously, a definitive diagnosis via a fine needle aspirate can be confounded by an insufficient or nondiagnostic sample, or if there is a significant component of inflammation present. Because alimentary lymphoma is easily confused with inflammatory bowel disease (IBD), a full-thickness tissue biopsy is often necessary to

establish a definitive diagnosis. A histologic evaluation of the diseased tissue will provide a more accurate evaluation of tissue morphology and degree of invasion. If an equivocal diagnosis is present, techniques such as immunohistochemical or immunocytochemical analysis, flow cytometric analysis and polymerase chain reaction-based clonality assays are available to characterize the disease and refine the diagnosis.

Currently, a histologic classification scheme similar to those described in humans and dogs does not exist for feline lymphoma. There are two histologic forms: high- (or intermediate) grade lymphoma and low-grade (or small cell) lymphoma. These histologic distinctions in combination with anatomic location are the most prognostic and will determine treatment.

Immunophenotype

Immunophenotyping is not commonly used for prognostication purposes in the cat as it is in dogs and humans. It is employed, however, to confirm the presence of a phenotypically identical population of lymphoid cells that make up the tumor. This can be completed on tissue samples via histochemical or cytochemical staining for CD3 (T cell expression) or CD79a (B cell expression). According to some studies, a T cell phenotype is more prevalent in cats with small cell or low-grade alimentary lymphoma and B cell phenotype is more common in large cell or high-grade lymphoma. As mentioned previously, cell morphology (large cell vs small cell) is used more commonly than a phenotypic distinction to determine treatment and prognosis.

Alimentary Lymphoma

Cats with alimentary lymphoma are typically diagnosed via abdominal imaging (e.g., ultrasound), which is abnormal in approximately 60–90% of cats. The appearance is variable, and may be of a circumferential mass with loss of GI wall layering, or of a diffuse small intestinal wall thickening of the muscularis, propria, and submucosa. Mesenteric lymphadenopathy is also common and has been reported in 45–80% of affected cats.

A cytologic or histologic assessment of a needle aspirate or needle biopsy samples from intestinal masses, enlarged lymph nodes or other abnormal-appearing organs is essential to establish a diagnosis. Endoscopic, laparoscopic or incisional biopsy achieved by laparotomy may also be performed. Full-thickness GI biopsies best distinguish inflammatory bowel disease from lymphoma and will differentiate a high- or low-grade intestinal lymphoma.

Mediastinal Lymphoma

For cats with mediastinal lymphoma, a diagnosis can be established via survey thoracic radiographs followed by thoracocentesis with cytologic examination of the fluid. The fluid lymphocyte count is usually greater than 4000/μL, with most appearing as intermediate or large lymphoblasts. In cases where fluid cytology is not diagnostic, aspiration or biopsy of the mass itself can be completed via ultrasound or computed tomography (CT) guidance. Immunophenotypic and clonality assessment may be helpful in equivocal cases.

Nasal Lymphoma

Nasal lymphoma differs from other sites in that it is often non-systemic and confined to the nose and/or sinuses. Nasal CT or magnetic resonance imaging (MRI), rhinoscopy, and biopsy are necessary to establish a diagnosis. Thorough staging with evaluation of regional lymph nodes, thorax, and abdomen is recommended if local radiation therapy is to be considered for sole treatment.

Renal Lymphoma

Renal lymphoma usually causes bilateral renomegaly which may be detected on physical exam. Clinical signs at presentation are a consequence of renal insufficiency. Ultrasound-guided renal biopsy or FNA is recommended to confirm the diagnosis.

Central Nervous System Lymphoma

Spinal CNS lymphoma usually causes hindlimb paresis or paralysis with or without back pain. Most tumors are extradural, and occur in the thoracolumbar or lumbosacral regions. Often there is no radiographic evidence of disease. The clinical signs of brain lymphoma are attributable to the region of brain affected. Advanced imaging with MRI or CT can be helpful in determining extent and location of the lesion, and to evaluate for multifocal disease. Because cerebral spinal fluid evaluation is not always definitive for lymphoma, a diagnosis may be attempted through cytologic evaluation of the bone marrow or kidneys since these organs are also involved in up to 70% of cases.

Staging

As in canine lymphoma, beyond those initial diagnostics performed to establish the diagnosis of lymphoma, additional diagnostics should be considered as part of complete staging.

A complete blood work-up including a CBC with differential blood cell count, serum biochemistry profile, urinalysis, and FeLV/FIV screen should be completed on all cats. While most cats will have an unremarkable blood profile, this is useful to evaluate for the presence of other co-morbid conditions.

A bone marrow aspirate is indicated in cats with blood dyscrasias to confirm the presence of lymphoma and rule out other etiologies. Results of a bone marrow

aspiration may help guide treatment if blood dyscrasias are present.

Thoracic +/- abdominal radiographs or preferably abdominal ultrasound are recommended to determine the presence and extent of disease within visceral organs.

Therapy

There is less known about multicentric lymphoma treatment protocols in the cat relative to the dog. While success of the various chemotherapy protocols is highly variable, the majority are capable of inducing a first remission of >6 months after induction. Protocol choice is based on cell type/grade.

Small Cell or Low-Grade Lymphoma

Cats with a well-differentiated or small cell form of lymphoma can have an excellent prognosis, and may survive for prolonged periods, with chlorambucil and prednisolone.

Large Cell or High-Grade Lymphoma

Similar to the dog, drugs with established activity in intermediate and high-grade lymphomas include cyclophosphamide (C), doxorubicin (H, hydroxydaunorubicin or doxorubicin), vincristine (O, Oncovin®,), methotrexate, CCNU (lomustine) and prednisone (P). Multiple protocols incorporate these drugs as first- or second-line treatments and are considered a COP- or CHOP-based protocol, depending on the drugs used. These multiagent chemotherapy protocols are used commonly for cats with intermediate to large cell (high-grade) lymphoma of any anatomic location (Table 134.3). Currently, few data exist to compare outcomes using the various modifications of treatment for cats; consequently a protocol may be based on client/veterinarian preference.

Unlike canine lymphoma, in which chemotherapy is often discontinued after a period of time as long as the pet continues to be in remission, comparable data do not exist in the cat. Consequently, many cats continue to receive maintenance chemotherapy for up to a year or longer. Also unlike in humans and dogs receiving doxorubicin-based protocols, cats are at low risk for cardiotoxicity though they are susceptible to its renal toxic effect. Renal function must be monitored with BUN, creatinine, and urine specific gravity, ideally before each treatment with doxorubicin. Corticosteroids may exacerbate cardiomyopathy in cats and these drugs should be avoided or used conservatively in patients with clinical or subclinical heart disease.

Renal Lymphoma

Because many cats with renal lymphoma have or will develop CNS involvement, treatment with a multiagent protocol incorporating a drug with CNS penetration (such as CCNU) is recommended.

Central Nervous System Lymphoma

Central nervous system lymphoma should be treated with chemotherapy or radiation therapy emergently as clinical signs, particularly paralysis, may become permanent if treatment is delayed.

Table 134.3 Modified COP protocol for treatment of feline lymphoma

Treatment week	Drug, dosage, and route
1 CBC/chemistry profile/UA as baseline prior to therapy	Vincristine 0.5–0.6 mg/M^2 Cyclophosphamide 200 mg/M^2 Prednisolone 2 mg/kg daily
2 Pretreatment CBC/plt	Vincristine 0.5–0.6 mg/M^2 Prednisolone 2 mg/kg daily
3 Pretreatment CBC/plt	Vincristine 0.5–0.6 mg/M^2 Prednisolone 1 mg/kg daily
4[a] Pretreatment CBC/plt and renal profile with USG if using doxorubicin	Vincristine 0.5–0.6 mg/M^2 Cyclophosphamide 200 mg/M^2 OR substitute with doxorubicin (1 mg/kg) if not in clinical remission Prednisolone 1 mg/kg daily
5/6 Posttreatment CBC/plt	Restage with ultrasound and/or thoracic radiographs
7 Pretreatment CBC/plt	Vincristine 0.5–0.6 mg/M^2 Cyclophosphamide 200 mg/M^2 Prednisolone 1 mg/kg daily
8/9	No treatment
10 Pretreatment CBC/plt	Vincristine 0.5–0.6 mg/M^2 Cyclophosphamide 200 mg/M^2 Prednisolone 1 mg/kg daily
11/12	No treatment
13 Pretreatment CBC/plt	Vincristine 0.5–0.6 mg/M^2 Cyclophosphamide 200 mg/M^2 Prednisolone 1 mg/kg daily
14/15	No treatment Restage when clinically indicated
16 Pretreatment CBC/plt	Vincristine 0.5–0.6 mg/M^2 Cyclophosphamide 200 mg/M^2 Prednisolone 1 mg/kg daily[b]

[a]If a clinical remission has not been achieved by week 4, then substitute with doxorubicin and alternate with vincristine/cyclophosphamide. Use doxorubicin only if adequate renal function has been established with renal profile and urine specific gravity.
[b]Continue every three weeks until relapse or for one year of continuous remission.
CBC, complete blood count; plt, platelets; UA, urine analysis; USG, urine specific gravity.

Nasal Lymphoma

If nasal lymphoma is confirmed to be nonsystemic, local radiation therapy may be indicated as a sole treatment.

Other Anatomic Locations

Other infrequently encountered forms of lymphoma in the cat include laryngeal or tracheal. Cats presenting with disease isolated to these locations can respond positively to local radiation therapy +/- chemotherapy for periods of 6–12 months.

Prognosis

Generally, the overall response rate and survival time in cats are much lower than those achieved in dogs. However, this varies and is determined by the anatomic location at presentation, grade of tumor, and viral status of the cat.

High-grade tumors progress rapidly but are more likely to respond to multiagent chemotherapy for a finite period of time, whereas low-grade tumors progress slowly and can be easily managed as chronic diseases.

Cats with mediastinal lymphoma respond well to chemotherapy initially, but the duration of response is usually short-lived (2–3 months).

Cats with high-grade alimentary lymphoma treated with a multiagent chemotherapy protocol can respond with median survival times of 210 days. A positive response to treatment is the best prognostic indicator. Cats achieving a complete or partial remission have a significantly longer survival time of >2 years.

Cats with nasal lymphoma can enjoy lengthy survival times of 1–3 years or more with radiation therapy +/- chemotherapy.

Central nervous system and renal lymphoma are uncommon but when encountered, cats can experience a short period of clinical benefit from chemotherapy and/or radiation therapy for a median of 2–6 months.

Conclusion

Cats and dogs with lymphoma can respond favorably to chemotherapy +/- radiation therapy. The treatments are generally well tolerated with most animals achieving a clinical benefit for variable periods of time. Prognosis is dependent on location, extent of disease, histologic grade, and phenotype. Cancer treatment in pets can be a rewarding experience. Most pet owners appreciate the dedication of the veterinarian and the additional quality time they gain with their pets.

Further Reading

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135

Plasma Cell Disorders

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Etiology/Pathophysiology

Plasma cell neoplasms develop from clonal proliferation of terminally differentiated immunoglobulin-producing B lymphocytes. They typically produce a homogenous monoclonal immunoglobulin which is why they are thought to originate from a single cell. However, not all neoplasms are secretory and some may be biclonal or even polyclonal. Reported plasma cell disorders (PCD) in dogs and cats include multiple myeloma (MM), cutaneous and noncutaneous extramedullary plasmacytoma (EMP), IgM (Waldenström) macroglobulinemia (WM), solitary osseous plasmacytoma (SOP), and plasma cell leukemia.

The etiology of PCD in dogs and cats is largely unknown. No retroviral association was found in cats. Chronic immune stimulation in rodent models and chronic infections in people have been associated with MM. Exposure to ionizing radiation is a well-known risk factor and agricultural chemicals, benzene, and petroleum products have been considered potential risk factors in humans.

Multiple myeloma usually originates from multiple bone marrow sites in dogs. In cats, multicentric noncutaneous EMP with or without bone marrow involvement may present as MM. The neoplastic plasma cells in MM typically secrete abnormal amounts of a single whole or partial (light or heavy chain) immunoglobulin called the M component, or paraprotein. In dogs, the M component is usually IgA or IgG with similar frequency. In cats, the IgG class is four times more common than IgA. IgM overproduction is uncommon in both species and is more often associated with WM, a form of lymphoplasmacytic lymphoma. The abnormal light chains are excreted in the urine and are called Bence Jones proteins.

Uncommon presentations in both species include biclonal gammopathies, nonsecretory MM, monoclonal gammopathies without hyperglobulinemia and cryoglobulinemia. Cryoglobulins are immunoglobulins that precipitate in temperatures below 37 °C, so they are usually lost in the clot when the blood is allowed to clot at room temperature.

Multiple myeloma negatively affects many organ systems as a result of tumor infiltration, high levels of circulating or deposited M component, production of cytokines by tumor cells or bone marrow microenvironment and the effects on the immune system.

Abnormal immunoglobulins can lead to hyperviscosity syndrome (HVS) when high protein levels are reached. The incidence of HVS is highest with IgM (WM) which is a pentamer and has a high molecular weight, followed by IgA-secreting myelomas which are dimers that can polymerize. IgG-associated HVS occurs less frequently. Increased serum viscosity leads to "sludging" of blood in the vasculature that results in hypoxia and bleeding diathesis leading to organ damage. HVS occurs in about 30% of dogs with MM and most commonly affects the central nervous system (CNS), eyes, cardiovascular system, and coagulation system.

Bleeding disorders are common in dogs with MM and the mechanism is likely multifactorial. Coating of platelets with paraproteins leads to decreased adhesiveness, failure to release platelet factor III, and thrombocytopathia. Paraproteins can also interfere with clotting factors and lead to abnormal fibrin polymerization. Thrombocytopenia due to bone marrow infiltration (myelophthisis) or immune-mediated disease may also contribute to bleeding. Approximately 33% of dogs and 25% of cats with MM have clinical evidence of bleeding.

Nonregenerative normocytic normochromic anemia is the most common hematologic abnormality in MM patients, present in about 66% of dogs and cats. Etiologies may include myelophthisis, decreased erythrocyte life span due to coating with paraprotein, blood loss, production of inhibitory cytokines by myeloma cells and decreased erythropoietin production due to renal

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dysfunction. Thrombocytopenia and neutropenia may also occur.

Suppression of normal immunoglobulin production is common and is suggested to result from normal feedback inhibition induced by the monoclonal gammopathy. In people, maturation of normal B cells to plasma cells is suppressed as well as T helper cell number and function. These abnormalities can lead to immunosuppression and, combined with neutropenia, increased risk for bacterial infections.

Osteolytic bone lesions are induced by secretion of osteoclast-activating factors from the bone marrow microenvironment and myeloma cells. These factors include the cytokines interleukin (IL)-1 beta, tumor necrosis factor (TNF)-beta, and IL-6. Osteolytic lesions may cause pain, lameness, spinal compression due to extradural tumor masses, or vertebral fractures which can lead to paresis or paralysis. Lytic bone lesions are detected in 50–60% of dogs with MM. In cats, skeletal involvement is more variable, noted to occur in 8% of cases in one case series and in up to 58–67% in other reports.

Hypercalcemia occurs in 15–20% of dogs and 9–25% of cats with MM. Hypercalcemia was present in 50% of dogs with MM at diagnosis when ionized calcium rather than total calcium was measured. The main proposed mechanism is direct bone osteolysis, although skeletal lytic lesions are more common than hypercalcemia. Hypercalcemia may be worsened by concurrent renal disease.

Renal disease is one of the serious complications of MM, reported in 30–50% of dogs and about 25% of cats. Light chains that are filtered by the glomerulus precipitate in the renal tubule, causing interstitial nephritis. Hypercalcemia, infiltration of the kidneys by myeloma cells, decreased renal blood flow secondary to hyperviscosity, amyloidosis, glomerulonephritis, and pyelonephritis following immunosuppression may also contribute to renal dysfunction.

Cardiac disease, a less common complication, may be explained by increased peripheral vascular resistance, excessive cardiac workload, and myocardial hypoxia secondary to hyperviscosity.

Waldenström macroglobulinemia is a rare disease in animals and is considered a form of lymphoplasmacytic lymphoma involving the spleen, lymph nodes, and bone marrow along with serum IgM-related signs of hyperviscosity or cryoglobulinemia. Osteolytic bone lesions and hypercalcemia are not present and Bence Jones proteinuria is uncommon.

Solitary PCD include EMP and SOP. They are defined as local accumulation of neoplastic monoclonal plasma cells without evidence of systemic PCD. Canine EMPs are distinct, usually solitary tumors unrelated to MM. The skin, especially the head, and extremities are affected most commonly, followed by the mucous membranes of the oral cavity (Figure 135.1) and the colorectal junction.

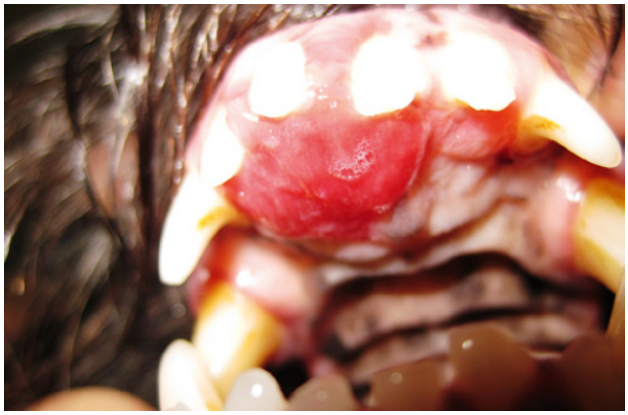


Figure 135.1 Oral extramedullary plasmacytoma in the maxilla of a dog.

Other sites such as gastrointestinal, trachea, larynx, eye, genitalia, and others are rare and comprise 1% of all EMP cases. Cutaneous, oral, and colorectal EMPs are usually benign but can be locally invasive and cause bone destruction in the oral cavity. In humans, cutaneous EMP is uncommon and is often part of a multicentric disease. In dogs, MM rarely exhibits cutaneous involvement. Fewer reports exist regarding solitary EMP in cats but their behavior and site distribution appear similar to dogs. The multicentric EMP as part of MM is more common in cats than dogs although incorporating abdominal ultrasound and cytology into the staging of MM may prove abdominal organ involvement is more common than previously thought. A recent study showed that 57% of dogs with MM that underwent abdominal ultrasound were cytologically confirmed to have liver, spleen, or abdominal lymph node involvement. Amyloid deposits of immunoglobulin origin occur in 3–13% of EMPs.

Solitary osseous plasmacytomas have been reported in the dog affecting the appendicular skeleton, zygomatic arch, and vertebrae. In humans (and probably in dogs), the prognosis is much better than for MM but about 50% of SOPs will eventually develop into MM.

Epidemiology

Multiple myeloma is uncommon in both dogs and cats, representing less than 1% of all malignancies. It comprises about 8% of all hematopoietic tumors and 3.6% of all primary and secondary bone tumors in dogs. The incidence in both species is lower than in humans.

Signalment

Multiple myeloma affects older animals with a median age of 8–9 years (range, 2–15) in dogs and 12–14 years in cats

(range, 4–18). There is no breed or sex predilection in dogs. In cats, it is most common in domestic short-hairs and a slight male predisposition has been reported. EMPs usually occur in middle-aged to older dogs (median age 9–10 years). The cocker spaniel and West Highland white terrier seem to be at increased risk. Solitary EMPs are less common in cats and SOP is rarely reported in both species.

History and Clinical Signs

Clinical signs of MM are variable, with a median duration of one month prior to diagnosis. In dogs, the most common presenting sign is lethargy and weakness (62%). Skeletal lytic lesions lead to lameness, pain and paresis or paralysis with vertebral involvement (47%). Bleeding disorders most commonly present as epistaxis or gingival bleeding (37%). Ocular and CNS abnormalities are caused by HVS, systemic hypertension or both. Ocular signs include retinal bleeding, enlarged tortuous retinal vessels, retinal detachment (35%), and acute onset of blindness. Hyphema, episcleral injection, corneal edema, and aqueous flare may also occur. CNS signs include dementia, personality changes, disorientation, and seizures (12%). Polyuria/polydipsia (25%) may develop secondary to renal disease and hypercalcemia. Cardiopulmonary signs (syncope, cyanosis, congestive heart failure [CHF]) are less common. Vomiting, anorexia, and weight loss have been seen in dogs with hypercalcemia and/or renal disease. Some dogs may present with secondary infections such as cystitis.

Physical examination findings may include pale mucous membranes, dehydration, fundic changes, neurologic deficits, fever, and cranial organomegaly.

In cats, lethargy, anorexia, and weight loss are the most common clinical signs. Vomiting and diarrhea, as well as cranial organomegaly and cutaneous or subcutaneous masses are more common than in dogs.

Cutaneous and mucosal EMPs usually appear as pink or red, raised, alopecic and sometimes ulcerated solid nodules, about 1–2 cm in diameter (see Figure 135.1), but they can range from 0.2 to 10 cm in diameter. The majority of tumors are single, but some dogs may develop more than one tumor simultaneously or sequentially. Oral EMPs can cause bleeding and decreased appetite. Colorectal EMPs can lead to hematochezia, rectal bleeding, tenesmus, and rectal prolapse. SOPs cause pain, lameness, or neurologic symptoms.

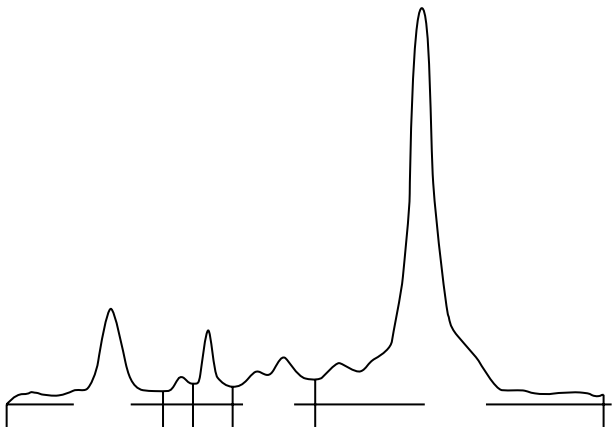
Diagnosis

Suspicion of MM usually arises in an animal presenting with appropriate clinical signs and hyperglobulinemia. Initial evaluation includes CBC, full chemistry panel, and urinalysis. Additional findings on these tests such as anemia, hypoalbuminemia, renal dysfunction, and hypercalcemia should prompt work-up for MM (Table 135.1).

Table 135.1 Frequency of abnormal diagnostic test results in dogs and cats with MM

Test abnormality	Dogs (%)	Cats (%)
Anemia (nonregenerative)	68	41–69
Thrombocytopenia	33–45	50
Leukopenia	25	37
Circulating plasma cells	10	5–27
Hypoalbuminemia	65	36
Hypocholesterolemia	Not reported	68
Renal azotemia	33	23–36
Hypercalcemia	17–50	9–25
Proteinuria	35	77
Bence Jones proteinuria	40	44–50
Hyperviscosity	32	35–44
Bone lysis (radiographs)	50	8–56

Serum protein electrophoresis (SPE) separates proteins based on their size and electrical charge. The immunoglobulins are contained in the beta and gamma fractions and monoclonal gammopathies produce a narrow peak in one of these fractions (Figure 135.2). Rarely,



Fractions	%	Ref. %	g/L	g/L
Albumin	12.9	55.8–66.5	16.4	43.0–51.0
Alpha 1	2.3	2.9–4.0	2.9	1.0–2.0
Alpha 2	5.3	7.1–14.5	6.7	5.0–8.0
Beta	9.8	8.6–14.8	12.4	6.0–9.0
Gamma	69.7	9.2–18.2	88.5	6.0–11.0

Figure 135.2 Serum protein electrophoresis results in a dog with MM. The albumin peak is on the far left and there is a tall, narrow spike in the gamma region on the right consistent with monoclonal gammopathy. Total protein level was 12.7 g/dL. *Source:* Courtesy of Dr Roni Minke, American Medical Laboratories, Hertzeliah, Israel.

MM produces a biclonal gammopathy. A dog with MM may still have a normal globulin level due to suppression of normal globulin production. Therefore, if findings support MM, SPE should be done even if total globulin level is normal. When monoclonal gammopathy is demonstrated, immunoelectrophoresis can determine the antibody type.

Urinalysis provides information on renal function, urinary tract infection, and proteinuria. However, urine dipsticks only measure albumin. Special heat precipitation methods are required to detect Bence Jones proteins. This is a qualitative test associated with a high rate of false-positive and -negative results in people. Urine electrophoresis or immunoelectrophoresis may be more reliable.

Bone involvement may appear on radiographs as multiple osteolytic lesions affecting mainly the axial skeleton, or as diffuse osteoporosis (Figure 135.3). Plain survey skeletal radiographs are recommended for detection of these lesions. It is best to start with thoracic, lumbar spine, and pelvic radiographs, unless pain is localized to other bones. Skeletal CT can be more sensitive than radiographs for detection of small lesions and spinal cord compression. Radionuclide bone scans are not recommended because MM lesions are primarily lytic and may be undetectable. Abdominal ultrasound is recommended in all cats and in dogs without bone marrow plasmacytosis. Most common abnormalities are splenomegaly, hepatomegaly, and changes in echogenicity or nodules in these organs.

Bone marrow aspiration is required for a definitive diagnosis of MM and is taken from routine sites. In some cases, aspiration or a needle core biopsy is taken directly from a lytic lesion if it is large enough and accessible. This is especially pertinent in cases of SOP. Normal bone marrow contains less than 5% plasma cells. Finding of >10% plasma cells in the marrow, especially if cellular atypia or clustering is present, is used to diagnose MM by some investigators, while the majority agree that >20% plasma cells is a more reliable value. The morphology of neoplastic plasma cells varies from normal to large pleomorphic cells with large cytoplasm, high mitotic index, and multinucleation (Figure 135.4). In cats (and less often in dogs), bone marrow infiltration may not be severe enough and visceral organ infiltration may be diagnostic instead.

In patients with hypercalcemia, ionized calcium is indicated for confirmation because binding of calcium to paraproteins will increase total calcium while ionized calcium remains normal. Hypocholesterolemia was reported in 68% of cats with MM in one study. A possible explanation is downregulation of cholesterol production by the liver to maintain oncotic pressure in the face of hyperglobulinemia. When HVS is suspected, serum viscosity can be measured in relation to water. Normal canine serum viscosity is 1.6–1.8 times that of water. Clinical signs of HVS usually appear when serum viscosity is greater than five times that of water.

Differential diagnoses for monoclonal gammopathy include B cell lymphoma, mainly chronic but also acute B cell lymphoid leukemia, WM, chronic infections such as *Ehrlichia canis* and leishmaniasis in dogs, feline infectious peritonitis (FIP) in cats, and monoclonal gammopathy of unknown significance (MGUS). The latter is a benign process, well recognized in humans but only a few cases have been reported in dogs and cats.

Diagnosis of EMP and SOP is made by tissue biopsy or fine needle aspirate. Most EMPs are not well



Figure 135.3 Lateral radiograph showing well-demarcated small "punched out" lytic lesions and a "lacy" trabecular pattern in the cervical vertebrae due to diffuse osteopenia in a dog with MM.

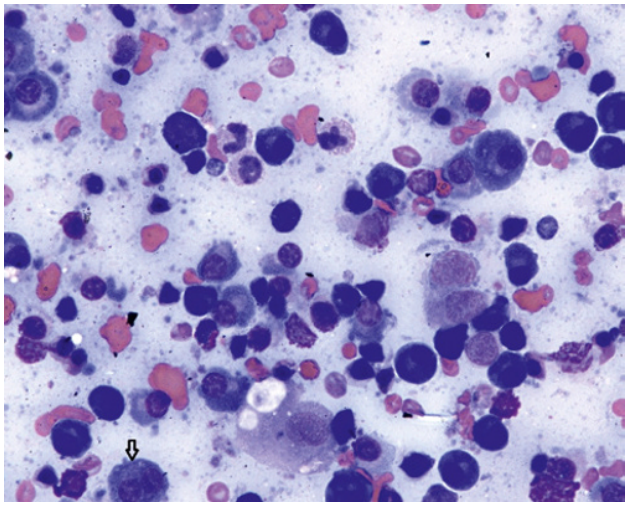


Figure 135.4 Bone marrow aspirate from a dog with multiple myeloma showing abundant plasma cells with a typical paranuclear clear zone of the golgi apparatus. A single bincucleate cell is present (*arrow*). *Source:* Courtesy of Dr Sharon Kuzi, Koret School of Veterinary Medicine, Israel.

differentiated and can be difficult to differentiate from other round cell tumors. Immunohistochemistry (IHC) is sometimes utilized in these cases to detect light and heavy chains. The majority of EMPs stain for lambda light-chains, similar to the physiologic distribution of light chains in normal canine and feline plasma cells. Staining for multiple myeloma oncogene 1/interferon regulatory factor 4 (MUM1/IRF4) is highly sensitive for EMPs but 21% of B cell lymphomas stain positive as well. It is therefore recommended to use it in combination with other round cell markers together with morphology of the cells. SOP, GI EMP, and multiple cutaneous EMPs in dogs can metastasize, or develop into MM. Therefore, it is important to fully stage them at diagnosis. Staging includes SPE (even if total globulin level is normal), bone marrow aspiration, survey skeletal radiographs, and abdominal ultrasound.

Therapy

Chemotherapy with melphalan and prednisone is the treatment of choice for MM in dogs. Although cure is unlikely, response to treatment is achieved in most dogs often for relatively long periods of time. Melphalan is prescribed at a dose of 0.1 mg/kg PO once daily for 10 days, then 0.05 mg/kg PO once daily continuously. An alternate pulse protocol with melphalan at 7 mg/m$_2$ (rounded to the nearest whole 2 mg tablet) given once daily for 5 days every 21 days is also used. Prednisone is given at a dose of 0.5 mg/kg PO once daily for 10 days, then 0.5 mg/kg PO on alternate days indefinitely or discontinued after 60 days. These protocols are usually well tolerated and the main toxicity of melphalan is myelosuppression, most commonly thrombocytopenia.

It is generally accepted that a reduction in serum levels of the M component by at least 50% is a reasonable therapeutic goal. In addition, clinical signs and clinical pathology abnormalities should also improve, usually within 2–4 weeks. Radiographic improvement of skeletal lytic lesions may take several months, and may only be partial. Routine monitoring of response to treatment and toxicity is usually done with a complete blood count (CBC), total globulin level, and Bence Jones protein (if originally present) every two weeks. A CBC should be checked at least once on day 7 of the pulse protocol. Once a good response is achieved and no cytopenias have been identified, follow-up can be done less often.

Melphalan and prednisone have also been used in cats but melphalan is more myelosuppressive than in dogs, and may cause prolonged neutropenias. Ideally, melphalan should be compounded for cats to allow accurate dosing and avoid hazardous exposure of humans. Use of chlorambucil, cyclophosphamide, CCNU, or multidrug therapy may be more suitable in cats with MM than melphalan and responses have been documented.

Chlorambucil has been recommended for the treatment of WM at a dose of 0.2 mg/kg PO once daily, although treatment with melphalan and prednisone may be effective as well.

Rescue therapy after disease relapse may be attempted with other alkylating agents including cyclophosphamide, chlorambucil, or CCNU. The VAD protocol which includes vincristine, doxorubicin, and dexamethasone has been extrapolated from humans, while others have used CHOP-based lymphoma protocols. There are only anecdotal data regarding these rescue protocols, but it appears that while response rate is quite high, most responses are of short duration.

Symptomatic animals presenting with severe complications of MM require supportive care simultaneously with diagnosis and initiation of antitumor therapy. Animals with severe signs of HVS (altered mentation, hemorrhage, retinal detachment, or CHF) can be treated with plasmapharesis. Renal dysfunction, especially with concurrent hypercalcemia, is treated with IV fluid diuresis until symptoms improve. Severe hypercalcemia can be treated with calcitonin in addition to fluid diuresis or with IV bisphosphonates if diagnosis is delayed. Prednisone is highly effective in treating hypercalcemia but it should not be started prior to making a definitive diagnosis as it may obscure results. Hypercalcemia usually resolves quickly after starting chemotherapy. Dogs with extensive lytic lesions should have exercise restriction and analgesia.

Bisphosphonates (BP) inhibit osteoclast activity and in human. They have been shown to reduce bone pain, the incidence of pathologic fractures and prolong time to first event. The more potent amino-bisphosphonates such as pamidronate or zoledronate also appear to have antitumor activity and zoledronate has shown a survival advantage over placebo and other BP in patients with symptomatic MM. Pamidronate or zoledronate probably have a role in the treatment of animals with osteolytic MM, but they have not yet been critically evaluated.

Large lesions can be treated with radiation therapy (RT). In addition, fractures in weight-bearing bones or vertebrae require surgical stabilization alone or combined with RT. Healing can occur, although it can be very slow and only if local tumor control is achieved. Patients presenting with a fever, other evidence of infection, or severe neutropenia should be treated with broad-spectrum antibiotics. Samples for culture and sensitivity prior to antibiotic therapy should be collected if infection is suspected.

The treatment of choice for EMPs is usually surgical resection. The cutaneous and mucosal EMPs are usually benign and complete surgical excision carries an

excellent prognosis. In some cases, RT has been used for nonresectable or recurrent EMPs as well as melphalan and prednisone alone, or combined with RT. In cases with SOP, surgical excision when possible or RT is the treatment of choice. Fracture repair, or spinal cord decompression and vertebral stabilization, followed by RT could be considered when appropriate. Chemotherapy may be used when RT is not available. Both modalities have resulted in prolonged local control that is not necessarily accompanied with bone remodeling.

Prognosis

Two larger case series of dogs with MM, treated with melphalan and prednisone, have been published to date, 32 years apart. One compared continuous and pulse protocols and found no statistically significant difference in any of the outcome variables, although a small cohort size and high numbers of censored dogs could have impacted the results. In both studies, some dogs received an initial dose of cyclophosphamide as well. In the first study (Matus et al), a complete response (undetectable serum monoclonal Ig) was observed in 43% of dogs, partial response (≥ 50% decrease in Ig) in 49% and no response in only 8%. The median survival time (MST) of all 37 dogs was 540 days and the addition of cyclophosphamide did not affect survival. In the second study (Fernandez et al), overall response rate was similar (86%), but most were defined as having a complete response. Median survival time for all 38 dogs was 930 days, almost double the time in the first study. Additionally, twelve dogs in the first study were treated with prednisone alone and their MST was 220 days. Matus reported that a response to treatment with chemotherapy was positively associated with survival. Hypercalcemia, Bence Jones proteinuria and extensive bone lesions were negative prognostic indicators for survival. Fernandez showed that renal disease and a high blood neutrophil to lymphocyte ratio around the time of diagnosis also negatively impacts survival. Ionized hypercalcemia and osteolytic lesions among other factors evaluated were not prognostic.

In cats, data are based on small numbers. Overall remission rate is lower and survival times shorter compared to dogs. A MST of 9.5 months was reported in one study and no cat lived more than six months in another.

The prognosis for solitary cutaneous and mucocutaneous EMPs in dogs is generally good. Surgical excision is curative in most cases. Local recurrence rate is reported to be approximately 5% (higher for oral tumors), nodal or systemic disease develops in 2% and new cutaneous EMPs occur in less than 2% of dogs. Cell type, proliferation rate, presence of amyloid, and cyclin D1 reactivity have no prognostic significance in dogs. Dogs with multiple cutaneous EMPs in the absence of MM have been assigned a diagnosis of cutaneous plasmacytosis (CP) based on the rare syndrome in humans, that usually follows an indolent course. In the first reported series, 21 dogs with CP were treated with chemotherapy, most with melphalan and prednisone. The overall response rate was 74%, complete response was 37%, median progression free survival was 143 days, but median overall survival was longer at 542 days. None of the dogs progressed to develop MM. In cats, EMP behavior is less predictable. Some remain localized and surgical excision can lead to long-term control while others progress rapidly to MM.

As in humans, veterinary patients with successfully treated SOP eventually develop local failure, new lesions or MM but they can enjoy long disease-free periods until progression. It is important to thoroughly stage them at initial diagnosis and to monitor routinely for local and systemic relapse with serum globulin levels, careful attention to bone pain, and additional diagnostics if indicated.

Further Reading

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136

Central Nervous System Tumors in Dogs and Cats

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Etiology/Epidemiology/Signalment

Central nervous system (CNS) tumors are infrequently seen in dogs and cats but with increased imaging capabilities (computed tomography, magnetic resonance imaging [MRI], etc.) and increased awareness of specific disease entities, there appears to be a subjective rise in the incidence of diagnosis. By definition, the CNS includes intracranial structures (brain and pituitary gland) as well as spinal cord. In these locations, tumors are typically classified as either primary or metastatic.

Intracranial

The incidence of primary intracranial neoplasia in veterinary patients has been estimated to be 14.5/100 000 in dogs and 3.5/100 000 in cats. The most common type in the dog is meningioma, but glial tumors (astrocytoma and oligodendroglioma), histiocytic sarcoma, choroid plexus tumors, primitive neuroectodermal tumors (PNET), and lymphoma can also occur. Meningioma and lymphoma, followed by pituitary tumors, are the most common primary tumors in cats.

Most dogs with primary neoplasia are >5 years of age with the exceptions of lymphoma, which can occur at any age, and glial tumors, which can occur in young dogs due to their purported genetic predisposition. In the cat, lymphoma can occur at any age, especially in young feline leukemia virus (FeLV)-positive cats.

Some dogs appear to be at higher risk for glial tumors, such as boxers and other brachycephalic breeds. In one recent study, it was reported that boxers represented 50% of all dogs receiving radiation therapy for a brain tumor. In dogs, genetic mutations have been identified in glial tumors, including the P53 tumor suppressor gene. Other mutations that are commonly seen in human brain tumors, including abnormal chromosome copy number aberration (CAN), have also been reported, indicating a possible similar etiology.

Historically, metastatic lesions to the CNS were regarded as uncommon but with improvement in treatment of primary tumors and increased diagnostic capabilities, there appears to be a subjective rise. It is now estimated that up to 50% of intracranial neoplasia in dogs are metastatic in origin. The most common tumor types are carcinomas, malignant melanoma, hemangiosarcoma, and lymphosarcoma.

Spinal Cord

The incidence of spinal cord neoplasia in both species has not been reported. In general, spinal tumors can be described in terms of their anatomic location: extradural, intradural/extramedullary, intramedullary, or mixed compartment. In one large retrospective study of 399 histopathologically confirmed spinal cord tumors in dogs, 48% were extradural, 13% were intradural/extramedullary, 6% were intramedullary, and 33% were mixed compartment.

The most common extradural primary spinal cord tumor in the dog is meningioma, whereas in the cat it is lymphoma followed by meningioma. Intramedullary spinal cord tumors are more likely to be primary (glial) than metastatic, especially in younger dogs. Metastatic intramedullary tumors are reported in both species and are more common in older animals.

Spinal nephroblastoma is a specific malignancy that arises from the embryonic remnants of the immature kidney and typically occurs in young dogs (<3 years of age). This tumor has a predilection for golden retrievers, German shepherd dogs, and arctic breeds. It is most

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often intradural/extramedullary and is located in the caudal thoracolumbar region.

Spinal lymphoma often affects young cats, is associated with FeLV, tends to occur in an extradural location in the thoracic and lumbar spine, and is usually present in multiple locations outside the CNS. In dogs, CNS lymphoma is sporadically identified. It is most commonly the T cell phenotype and located extradurally but can be seen in any location.

Solitary spinal plasmactyomas (benign and malignant proliferation of plasma cells) have been described in both dogs and cats. Some lesions will remain solitary although progression to systemic or multiple myeloma is possible. Please refer to Chapter 135 for more information.

Carcinomas and hemangiosarcoma are the most commonly reported secondary spinal cord tumors in dogs. Osteosarcoma is the most commonly reported in cats. While initially thought to be very rare, the incidence of metastatic lesions in the CNS has risen as diagnostic imaging capabilities and control of the primary disease have improved.

History and Clinical Signs

Intracranial

Most patients with CNS neoplasia will present with altered neurologic function (dull, nerve deficits, paresis, etc.) but this is not universal. Some present with only subtle symptoms such as lethargy, depression or neck pain. Headaches are a common presenting symptom in humans but recognition of this symptom in veterinary patients is extremely difficult. Seizure or seizure-like activity as a presenting clinical finding is more common in dogs than in cats.

Cats and dogs with pituitary tumors may present with a variety of symptoms, many of which are nonneurologic and relate to the endocrine abnormalities of hyperadrenocorticism (polyuria/polydipsia). In cats, unregulated diabetes secondary to acromegaly is common due to excessive growth hormone production. Initially, neurologic abnormalities may be subtle and limited to mild lethargy and disorientation but often progress to more severe abnormalities (seizures, mentation changes, neurologic deficits) with time.

Spinal Cord

Spinal cord neoplasia should be suspected in any patient with a history of forelimb or hindlimb paresis or paralysis. Those presenting with spinal pain should also be suspect as pain is a common presenting symptom in both cats and dogs. Onset of signs may be acute, as with lymphoma, but may be slowly progressive with more slowly growing neoplasia such as meningioma.

Diagnosis

Intracranial

All patients with neurologic symptoms should be considered as possible oncology cases. As such, a stepwise approach is encouraged to allow for accurate staging and identification of a primary tumor, if one exists, prior to surgical intervention, radiation therapy or chemotherapy. Full blood analysis, urinalysis, three-view thoracic radiographs, and abdominal ultrasound should be performed prior to or in conjunction with advanced imaging (CT/MRI/positron emission tomography [PET]).

Magnetic resonance imaging has dramatically changed the ability of the clinician to identify small subtle lesions and as such is the preferred method of diagnosing brain and spinal cord neoplasia. Improvement in technology has increased the utility of CT imaging but MRI is still recommended if available. Involvement and consultation with a radiation oncologist early in the process will allow for proper positioning of the patient should radiation therapy be pursued. With MRI, the majority of dogs and cats will have a hypo- to isointense lesion on T1-weighted and hyperintense on T2-weighted images with a variable amount of peritumoral edema. Contrast enhancement with gadolinium is variable and more common with high-grade neoplasia given the disruption of the vasculature. Cystic lesions are more common with meningioma. The presence of a "dural tail" on contrast-enhanced T1 images has historically been associated with meningioma but can be seen with any neoplasia. This finding results from thickening and contrast enhancement of dural tissue extending from the primary tumor in a tail-like fashion. Other MRI and CT features of specific brain neoplasia types have been described but there is considerable overlap among tumors (Figures 136.1 and 136.2).

With the exception of lymphoma, cerebrospinal fluid (CSF) analysis is rarely useful in distinguishing neoplastic intracranial/spinal cord disease from inflammatory lesions as it rarely reveals neoplastic cells. Analysis often reveals increased protein levels, sometimes with elevated cell counts. If CNS lymphoma is suspected, more advanced testing of CSF such as antigen receptor gene rearrangement and/or flow cytometry should be pursued.

Histopathologic diagnosis of intracranial tumors requires biopsy and the use of stereotactic CT guidance in obtaining the sample. This advanced procedure has become more commonplace. Associated complication rates are reported to range from 12% to 27% with a 5–9%

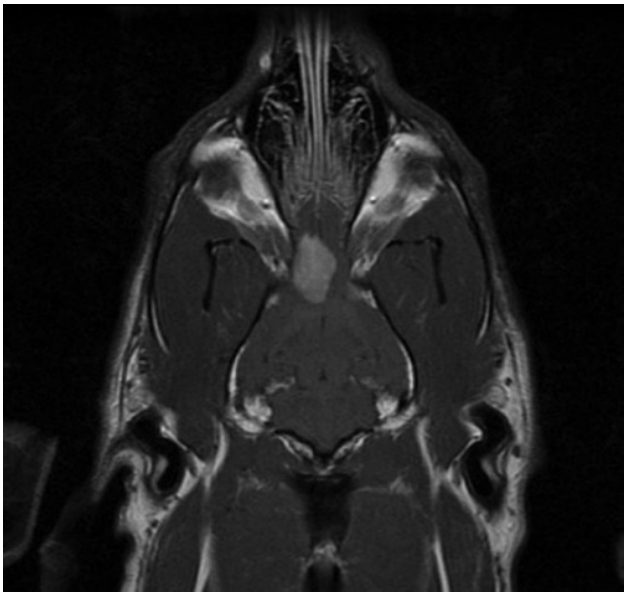


Figure 136.1 T1-weighted post-contrast (gadolinium) coronal image of a frontal lobe mass in a 9-year-old, male, golden retriever. Surgical excision was performed. Histopathology was consistent with histiocytic sarcoma. The dog's only symptom was acute onset of seizures.

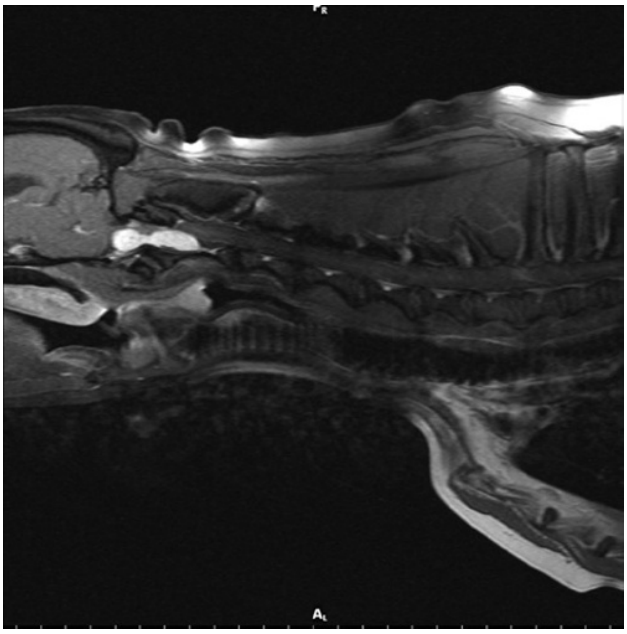


Figure 136.2 T1-weighted postcontrast (gadolinium) sagittal image of a cervical spinal cord tumor in an 11-year-old male castrated boxer, presenting for acute tetraparesis with associated neck pain. The mass is consistent with a meningioma given the extraaxial location and presence of a dural tail at the caudal extent of the mass. Surgical excision and biopsy were not performed. The dog received 48 Gy radiation therapy (16 × 3 Gy) and adjuvant hydroxyurea with nearly complete resolution of the neurologic signs/neck pain and was alive two years following treatment.

mortality rate, but will continue to decrease as experience with the procedure increases. Currently, not all patients receive histopathologic confirmation due to the cost and risk of potential complications. To mitigate some risk, cytology can be considered instead but this too is not commonly performed. Hence many patients are treated without a true diagnosis.

Dogs with suspected hyperadrenocorticism and cats with suspected acromegaly or insulin resistance should be evaluated with CT or MRI. Small pituitary masses may escape detection with CT but larger lesions can be detected with CT especially with newer generation CT imagers.

Spinal Cord

As with intracranial neoplasia, full staging including three-view thoracic radiographs, full blood analysis, urinalysis, and abdominal ultrasound should be performed before or in conjunction with advanced imaging (CT/MRI/PET). Survey spinal radiographs should be performed to evaluate for possible bony lysis. Although rarely helpful, lysis may be present and may indicate a neoplastic process is emanating from outside the CNS with secondary invasion to spinal cord, as in the case of skeletal neoplasia (osteosarcoma, chondrosarcoma) or rarely soft tissue tumors (soft tissue sarcomas, carcinomas). As with intracranial tumors, due to cost, need for advanced diagnostic equipment and risk of potential complications, many patients with spinal neoplasia are treated without a definitive diagnosis.

Treatment/Prognosis

Central nervous system neoplasia, like other tumors, can be managed with a combination of surgery, radiation, and chemotherapy. However, the veterinary literature is limited to uncontrolled and retrospective studies based on relatively small numbers of patients.

Medical Management

Nonspecific treatment options include antiinflammatory doses of corticosteroids for peritumoral edema and anticonvulsant therapy if seizures are a component of the clinical presentation. Phenobarbital, Keppra® (levetiracetam), and zonisamide are all options for control of seizures. Unfortunately, supportive care alone is associated with a poor prognosis in the vast majority of patients. Published survival times in such a group are generally between one and 10 weeks but individual patients may far exceed this.

Surgery

Intracranial

Depending on the location, surgical intervention is recommended as a sole therapy for well-circumscribed meningiomas or a prelude to postoperative radiation therapy and/or chemotherapy. Surgery alone for meningioma in dogs is associated with a median survival time of 4.5–7 months. Radiation therapy in the postoperative setting has increased that median to 16–30 months. Other surgical techniques such as ultrasonic aspiration or endoscopic-assisted surgical resection have resulted in survival times of 41 and 70 months in dogs, demonstrating the utility of more aggressive approaches. Surgery as sole therapy for nonmeningioma tumors is more variable, case dependent, and generally results in median survival times of months rather than years.

Meningioma in the cat is often less aggressive and invasive compared to the dog. Hence, the prognosis with surgery as sole therapy is good to very good with median survival times of 23–28 months.

Surgical approaches to the pituitary gland (transsphenoidal hypophysectomy) have been described but management is usually accomplished with fractionated external beam radiation therapy or more recently radiosurgical techniques in both dogs and cats.

Spinal Cord

Outcomes in dogs and cats with spinal cord neoplasia are understandably highly variable and there is considerable perioperative mortality due to poor return to function. Overall median survival in one study of 37 dogs was 240 days if they survived 20 days following surgery, but 40% did not survive to that point. In a separate study evaluating surgery for intraspinal meningioma, clinical improvement was noted in all dogs surviving the perioperative period but recurrence of clinical signs was at a mean of 19 months. Only a minority were disease free long term, thus indicating the need for postoperative radiation therapy. Postoperative radiation therapy did appear to have a benefit based on time to neurologic deterioration but recurrence of signs and/or tumor was still noted anywhere from 18 to 36 months. In cats undergoing surgical treatment of spinal cord tumors, improvement was reported in 25/26 cases but the median survival time for those with malignant neoplasms was 110.5 days, compared with 518 days for those with benign tumors. In this study, the vast majority of cats eventually succumbed to disease-related problems.

Radiation Therapy

Radiation therapy has evolved over the past several decades from relatively unsophisticated planning techniques to the current state utilizing 3D computer planning and modern technology. Long-term efficacy of radiation therapy alone is limited given the tolerance of the brain and as macroscopic tumor control is generally not as rewarding as adjunctive treatment following cytoreductive surgery. Table 136.1 gives a summary of treatment-related outcomes of CNS tumors.

Recently, stereotactic radiosurgical (SRS) approaches have been employed which allow for one or two fractions of high-dose radiation to be delivered rather than the conventional 15–25 daily fractions of lower doses per fraction. This high dose per fraction is limited to the tumor and a small volume of normal surrounding tissue. This form of treatment theoretically minimizes the risk of complications to normal tissues while providing ablative doses to the tumor. SRS is still in the investigational stage in veterinary oncology and direct comparison to conventional fractionated radiation therapy has not been performed. However, preliminary results in the literature are encouraging and the shortened overall treatment times and minimal dose to noninvolved tissues are attractive to both clinicians and owners and SRS likely represents the future of radiation therapy for brain neoplasia.

Side-Effects

Acute and late developing radiotherapy side-effects vary depending on total dose given, dose per fraction, and the total volume and specific tissue type being irradiated. Late-term side-effects are rare (<20%) but when they occur, management is challenging as they are often life-threatening. Of the late effects, brain necrosis is the most common but others including spinal cord myelopathy can occur. Unfortunately, the clinical distinction between these late side-effects and tumor recurrence is difficult and often requires histopathology.

Acute side-effects of CNS irradiation are rare and often limited to surrounding normal structures in the treatment field such as the oral cavity, otic and ocular structures, and gastrointestinal tract. A syndrome of delayed acute CNS effects can be seen several months after completion of radiation therapy and are manifested by responsiveness to corticosteroids. This syndrome is thought to be a transient demyelination of the white matter rather than true necrosis which is the more classic delayed effect.

Intracranial

Due to the limitations of available veterinary clinical studies, the prognosis following irradiation of many primary intracranial tumors, especially those of glial origin, is largely unknown (see Table 136.1). Based on what has been reported, median survival time following irradiation may range from four months to greater than four

Table 136.1 Summary of outcomes of dog and cats with brain neoplasia

Study	Tumor type	Number of patients	Treatment	Median survival time
Troxel *et al.*	Meningioma	34 cats	Surgery	685d
Greco *et al.*	Meningioma	17 dogs	Surgery (aspirator)	1254d
Axlund *et al.*	Meningioma	14 dog 12 dogs	Surgery Surgery + radiotherapy (RT)	210d 495d
Brearley *et al.*	Meningioma Intraxial tumor Pituitary tumor	41 dogs 34 dogs 8 dogs	RT	347d 282d 147d
Gallagher *et al.*	Meningioma	17 cats	Surgery	3–72-month range 11 cats 810d
Turrel *et al.*	Meningioma, sarcoma, astrocytoma	2 dogs 1 dog 1 dog	RT	322d
Heidner *et al.*	Meningioma Other types Unknown	9 dogs 8 dogs 8 dogs	RT +/- surgery +/- hyperthermia	137d overall
Evans *et al.*	Meningioma Lymphoma Pituitary adenoma Metastatic carcinoma Oligodendroglioma Granulomatous Meningoencephalitis Unknown	4 dogs 1 dog 1 dog 1 dog 1 dog 1 dog 1 dog 5 dogs	RT	1545d (39 Gy) 519d (45 Gy)
Iwamoto *et al.*	Meningioma Glioma Pituitary	18 dogs 6 dogs 1 dog	RT	Not reported
Larue *et al.*	Unknown	65 dogs	RT +/- surgery	405d
Spugnini *et al.*	Meningioma Glioma Choroid plexus	21 dogs 4 dogs 3 dogs	RT	250d
Kent *et al.*	Pituitary tumor	19 dogs	RT	1405d
Mayer *et al.*	Pituitary tumor	8 cats	RT	522d
Bley *et al.*	Extraxial tumor Intraaxial tumor Pituitary tumor	22 dogs 13 dogs 13 dogs	RT	1174d
Sellon	Pituitary tumor	11 cats	Radiosurgery	750d

Source: Adapted from Warren E, Narak J, Axlund T, Smith A. Treatment of intracranial tumors. In: Twedt D, Bonagura J, eds. *Kirk's Current Veterinary Therapy XV*. St Louis, MO: Elsevier, 2014, pp. 1039–47.

years depending on tumor type, prescription dose, and other variables. Regardless, the long-term efficacy of radiation therapy when delivered as sole therapy is limited given the tolerance of the CNS and macroscopic tumor control is generally not as rewarding as when delivered as adjunctive treatment following cytoreductive surgery. For meningioma in the dog, a median survival of approximately one year can be anticipated with radiation therapy. When radiation therapy is delivered as an adjunct to surgery, median survival increases to 16–30 months.

For cats and dogs with pituitary macroadenoma or macroadenocarcinoma, radiation therapy has been recommended and results in good outcomes with both fractionated therapy and radiosurgical techniques. Conformal three-dimension radiation therapy has been described for this tumor in both species and outcomes have been very good to excellent for control of both neurologic signs in affected patients and endocrine abnormalities. Of note, the endocrine manifestations may take several months to improve, which necessitates ongoing monitoring.

Spinal Cord

Radiation therapy of spinal cord tumors has been described in the veterinary literature but studies are limited by low case numbers and lack of histopathologic confirmation in the majority of patients. As with intracranial irradiation, a similar limitation of dose is encountered in the spinal cord and control times are affected by the spinal cord tolerance.

In one study, primary radiation therapy for spinal cord tumors (no histopathologic confirmation) resulted in median control of nine months. In a separate study evaluating surgery for spinal meningioma, those that underwent postoperative radiation therapy appeared to have a benefit based on time to neurologic deterioration but recurrence of signs and/or tumor recurrence was noted anywhere from 18 to 36 months. It is important to recall that deterioration of neurologic condition may be related to tumor recurrence but may also be related to spinal cord damage/necrosis. Therefore, documentation of true tumor recurrence is recommended prior to considering repeat irradiation and/or surgical intervention.

Chemotherapy

There is very little in the veterinary literature regarding chemotherapy for CNS neoplasia with the exception of standard chemotherapy for canine and feline lymphoma. The blood–brain barrier represents a significant obstacle to the delivery of chemotherapy to the brain and spinal cord. Survival times of dogs with unconfirmed (no biopsy) brain tumors treated with lomustine (CCNU) were very similar to patients treated with supportive care alone (93 vs 60 days).

Hydroxyurea is an alkylating agent most commonly used in veterinary medicine for the management of polycythemia. Recently, it has been used as an adjuvant to surgery and/or radiation therapy for dogs with intracranial and spinal meningioma. In one such study, oral hydroxyurea in combination with glucocorticoids was administered to 33 dogs with MRI-diagnosed meningioma, resulting in a significantly longer survival time than observed in 10 dogs treated with glucocorticoids alone.

Temozolamide has recently been evaluated in management of canine glial tumors. Although the data in veterinary oncology are preliminary and no strong recommendations can be made regarding efficacy and comparison with other chemotherapy approaches cannot be made, results in the human literature are encouraging.

For patients with CNS lymphoma, options in addition to standard chemotherapy include lomustine, hydroxyurea, and the antimetabolite cytosine arabinoside which cross the blood–brain barrier. The role of chemotherapy specifically for spinal cord neoplasia is not known, but similar chemotherapeutics are recommended depending on final diagnosis when possible.

Newer Therapies

With increased understanding of how the immune system functions in tumor environments, immunotherapy, in particular tumor vaccination and gene therapy, has recently been developed to aid in the treatment of canine brain tumors but these approaches remain investigational.

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137

Cancer of the Nose and Mouth

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Oral Tumors

Etiology/Pathophysiology

A wide variety of malignant and benign cancers develop in the oral cavity. In dogs, the most common malignant oral tumors in order of frequency are malignant melanoma, squamous cell carcinoma, and fibrosarcoma. In cats, squamous cell carcinoma is the most common oral cancer, with fibrosarcoma second. Risk factors for the development of oral squamous cell carcinomas in cats include flea collars and high intake of either canned food or, specifically, canned tuna fish.

Oral malignant melanoma (OMM) is a highly malignant tumor with frequent metastasis to regional lymph nodes and lungs. Metastasis has been reported in 80–100% of cases, and is associated with site, size, and stage of tumor. Squamous cell carcinoma (SCC) frequently invades bone in both the dog and cat. The metastatic rate for nontonsillar SCC in the dog is approximately 20% but nearly 100% of cases with tonsillar SCC metastasize to the retropharyngeal lymph nodes. The metastatic rate of oral SCC in the cat is unknown, as control of local disease in cats is rarely achieved. Oral fibrosarcomas (FSA) are locally invasive but rarely (<30%) metastasize to regional lymph nodes or lungs. At times, these tumors may histologically appear benign and may be reported as a fibroma or low-grade fibrosarcoma. A well-described syndrome in large-breed dogs, occurring most commonly on the hard palate and maxillary arcade, has been termed "histologically low-grade, biologically high grade" fibrosarcoma. Despite the benign histologic appearance of these tumors, they tend to grow rapidly, metastasize, and invade bone. Rapid recurrence is common.

Epulides are relatively common neoplasms in dogs, but rare in cats. Epulides appear similar to gingival hyperplasia. In general, four types of epulides have been described in the dog: fibromatous, ossifying, acanthomatous, and giant cell. The nomenclature is unfortunately confusing and varied, and the clinician is encouraged to speak directly to the pathologist if there are any questions over terminology. The term *epulis* strictly refers to expansile gingival lesions; more recently, it has been shown that some of these tumors do not involve the periodontal ligament, with many of the fibromatous and ossifying types being derived from the gingiva only. Periodontal odontogenic fibroma has recently been accepted as the correct terminology to use to classify both the fibromatous epulis and ossifying epulis, as these epulides are variations of the same lesion. Also, the acanthomatous epulis has recently been renamed acanthomatous ameloblastoma. A study in 2011 characterized the clinicopathologic features in 153 dogs with oral tumors of possible ondontogenic origin and found that the three most common lesions were canine acanthomatous ameloblastoma, peripheral odontogenic fibroma, and focal fibrous hyperplasia which is a reactive lesion resulting from chronic inflammation.

Acanthomatous ameloblastoma is a benign tumor with aggressive local behavior and frequent invasion into underlying bone. The rostral mandible is the most common site. Fibromatous and ossifying epulides, unlike acanthomatous ameloblastoma, are noninvasive. They are slow-growing, firm masses and are usually covered by intact epithelium. Ossifying epulides usually have a broad base attachment and are less pendunculated than fibromatous epulides. These two epulides vary histologically by the presence or absence of bone formation within the tumor.

Epidemiology

The oral cavity is the site of approximately 6% of all neoplasms in dogs, and oral cancer is the fourth most common cancer overall. In cats, cancer of the oral cavity accounts for 3–12% of all cancers.

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Signalment

In contrast to other malignant oral tumors, OMM tends to occur in smaller breed dogs as well as some large breeds, with an average age at presentation of 12 years. Cocker spaniel, miniature poodle, Anatolian sheepdog, Gordon setter, chow chow, and golden retriever are overrepresented. The average age of a dog presenting with an oral SCC is 8–10 years, while the average age for a cat is 10–12 years. Oral FSAs tend to occur in large-breed dogs, particularly the golden and Labrador retriever. The average age at presentation is 7–9 years and there appears to be a male predisposition. Dogs presenting with fibromatous and ossifying epulides are typically 8–9 years, and a male predisposition has been reported. Shetland and old English sheepdogs are predisposed to acanthomatous ameloblastomas. The average age at presentation is 7–10 years, and a sex predisposition is not reported.

History and Clinical Signs

Cats and dogs with rostral oral cancer commonly present for a mass noted by the owner. Cancer in the caudal oral cavity is rarely noted by owners and the animals often present at an advanced stage of disease, resulting in fewer options for treatment. Clinical signs may include hypersalivation, exophthalmos or facial swelling, epistaxis, weight loss, halitosis, bloody oral discharge, dysphagia or pain on opening the mouth. Occasionally, cervical lymphadenopathy (especially in squamous cell carcinoma of the tonsil) is also found. Complete oral examinations should always be performed during health exams as early intervention may allow for more treatment options and an improved prognosis.

Diagnosis

Due to the wide range of cancer behavior and recommended treatment options for oral cancers, diagnostic evaluation is critical. A biopsy is required for the definitive diagnosis, and this will assist the clinician in determining the biologic behavior and prognosis of the tumor. Impression smear or fine needle aspirate cytology preparations of the tumor are generally not rewarding, as many oral tumors are associated with a high degree of necrosis and inflammation. Most animals will require a short general anesthesia for careful mass evaluation, regional radiographs, and biopsy. An incisional biopsy of the mass is recommended.

Advanced imaging is recommended for oral tumors arising from the maxilla, palate, and caudal mandible. Computed tomography (CT) scans are generally preferred to magnetic resonance imaging (MRI) because of superior bone detail. Both provide more information on the local extent of the tumor than regional radiographs. Information obtained from CT or MRI is critical in the planning of definitive surgery and radiation.

Regional lymph nodes should be carefully palpated for enlargement or asymmetry. Caution should be exercised, however, when making clinical judgments based on palpation alone, as lymph node size is not an accurate predictor of metastasis. Lymph node aspirates should be performed in all animals with oral cancers, regardless of their size or mobility. Three-view thoracic radiographs are recommended to evaluate animals for evidence of pulmonary metastatic disease. Thoracic CT scans should be considered for animals with highly metastatic tumor types such as OMM, since CT scans are more sensitive for detecting pulmonary metastatic lesions. Based on these diagnostic steps, oral tumors are then staged according to the World Health Organization's staging scheme (WHO) (Table 137.1).

Table 137.1 WHO staging system for oral tumors

Stage	Tumor size and metastasis status
I	<2 cm diameter tumor
II	2 to <4 cm diameter tumor
III	>/= 4 cm diameter tumor and/or lymph node metastasis
IV	Distant metastasis

Therapy

Surgery

Surgical resection is the gold standard for oral tumors and is the most commonly used modality for achieving local control. The surgical approach depends on tumor type and location. The majority of tumors involving the maxilla, mandible, and hard palate will have underlying bone involvement so surgical resection should include bony margins to increase the likelihood of complete excision. Minimum margins of at least 2 cm, and preferably 3 cm, are recommended for malignant tumors such as SCC, OMM, and FSA in the dog.

Radiation Therapy

Radiation therapy can be used with palliative or curative intent, or as an adjunct to surgery for incompletely resected tumors or tumors with aggressive local behavior. Radiation therapy can be considered a primary treatment of canine oral SCC, OMM, and some benign tumors such as epulides. These tumors are radiation responsive, even when treated in the setting of gross disease. Radiation protocols used for the treatment of these tumors have involved daily or alternate-day treatments

consisting of 2.7–4.2 Gy per fraction with a total dose ranging from 48 Gy to 57 Gy. More recently, stereotactic radiation is being used as treatment of non-resectable oral tumors. Protocols typically consist of 1-3 high doses of radiation precisely targeted at the tumor, with rapid dose fall off outside of the tumor. These protocols are proving to provide durable control of disease, with decreased acute side effects when compared to traditional radiation protocols; however published studies are still limited.

When using radiation therapy alone, tumor control is better achieved with smaller lesions (T1 or T2 tumors). With megavoltage radiation, local recurrence is reported in up to 30% of cases. When compared to T1 tumors, tumor progression is three times more likely with T2 tumors and 5–8 times more likely with T3 tumors. Local tumor control and survival time, however, can be improved by combining surgery and radiation therapy.

Acute radiation side-effects are common during treatment of oral tumors, but these are generally self-limiting. They can include alopecia and moist desquamation, oral mucositis, dysphagia and ocular changes such as blepharitis, conjunctivitis, keratitis, and uveitis. Late side-effects are rare (<5%), but are much more serious as they are permanent. Late side-effects include skin fibrosis, bone necrosis and oronasal fistula formation, development of a second malignancy within the radiation field, keratoconjunctivitis sicca, cataract formation, and ocular atrophy.

Chemotherapy

Frontline treatment for most oral tumors is control of local disease with surgery and/or radiation therapy. Chemotherapy is indicated for some tumors due to their high metastatic potential. OMM and tonsillar SCC are both highly metastatic tumors, but unfortunately their response to chemotherapy is low.

The nonsteroidal antiinflammatory drug piroxicam, a COX-2 inhibitor, has been shown to have some effect against canine oral SCC. Expression of COX-2 has also been noted in feline oral SCC, but no improvement has been seen in the management of these tumors when piroxicam has been used.

Immunotherapy

A DNA vaccine against tyrosinase is now commercially available for the adjunctive treatment of dogs with OMM. To maximize chances of long-term survival, it has been found that the vaccine is most effective when residual disease is minimized and local regional control has been achieved. Adverse reactions following administration of the vaccine have been found to be minimal, with the most notable side-effects consisting of bruising and hematoma formation.

Prognosis

Malignant Melanoma

The prognosis for dogs with oral malignant melanoma is guarded. In one study, median survival time (MST) of dogs with untreated oral melanomas was two months. Aggressive resection by mandibulectomy or maxillectomy can be effective for control of these tumors but postsurgical recurrence has been reported to develop in 8–85% of dogs and metastasis to regional lymph nodes, lungs, or other viscera may develop in as many as 95%. Metastasis, particularly to the lungs, is the most common cause of death, being reported in 15–67% of dogs. Median survival times for dogs with OMM treated with surgery are approximately 17–18 months, 5–6 months, and three months with stage I, II, and III disease, respectively.

Coarse fraction radiation treatment effectively achieves local control in dogs with melanomas. Reduction in tumor size is attained in 83–100% of dogs, and a complete response rate has been reported to be as high as 70%. In a retrospective study of 140 dogs with OMM treated with radiation therapy, it was found that systemic chemotherapy had no impact on the development of metastatic disease, time to first event, or survival. In the same study, tumor location, bone lysis, and tumor volume were all variables identified to predict time to first event and survival. If none of these risks were present, median survival for dogs with malignant melanomas treated with radiation therapy was 21 months, and if one, two, or three risk variables were present, median survival time was 11 months, five months, or three months, respectively.

The use of immunotherapy for malignant melanoma is showing some promise, but most results involve small numbers of dogs in phase I trials. Xenogeneic vaccine studies for dogs with stage I–III OMM report median survival times of almost three years when local regional control had been achieved and patients received vaccine versus 1.5 years when patients were given the same vaccine, but failed locally.

Canine Squamous Cell Carcinoma

Following mandibulectomy for canine nontonsillar SCC, the median survival ranges from 19 to 26 months versus 10–19 months following a maxillectomy. Tonsillar SCC carries a graver prognosis. Due to higher local recurrence and metastatic rates, studies report one-year survival times of only 10%.

Full-course radiation therapy, either alone or as an adjunct following incomplete surgical resection, is also a successful treatment modality for the management of oral SCC in dogs. With full-course radiation, a study of 39 dogs reported an overall median progression-free

survival time of 36 months. Local tumor recurrence was a more common cause of first treatment failure than regional metastasis to lymph nodes. Dogs with T1, T2, and T3 tumors had a progression free, one-year survival rate of 89%, 83%, and 41% respectively, and a three-year progression-free survival rate of 74%, 53%, and 23%, respectively. A study of 14 dogs treated with full-course radiation therapy as the primary treatment modality reported median disease-free interval and survival of 12 and 14 months, respectively. The median disease-free interval was 16 months in dogs 9 years or less, and seven months in dogs older than 9 years of age.

Feline Squamous Cell Carcinoma

The prognosis for feline SCC is poor, as there is no known consistent, effective treatment for gaining local control. In one series of 52 cats, the one-year survival rate was less than 10% with median survival times of three months for surgery, surgery and radiation therapy, radiation therapy and low-dose chemotherapy, and radiation therapy with hyperthermia. Other studies investigating surgery alone, have reported median survival times of 5.5–7.5 months, but only tumors of the mandible were considered resectable. In a separate study the combination of surgery and radiation reported a survival time of 14 months. All cases were arising from the mandible.

Radiation therapy alone is generally ineffective in the management of cats with oral SCC. However, the combination of radiation with radiation sensitizers or chemotherapy has resulted in response rates from 70% to 100% and median survival times of approximately 3–6 months. A recent prospective study including 31 cases of oral SCC in cats evaluated the effectiveness of an accelerated radiation therapy protocol and concomitant carboplatin for treatment. Median survival for all cats in this study was 5.4 months, while cats with tumors of tonsillar origin or cheek responded best to therapy with a mean survival of two years.

Fibrosarcoma

The prognosis for dogs with oral fibrosarcoma is guarded. Multimodal treatment with surgery and radiation therapy of the local disease results in the best survival rates. Following maxillectomy or mandibulectomy alone, local recurrence is reported in up to 60% of dogs with a median survival time of 10–12 months and a one-year survival rate of 50%. Oral fibrosarcomas are considered to be radiation resistant. A smaller tumor size improves the outcome following radiation therapy, with the median progression-free survival time of 45 months for dogs with T1 tumors compared to 31 months and seven months for T2 and T3 tumors, respectively. When radiation therapy is used as an adjunct to surgery, a median survival time of 18–26 months is reported. A study completed in 2011 reported the outcome in 29 dogs with oral fibrosarcomas treated with surgical excision with or without adjuvant radiation. The median survival time in this study was reported to be approximately two years with a one- and two-year progression-free survival rate of 88% and 58%, respectively.

Epulides

The prognosis for dogs with epulides is excellent following treatment with either surgery or radiation therapy. In contrast to fibromatous and ossifying epulides, wide local excision of adjacent soft tissue and bone is necessary for cure of acanthomatous ameloblastomas. Local recurrence rate following bone-removing surgery is less than 5%.

Radiation therapy is indicated for acanthomatous ameloblastomas that are not curable with surgery alone. In a prospective clinical trial, 47 dogs with acanthomatous ameloblastomas (39 dogs) or fibromatous or ossifying epulides (eight dogs) were treated with 12 fractions of 4 Gy, three times a week to a total dose of 48 Gy. Clinical stage was the only significant prognostic factor, with dogs that had stage T3 tumors having a 7.9 times higher risk of tumor recurrence than dogs with stage T1. In a 2004 study of 57 dogs treated with radiation therapy, the median overall survival time was four years.

Intralesional bleomycin has also been described for the treatment of acanthomatous ameloblastomas. With this treatment, a complete response was sustained in all four dogs treated for greater than one year with no local recurrence.

Nasal Tumors

Etiology/Pathophysiology

Carcinomas, including adenocarcinoma, squamous cell carcinoma, and undifferentiated carcinoma, comprise nearly two-thirds of nasal tumors in the dog while sarcomas, including fibrosarcoma, chondrosarcoma, osteosarcoma, and undifferentiated sarcoma, comprise the bulk of the remaining tumors. In the cat, lymphoma and carcinoma are the most common tumors of the nasal cavity. It has been speculated that dogs living in urban environments may be at higher risk for developing nasal tumors, and some studies have also associated the exposure of environmental tobacco smoke as an increased risk factor, but this finding is not consistent. Nasal lymphoma in cats is typically feline leukemia virus (FeLV) antigen negative, and definite risk factors have not been reported.

Nasal tumors are locally invasive tumors that carry a relatively low metastatic rate. Metastasis at the time of diagnosis is seen in approximately 10% of animals, but may be as high as 40–50% at the time of death. Death, however, is usually attributable to local disease progression rather than metastatic lesions. Most common sites of metastasis are the regional lymph nodes and lungs. Less common sites include bones, kidneys, liver, skin, and brain.

Epidemiology

Nasal tumors account for approximately 1% of all neoplasms in dogs and cats.

Signalment

The average age at the time of diagnosis for canine and feline nasal tumors is 10 years. It appears that medium- and large-breed dogs may be more commonly affected. Also, a slight male predilection has been suggested in dogs, and dolichocephalic breeds may be at an increased risk.

History and Clinical Signs

The most common clinical signs associated with nasal tumors include epistaxis, bloody or mucopurulent nasal discharge, facial deformity, sneezing, dyspnea, stertorous breathing, exophthalmia, and ocular discharge secondary to obstruction of the nasolacrimal duct. The average duration of clinical signs before diagnosis is three months. All of these clinical signs can overlap with other intranasal diseases, but a strong suspicion for cancer should be made in older animals with an intermittent and progressive history of initially unilateral and/or mucopurulent discharge.

Diagnosis

Definitive diagnosis of a nasal tumor requires a tissue biopsy but historical information and diagnostic imaging can be highly suggestive of cancer. Conventional radiography can be helpful in the diagnostic evaluation of dogs, but CT is preferred as it provides improved anatomic detail, determination of the extent of the tumor, and identification of nasal cavity abnormalities. A CT scan also allows for detection of CNS invasion. Certain findings on CT are correlated with a diagnosis of cancer in dogs, but none of these alone or in combination are definitively diagnostic. A tissue biopsy is always required. Once a definitive diagnosis has been made, fine needle aspirates of regional lymph nodes should be completed, along with three-view thoracic radiographs.

Several staging systems based on radiographic or CT findings have been proposed in canine nasal tumors but their prognostic significance remains controversial. The Adams modified staging system developed in 2009 is the most recent system that has been adapted (Table 137.2). With this system, dogs with unilateral intranasal involvement confined to the nasal cavity had the longest median survival time of 23.4 months when treated with definitive radiotherapy. Those with cribriform involvement had the shortest median survival time of 6.7 months.

Therapy

Treatment of nasal tumors is directed primarily at the control of local disease. Unfortunately, the disease is often extensive. Curative surgery is not possible as bone invasion occurs early in the course of the disease. Hence, radiation therapy is the standard of care. The combination of a cytoreductive surgery followed by radiation therapy for the treatment of nasal tumors has been evaluated, but has not been shown to improve clinical outcome in dogs when compared to megavoltage radiation alone.

With definitive or curative intent radiation, the goal of treatment is to deliver the maximum radiation dose to the tumor while minimizing the dose to surrounding normal tissues. Most radiation therapy done in veterinary medicine involves the use of conventional computerized treatment planning. However, with advances in the field of radiation oncology, the use of intensity-modulated radiation therapy (IMRT) has proven to be a very good option for the treatment of nasal tumors. IMRT allows for the optimization of radiation dose delivery to complex tumor volumes with rapid dose drop-off to surrounding normal tissues. When IMRT is used, normal tissue toxicities are greatly reduced while higher cumulative doses of radiation are delivered to the tumor. Traditional definitive protocols involve the administration of a total radiation dose of 40-57 Gy in 10-19 fractions of 3-4.2 Gy, over a 2-4 week period.

Table 137.2 Adams 2009 modified staging system for canine nasal tumors

Stage	Remarks
T1	Confined to one nasal passage, paranasal sinus, or frontal sinus with no bony involvement
T2	Any bony involvement, but no evidence of orbital, subcutaneous, or submucosal mass
T3	Involvement of orbit or subcutaneous or submucosal mass
T4	Tumor extension into the nasopharynx or cribriform plate

Computerized treatment planning using CT images of the patient are recommended to enhance normal tissue sparing while ensuring appropriate dose distributions within the tumor. For IMRT, CT and computer planning is required. Stereotactic radiation, which is similar to IMRT, is the specific treatment of choice for most nasal tumors. Protocols consist of the precision delivery of curative intent therapy in 1-3 high dose fractions.

With stereotactic and/or traditionally fractionated IMRT, acute toxicities that effect the rapidly dividing tissue of the oral cavity, nasal cavity, skin, and eye can be seen, but are typically very limited. Oral antibiotics, analgesics, and/or artificial tears can be used as needed to counteract and support any treatment related side effect. Life limiting late side effects such as bone or brain necrosis are possible, but the risk is expected to be less than 5%.

Palliative radiation therapy can also be considered for the treatment of nasal tumors. With palliative radiation protocols, side-effects are limited. Alleviation of clinical signs has been reported in up to 95% of dogs treated, with median survival times reported to be approximately 4–6 months. Chemotherapy has also been evaluated for the treatment of nasal tumors in dogs. Clinical responses are seen with chemotherapy, but the response is usually not durable.

Prognosis

Canine Nasal Tumors

The long-term prognosis for dogs with nasal tumors is very dependent on the treatment pursued. A retrospective study of 139 dogs with nasal tumor evaluated those that did not receive therapy. Their overall median survival time was approximately three months. This study also found that dogs presenting with epistaxis had a significantly shorter median survival time than those without epistaxis. Surgery as the sole treatment of nasal tumors results in a median survival time of only 3–6 months, with a high rate of acute and chronic morbidity. Curative-intent, high-energy megavoltage radiation alone results in a median survival time of 8–19.7 months, with one- and two-year survival rates ranging from 43% to 60% and 11% to 44%, respectively. The combination of surgery followed by postoperative radiation reports survival times ranging from 4.1 months to 15.2 months, adding no benefit to radiation therapy alone. In a small series of 13 dogs that underwent preoperative radiation followed by surgical exenteration of residual disease, a survival advantage was demonstrated (MST 47 months). However, these patients experienced significant late side-effects including rhinitis (bacterial and fungal), osteomyelitis, and fistula formation. A study in 2011 evaluated definitive reirradiation of nine dogs with nasal tumors and found that reirradiation is a viable treatment option for canine nasal tumors with tolerable acute and late side-effects. The MST time for the patients in this study was 30 months.

Feline Nasal Tumors

Reports of treatment for feline nasal tumors are lacking. One study including 16 cats with nonlymphoproliferative neoplasms treated with a definitive course of radiation to a total dose of 48 Gy reported a MST of 12 months. This treatment resulted in minimal acute side-effects and modest chronic ocular side-effects. When radiation therapy protocols are used for the treatment of feline nasal lymphoma, long-term control of local disease is favorable and it has been reported that higher total doses (greater or equal to 32 Gy) of radiation therapy may confer an additional survival benefit. The role of chemotherapy for the treatment of feline nasal lymphoma is undefined. Median survival times for cats receiving radiation therapy +/- chemotherapy for the treatment of nasal lymphoma range from 13 to 31 months.

Cancer of the Pharynx

Pharyngeal tumors are rare and little information has been reported in literature. In cats, lymphosarcoma is the most commonly reported. In dogs, extramedullary plasma cell tumor, osteosarcoma, chondrosarcoma, fibrosarcoma, and carcinomas have all been reported. Malignant tumors of the pharynx are more common; however, benign tumors have been reported in dogs. These include rhabdomyoma, angioleiomyoma, and oncocytoma. Rhabdomyomas are minimally invasive and have a predilection for young male dogs.

Surgery is the treatment of choice for pharyngeal tumors. Many benign tumors can be removed while preserving function, while radical procedures such as permanent tracheostomy and complete laryngectomy are required for malignant tumors. Chemotherapy and radiation therapy can also be considered. Surgical removal of pharyngeal rhabdomyoma is often considered curative.

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138

Tumors of the Eye and Ocular Adnexa

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Tumors of the Ocular Adnexa

Tumors of the eye, orbit, or adnexa may be painful and disfiguring, impair vision, and elicit concern that life-threatening disease may be present elsewhere in the body. Even benign ocular tumors may cause blindness and loss of the eye simply by virtue of their location. Although both ocular and periocular tumors are reportedly uncommon, their actual frequency is undoubtedly greater as most presumably benign ocular tumors, especially those affecting the canine eyelid, are not histologically examined. Histopathologic examination, however, is essential to ensure proper diagnosis and treatment.

Eyelids, Third Eyelid, Conjunctiva, and Cornea

The etiology of ocular adnexal tumors is poorly understood but suspected causes include chronic inflammation, exposure to ultraviolet light, and viral infection (e.g., papillomavirus). In dogs, more than 85% of eyelid and conjunctival neoplasms consist of sebaceous or meibomian gland adenomas and epitheliomas, papillomas, and melanomas. The substantial majority of these tumors are benign. Even histologically malignant canine eyelid tumors rarely metastasize, although they may be more locally invasive and likely to recur after surgery. In cats, however, most feline eyelid and ocular surface tumors are malignant.

Meibomian Gland Adenoma/Epithelioma

Although rare in other species, benign meibomian gland adenomas and epitheliomas are the most common eyelid margin tumor in middle-aged to older dogs. They may grow rapidly, first starting as a nodular swelling of the meibomian gland and eventually appearing as a proliferative mass exiting the meibomian gland orifice on the lid margin.

Papillomas

In contrast, viral papillomas appear as verrucous masses originating from the conjunctiva in young dogs. They are well demarcated, superficial, and grow rapidly. Surgical manipulation has been reported to disperse new papillomas over the ocular surface. Papillomas, like histiocytomas, usually resolve spontaneously in young dogs, although persistence in older dogs is common. Other forms of benign papillomas in dogs include squamous papillomas, which are of unknown etiology and occur at any age, as well as reactive papillomas, which are seen secondary to other conditions that result in chronic irritation.

Squamous Cell Carcinoma

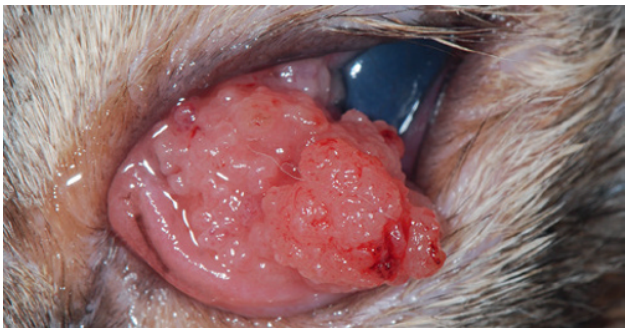
Squamous cell carcinoma (SCC) has a predilection for the lower eyelid and medial canthus of white cats, and comprises the majority of feline eyelid and third eyelid tumors. It is less frequently reported in dogs, however, in both species it tends to affect older animals. Predisposing factors include exposure to solar radiation, lack of adnexal pigmentation, and chronic ocular surface irritation. Ocular surface SCC has a predilection for the limbus, although it may also invade the cornea. SCC appears as a focally thickened, roughened, pink-to-red lesion or as an ulcerated lesion which is slow to heal. Metastasis to regional lymph nodes occurs late in the course of disease and distant metastasis is uncommon. SCC of the third eyelid tends to more readily invade the orbit than ocular surface or eyelid SCC (Figure 138.1a).

Hemangioma/Hemangiosarcoma

Adnexal vascular endothelial tumors are uncommon in dogs and rare in cats. As with ocular surface SCC, solar radiation is believed to be a risk factor. They usually arise from the nonpigmented conjunctiva of the lateral

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(a)



(b)

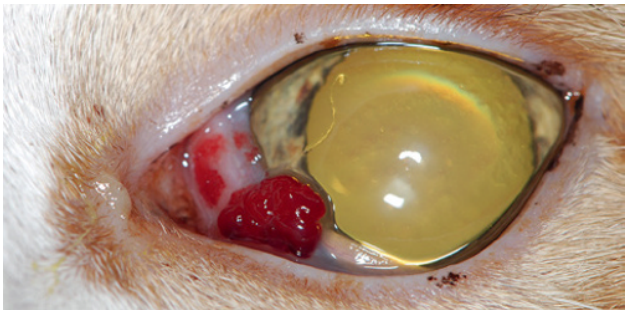


Figure 138.1 (a) Squamous cell carcinoma involving the third eyelid of a cat. Note the proliferative and ulcerated mass extending from the anterior surface of the third eyelid. (b) Hemangioma of the third eyelid of a cat. Note the bright red, exophytic mass extending from the leading edge of the third eyelid. *Source*: Courtesy of University of Wisconsin-Madison Comparative Ophthalmology Service Collection.

limbus or leading edge of the third eyelid and appear as relatively superficial, focal, raised, soft, red masses with visible feeder vessels (Figure 138.1b). Ulceration is common in larger masses. Metastasis of primary conjunctival vascular tumors, even when classified as hemangiosarcoma, is rare although it may recur following simple excision. It is critical to differentiate a primary ocular hemangiosarcoma from a metastatic lesion.

Melanocytoma/Melanoma

Dermal melanocytic tumors of the eyelid are common and typically benign in dogs, while in cats they are rare and more malignant. Melanocytic tumors of the conjunctiva are infrequent and malignant in both species (although distant metastasis tends to be uncommon). Conjunctival melanomas involving the nictitating membrane and superior palpebral conjunctiva may have greater metastatic potential. In both cats and dogs, conjunctival melanomas often locally recur following surgical excision, and may invade the orbit and spread to regional lymph nodes or lungs.

Adenoma/Adenocarcinoma

Adenocarcinomas are the most common tumor of the gland of the third eyelid. They appear as a localized, firm, smooth, pink swelling arising from the posterior surface of the nictitans. They mimic prolapse of the gland of the nictitans (i.e., cherry eye), but a key differentiating feature is their occurrence in older dogs and cats. Recurrence is common if the entire gland is not removed, and metastasis, especially to the regional lymph nodes and orbit, is possible.

History and Clinical Signs

In addition to a mass lesion, other clinical signs of eyelid or ocular surface tumors may include epiphora, conjunctival vascular injection, ocular discharge, elevation of the third eyelid, conjunctival/corneal erosion or ulceration, and corneal vascularization or pigmentation. Palpebral conjunctival masses often protrude when they no longer can be accommodated by the space between the eyelid and globe. Advanced tumors invading the orbit may result in exophthalmia or enophthalmia, depending on their location. Large tumors and sebaceous adenomas often have a substantial inflammatory component and may be secondarily infected.

Diagnosis

The extent of conjunctival involvement should be determined by everting the eyelid (and third eyelid if affected). Careful palpation of the lesion by inserting a lubricated finger in the conjunctival cul-de-sac can aid in determining the full extent of the tumor and whether bony involvement has occurred. Nasolacrimal lavage and possibly positive contrast dacryocystorhinography may help characterize medial canthal masses. Fluorescein staining should be used to determine the integrity of the ocular surface.

Small eyelid and ocular surface tumors are best diagnosed and treated by excisional biopsy. Fine needle aspiration (FNA) or incisional biopsies of larger tumors aid in determining prognosis and planning definitive therapy. Orbital ultrasound, skull radiographs, computed tomography (CT), magnetic resonance imaging (MRI), regional lymph node cytology, and thoracic radiographs may be required to localize or clinically stage potentially malignant tumors such as SCC, third eyelid adenocarcinomas, and conjunctival melanomas.

Therapy

Specific therapy varies with tumor type, size, location, and extent; whether the eye still has vision; the animal's

expected lifespan; the amount of discomfort due to the mass; and any financial constraints of the owner. All eyelid tumors, whether benign or malignant, may affect vision or ocular comfort. Excision is indicated for all eyelid tumors in cats, rapidly growing masses, those irritating the eye or impairing eyelid function, if the owner is concerned, or the mass is cosmetically unappealing. In young dogs, even large papillomas or histiocytomas that are nonirritating may be monitored as spontaneous regression is common.

Tumors involving less than one-fourth to one-third of the palpebral fissure length are best treated by a V-plasty (wedge) or four-sided (house) excision. In the latter technique, the incision is made perpendicular to the eyelid margin (rather than obliquely), resulting in superior apposition of the eyelid margins and greater wound stability, especially in larger tumors. It may be possible to shrink large tumors that are infected or inflamed with antibiotic or antiinflammatory therapy such that a wedge or four-sided excision becomes possible. Electrosurgical excision may result in substantial scarring of the eyelids. Carbon dioxide (CO_2) laser ablation may be appropriate for some smaller tumors.

Tumors greater than one-fourth to one-third of the eyelid typically require reconstructive blepharoplasty or other therapeutic modalities. Depending on tumor type, alternative therapies include systemic chemotherapy (e.g., lymphoma, mast cell tumors), local infiltration with chemotherapeutic agents (e.g., SCC), and/or local radiation therapy (e.g., SCC). These modalities may completely eliminate the tumor or reduce it so that a less extensive surgical procedure is possible. Reconstructive blepharoplasty, however, is the procedure of choice if surgical cure is a possibility, other modalities are unlikely to substantially reduce the tumor, or if the tumor type requires extensive margins.

Liquid nitrogen cryosurgery may be an alternative to extensive blepharoplasty for some eyelid and corneal tumors. It is fast, technically simpler than reconstructive blepharoplasty, and usually allows the nasolacrimal puncta and canaliculus to be preserved. Often cryosurgery can be performed with only sedation or local/topical anesthesia, which is helpful in older or debilitated patients. After sedation/anesthesia, the mass is isolated with chalazion forceps and debulked flush with the lid margin. Using a closed probe that approximates the diameter of the mass as much as possible, an iceball is formed and allowed to extend 3–5 mm beyond the visible margins of the mass in a double freeze-thaw cycle. If the tumor is large, the iceballs should overlap. If complete regression is not achieved 2–3 weeks after the first session, additional treatments may be performed. Marked postoperative swelling and usually transient depigmentation of the frozen tissue are expected.

Tumors involving the conjunctiva and third eyelid (especially conjunctival hemangiosarcomas, melanomas, and third eyelid adenocarcinomas) are best treated by wide surgical excision, sometimes to the point of exenteration. Excision of the entire third eyelid may result in keratoconjunctivitis sicca. Cryosurgery may allow the third eyelid to be spared in papillomas and early SCC. It can also be a useful adjunct to excision in advanced canine conjunctival melanomas and SCC. Superficial keratectomy/sclerectomy, often followed by cryosurgery, is preferred for many corneal and scleral tumors, although some tumors require full-thickness corneal/scleral resection and placement of a donor graft.

Prognosis

With treatment, the prognosis for most canine primary eyelid tumors is excellent. Even histologically malignant primary lid tumors rarely metastasize, and recurrence rates are low. Recurrences, however, need to be differentiated from new primary eyelid tumors as these are common. The prognosis for feline eyelid tumors is guarded, as most eyelid tumors in cats are malignant. Conjunctival melanomas and adenocarcinomas of the third eyelid frequently recur even if all clinically visible tumor is removed. Conjunctival hemangiosarcomas most likely have a good prognosis because total excision may be curative, although recurrence and loss of the eye may occur.

Limbal (Epibulbar) Melanoma

Limbal melanomas are typically benign, sessile, heavily pigmented masses originating from melanocytes in the limbal sclera or subconjunctival connective tissue of middle-aged dogs and cats. The majority are located in the superior limbal region, suggesting that solar radiation may be a risk factor. Growth is slow and confirmed metastasis has not been reported. Clinical signs are generally mild and may include localized corneal invasion, epiphora, and mild conjunctival irritation. Differential diagnoses include conjunctival melanoma, uveal melanoma invading the sclera, metastatic melanoma, and staphyloma or coloboma. Gonioscopy and ocular ultrasound aid in differentiating invasive intraocular tumors from limbal melanomas.

Therapy should be considered if the tumor has invaded the eye, the animal is painful, or if growth is rapid. Observation alone is often an appropriate approach in older dogs given the benign nature and usually slow

growth rate of these tumors. If intervention is required, lamellar keratectomy/sclerectomy with graft placement, cryosurgery or laser photocoagulation may be curative or reduce the size of the mass such that it no longer threatens vision for the remainder of the animal's life. Cryotherapy or beta-irradiation may also substantially reduce the risk of recurrence following local excision. Enucleation is curative and indicated if the mass has entered the eye and there is ocular discomfort.

Intraocular Tumors

Primary Tumors

Primary intraocular tumors occur more frequently than metastatic intraocular neoplasms in dogs and cats. They most commonly originate from the uvea, and their etiology is poorly understood.

Canine Anterior Uveal Melanocytoma/Melanoma

Intraocular melanocytomas arising from the iris or ciliary body comprise the majority of canine intraocular tumors. Most tumors are benign and detected in older dogs (7 years of age or older) although more rapidly growing pigmented iridal masses have been described in young dogs. Malignant intraocular melanomas may be locally invasive but distant metastasis (usually hematogenously) is rare.

Ocular melanosis of cairn terriers is a distinct clinical entity that resembles a diffuse and benign form of uveal melanoma. It is a bilateral disorder in which the iris becomes thickened and more darkly pigmented, followed by release of pigment into the aqueous and pigment deposition in the sclera/episclera. Secondary glaucoma is common. Some cairn terriers may have overt uveal melanocytic tumors, but in most dogs the pigmented cells are nonneoplastic (Figure 138.2).

Choroidal Melanocytoma/Melanoma

These rare melanocytic tumors generally originate from the peripapillary choroid and appear as well-delineated, raised, subretinal pigmented masses. They may remain virtually static for many years, although others may extend into the overlying retina, sclera,

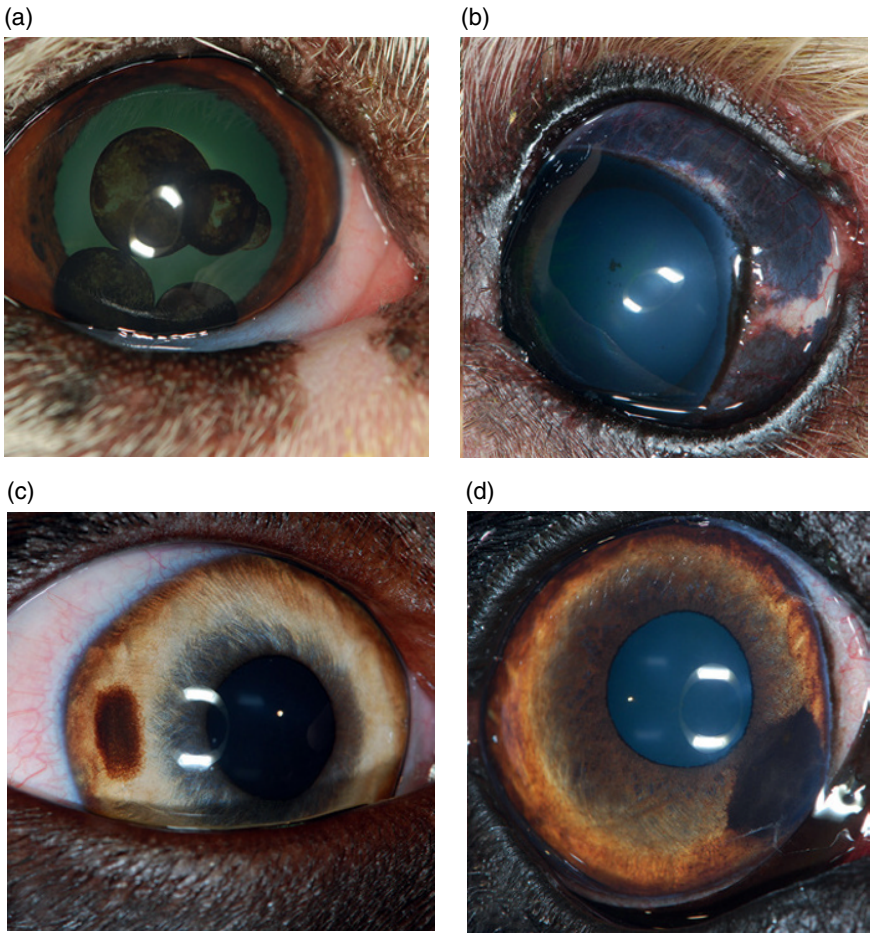


Figure 138.2 (a) Free-floating uveal cysts in the anterior chamber of a dog. Note that the spherical, fluid-filled cysts transilluminate. (b) Cairn terrier with ocular melanosis characterized by diffuse pigment deposition in the sclera and episclera. (c) Iris nevus (freckle) in a dog. Such lesions should be closely monitored for signs of progression. (d) Canine anterior uveal melanoma. Note the heavily pigmented and raised iris mass. *Source*: Courtesy of University of Wisconsin-Madison Comparative Ophthalmology Service Collection.

optic nerve, and orbit. Although usually considered benign, such invasion warrants a more cautious prognosis. Small tumors are typically asymptomatic although larger tumors frequently present with chronic uveitis, secondary glaucoma, retinal detachment, intraocular hemorrhage, or blindness. Ocular ultrasonography may be required to identify the mass in these patients. Therapy is usually enucleation if the mass is progressive or the eye is painful. Diode laser ablation is an alternative treatment for small masses that do not involve the optic nerve.

Feline Diffuse Iris Melanoma

Diffuse iris melanomas are the most common primary intraocular tumor in cats. Although the prodromal period may be quite long, most cats are 9 years of age or older at the time of diagnosis.

The most common clinical sign is slowly progressive diffuse iridal hyperpigmentation. Occasionally, a pigmented iridal nodule or amelanotic mass is seen. The diagnosis is generally made clinically, and is based on the presence of progressive iridal hyperpigmentation and thickening or irregularity of the iris surface or pupil (Figure 138.3). Secondary glaucoma may occur. Diffuse iris melanoma is differentiated from chronic anterior uveitis with iridal hyperpigmentation by the absence of other signs of uveitis and a more protracted course.

(a)



(b)

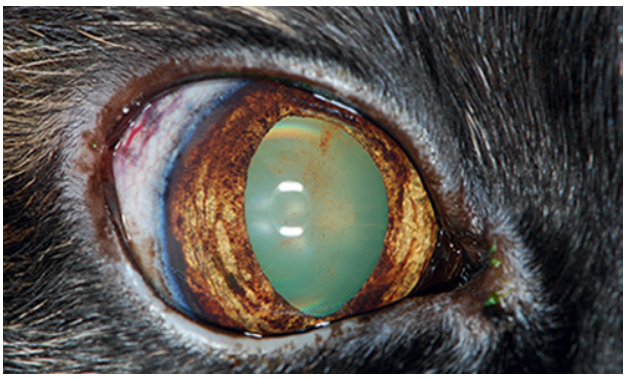


Figure 138.3 (a) Feline diffuse iris melanoma. The right iris is diffusely and heavily pigmented and the pupil is slightly more dilated due to stromal invasion of neoplastic cells (anisocoria). The left iris has multifocal nevi (freckles). (b) Exfoliated pigment from the iris is present on the anterior lens capsule. *Source*: Courtesy of University of Wisconsin-Madison Comparative Ophthalmology Service Collection.

Diffuse iris melanoma has the potential to distantly metastasize, especially to the liver and lungs. Iris hyperpigmentation, however, is typically very slowly progressive, often requiring months to years to progress to the point at which the eye must be enucleated, and an additional 1–3 years after that before metastatic disease may become evident. No single morphologic feature is predictive of outcome, but metastasis has been linked to a greater mitotic index, larger tumors, extension through the iris into the ciliary body stroma, and involvement of the scleral venous plexus.

The treatment of diffuse iris melanoma is controversial. Because these eyes initially retain vision and are comfortable, in the ideal setting, enucleation would be delayed until just prior to malignant transformation, invasion into other ocular structures, secondary glaucoma, or metastasis. Such precise timing; however, is seldom possible. Enucleation is recommended if iris hyperpigmentation progresses to involve virtually all of the iris surface, pigmented cells are present in the aqueous humor and trabecular meshwork, the pupil is distorted (indicating iridal stromal invasion), invasion into the ciliary body or scleral appears imminent, or intraocular pressure is elevated. However, it is unknown whether early enucleation leads to increased survival.

As an alternative to enucleation, some veterinary ophthalmologists have attempted to ablate small, focal, hyperpigmented foci with a diode laser in an effort to preserve vision and the eye. The long-term success rate and side-effects of this procedure, however, are unknown.

In practice, slowly progressing lesions, especially in older cats with other life-limiting disorders, are often simply monitored, ideally by comparison to baseline photographs. In many cats, the progression may be so slow that the patient can be followed for many years to a decade or more without apparent metastasis.

Iridociliary Epithelial Tumors

Primary iridociliary epithelial tumors (e.g., ciliary body adenomas, adenocarcinomas, pleomorphic adenocarcinomas) are occasionally observed in middle-aged to older dogs and cats. Most are benign, fairly well-delineated, slow-growing masses that originate from the ciliary body or the posterior iris epithelium (Figure 138.4). They are often nonpigmented, although some epithelial tumors are pigmented and clinically indistinguishable from anterior uveal melanocytomas.



Figure 138.4 Canine iridociliary epithelial tumor. There is a nonpigmented, vascular ciliary body adenoma filling the posterior chamber and pushing the inferior iris forward. *Source:* Courtesy of University of Wisconsin-Madison Comparative Ophthalmology Service Collection.

Clinical signs include a retroiridal mass that may displace the iris or lens and in advanced cases, secondary glaucoma, intraocular hemorrhage, and ocular pain.

Tumors that invade the sclera are typically classified as adenocarcinomas and have anaplastic features, but metastasis is uncommon and occurs late in the course of the disease, if at all. However, a few cases of truly malignant pleomorphic adenocarcinomas with fatal metastasis have been reported in dogs. Dogs affected with this rare form usually have long-standing ocular disease that was initially thought to be inflammatory or traumatic in origin.

Due to the possibility of malignancy, early enucleation of ciliary body tumors has been recommended, although benign adenomas may remain static for years. This makes enucleation controversial for small tumors unassociated with secondary ocular disease. Local intraocular resection or laser photoablation in an effort to preserve vision and ocular comfort has been described.

Feline Ocular Posttraumatic Sarcoma

A unique entity in cats, sarcomas following ocular trauma are second only to melanomas in frequency as a primary feline ocular tumor. Most cats are middle-aged to older and the latency period following ocular trauma to tumor development averages six to seven years. There are three morphologic subtypes: spindle cell sarcoma (the most common), round cell, and osteosarcoma/chondrosarcoma. The cell of origin in the three subtypes is unclear, although damage to the lens and chronic uveitis are common historical complaints.

Most eyes are blind from the preceding trauma or chronic inflammation, and the most common presenting signs are white, tan, or pink mass filling the anterior chamber and distortion of the globe. Extension beyond the sclera or into the optic nerve may be seen ultrasonographically and are poor prognostic indicators. Growth along the optic nerve into the chiasm and brain, invasion of regional lymph nodes, and distant metastasis have been reported. Early enucleation of suspicious globes with removal of as much of the optic nerve as possible is recommended, although it is unclear if this prolongs survival.

History and Clinical Signs

Common presentations of intraocular tumors include a visible mass involving intraocular tissues, sclera or occasionally the orbit, as well as glaucoma, hyphema, or anterior uveitis. Intraocular neoplasia should always be considered in animals with hyphema, glaucoma, or both when there is no history of trauma or coagulopathy. Small masses frequently have no clinical signs. Pigmentation is not a reliable indicator of tumor type.

Diagnosis

Usually, the clinical or ultrasonographic appearance (if the media are opaque) is strongly suggestive of intraocular neoplasia. It may be difficult to differentiate organizing blood clots from neoplastic mass lesions and more invasive diagnostic procedures may be required. Because most anterior uveal brown or black masses are cystic and not neoplastic, transillumination or ultrasonography should be attempted before resorting to more invasive procedures. Uveal cysts typically are spherical, may be attached to the ciliary body or free-floating in the anterior chamber, and allow bright light to pass through them (see Figure 138.2a). Once suspected, most primary canine intraocular tumors that are not blinding nor causing discomfort are observed for progression, although occasionally FNA (with its risks of inflammation, infection, and hemorrhage), intraocular resection, or enucleation are used for diagnostic purposes. It is also important to rule out metastasis from another primary site (e.g., oral cavity or nailbed) to the eye, or from the eye to other organs (especially lungs and liver).

Therapy

Because the risk of metastasis is low and the ability of enucleation to prevent metastasis in the few malignant

tumors that have been reported is unproven, it is difficult to automatically advise enucleation of normotensive, noninflamed, visual eyes. Therefore, canine primary intraocular tumors are generally photographed and carefully followed for progression. Enucleation is advised if malignancy is a concern or if intractable uveitis, chronic hyphema, or secondary glaucoma is present. Isolated primary masses involving only the iris or a portion of the ciliary body may be amenable to local resection by sector iridectomy/cyclectomy with preservation of the globe, but this procedure requires an accomplished ophthalmic surgeon and often has unsatisfactory long-term results. Transscleral and transcorneal Nd:YAG or diode laser therapy may induce remission in small to moderate-sized primary intraocular tumors while also preserving vision.

Prognosis

The prognosis for histologically benign intraocular tumors is excellent. Enucleation is curative but blinding. Attempts at local excision or laser photoablation may only be palliative, especially if the ciliary body or trabecular meshwork is involved.

Secondary Uveal Neoplasms

Because the uveal tract is highly vascular, numerous malignant tumors have been reported to metastasize to the eye. Lymphoma is the most common secondary intraocular tumor in the dog and cat, with ocular lesions affecting approximately one-third of dogs with the disease. Common clinical signs include a severe uveitis, in which the amount of anterior chamber cell/flare is disproportionally severe compared to the degree of conjunctival hyperemia and pupillary miosis. Other clinical signs include secondary glaucoma, retinal hemorrhage and detachment, hyphema, conjunctivitis, and keratitis characterized by corneal infiltrates, edema, vascularization, and intrastromal hemorrhage. Exophthalmia from orbital invasion and vision loss due to optic nerve or central nervous system (CNS) disease may also occur. Dogs with intraocular lymphoma survive only 60–70% as long as dogs without ocular involvement when treated with cyclophosphamide, vincristine, and prednisolone (COP), or with doxorubicin. Ocular signs may be palliated by topical or systemic corticosteroid therapy, but the most effective therapy is systemic chemotherapy directed at the cancer itself. Enucleation may be necessary for pain relief in some patients.

Tumors of the Orbit and Optic Nerve

Orbital neoplasia may be primary, secondary to extension of adjacent tumors into the orbit, or the result of distant metastasis. In cats and dogs, 90% or more of orbital tumors are malignant, and regional infiltration (including into the CNS) or distant metastasis is common. Numerous types of orbital tumors have been described in cats and dogs. Tumors involving the optic nerve are rare, although secondary invasion of the nerve may occur in feline posttraumatic sarcomas, feline SCC, canine choroidal melanomas, and canine meningiomas.

Primary Orbital Tumors

Sarcomas

Mesenchymal tumors are among the most common canine primary orbital tumors. These include osteosarcomas, fibrosarcomas, reticulum cell sarcomas, and neurofibrosarcomas. Orbital tumors should be histologically graded for a more accurate prognosis but most sarcomas are locally invasive and carry a poor prognosis.

Canine Lobular Orbital Adenoma

Lobular adenomas, perhaps originating from the lacrimal gland, may involve the anterior orbit in dogs. They typically present as soft, smooth conjunctival swellings, or space-occupying orbital lesions that can cause either enophthalmia or exophthalmia. Lobular orbital adenomas are composed of multiple friable lobules, making complete surgical excision challenging. Although benign, recurrence is common, often 1–2 years after excision.

Meningioma

Canine orbital meningiomas are uncommon tumors which tend to grow slowly and rarely metastasize. Invasion of surrounding tissues, including bone and the CNS, is possible.

Glioma

Gliomas are rare primary optic nerve tumors in dogs. The metastatic potential of gliomas appears to be low, but invasion into the retina or the ventral aspect of the brain is possible.

History and Clinical Signs

Orbital neoplasia is typified by slowly progressive exophthalmia, absent to minimal pain on opening the mouth, difficulty in retropulsing the eye, and deviation of the globe. Nasal or sinus tumors that suddenly erode into the orbit occasionally result in acute exophthalmia and substantial orbital pain. If the mass is anterior to the equator of the globe, enophthalmia may occur. Chronic epiphora secondary to obstruction of the nasolacrimal duct, exposure keratoconjunctivitis, palpable orbital masses, or unexplained orbital pain also suggest orbital neoplasia. Measurement of corneal diameters and

intraocular pressure (IOP) allows differentiation of buphthalmia from glaucoma (large corneal diameter and high IOP) and exophthalmia (normal corneal diameter and IOP).

Optic nerve lesions may result in unilateral or bilateral blindness (the latter if the optic chiasm is affected), which may be sudden in onset, as well as optic nerve head pallor, papilledema, or marked protrusion and congestion of the optic disc on ophthalmoscopy. Relatively mild exophthalmia with vision loss suggests optic nerve neoplasia because other orbital tumors typically cause profound exophthalmos before visual loss. Tumors affecting more posterior portions of the optic nerve may not cause exophthalmia or a visible change in the optic nerve head.

Diagnosis

Differential diagnoses include nonneoplastic orbital inflammatory diseases such as granulomas, cellulitis, abscesses, and myositis of the extraocular and masticatory muscles. Inflammatory orbital disorders typically exhibit marked pain on opening the mouth. The location of an orbital mass can usually be determined by careful physical examination, including determination of the direction of malposition of the eye, retropulsion of the globe, palpation of the orbit, and oral examination caudal to the last molar.

In addition to physical examination, cytology of regional lymph nodes, orbital imaging (computed tomography, magnetic resonance imaging, orbital ultrasound), thoracic radiographs, and possibly abdominal ultrasonography should be performed. In one study of cats with orbital neoplasia, 59% had orbital bone lesions on skull radiographs and 15% had evidence of metastasis on thoracic radiographs. CT or MRI offers far superior visualization of the orbit and facilitates planning of either radiation or surgical therapy (Figure 138.5).

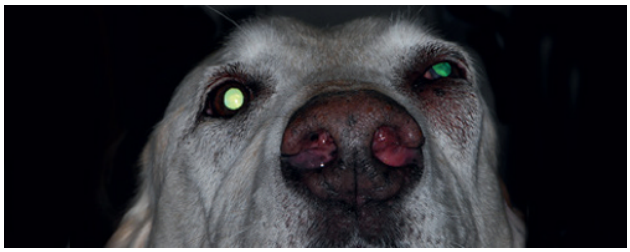
Histologic characterization by FNA or needle core biopsies (performed via the mouth or through the periocular skin), with ultrasound or CT guidance if necessary, is essential for arriving at a definitive diagnosis. It is important to avoid the globe, major orbital blood vessels, and optic nerve when collecting these samples. If less invasive methods of obtaining specimens are nondiagnostic, exploratory orbitotomy or exenteration may be required. If the optic disc appears normal, electroretinography, MRI, and cerebrospinal fluid taps may aid in distinguishing optic nerve neoplasia from sudden acquired retinal degeneration syndrome and posterior optic neuritis.

Therapy

Primary orbital and optic nerve tumors that have not disseminated elsewhere may be amenable to surgical excision. If bony involvement is not present, orbital exenteration by widely dissecting around the mass (stripping periorbita if necessary) is usually preferred, as the advanced stage of the tumor at the time of diagnosis typically makes it impossible to completely excise the mass and preserve a functional or comfortable eye. If periorbital bones are involved, a radical orbitectomy, which resects the affected orbital tissues and surrounding bones, may be considered. When treating optic nerve tumors, as much of the orbital optic nerve as possible should be removed in an attempt to obtain clear margins.

If preservation of a comfortable eye and vision appears possible, a variety of orbitotomy techniques have been described, ranging from small incisions through the eyelid or mouth to reflection of the zygomatic arch, temporalis muscle elevation, and zygomatic process osteotomy. Postoperative complications are common and may include secondary enophthalmia with entropion, diplopia (double vision), facial nerve palsy, and severe orbital hemorrhage. Surgical debulking can be palliative in some patients, and some dogs may survive a year or more with minimal therapy.

(a)



(b)

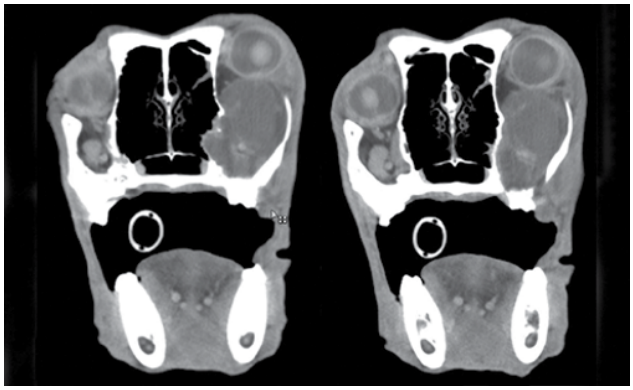


Figure 138.5 (a) Orbital mass in a dog with exophthalmos and dorsal deviation of the left globe. (b) Sequential postcontrast transverse CT images of the same dog. There is an aggressive soft tissue orbital mass with lysis of the left palatine, lacrimal, frontal, and zygomatic bones and extension into the nasal cavity (*left*) and oral cavity (*right*). *Source:* Courtesy of University of Wisconsin-Madison Comparative Ophthalmology Service Collection.

The value of chemotherapy and radiation therapy (RT), either alone or as an adjunct to surgery, is unclear, although chemotherapy for orbital lymphoma may be effective. Systemic corticosteroids may reduce perineuronal swelling and permit some patients with optic nerve meningioma to maintain vision for several weeks to months. RT may be helpful in the case of nasal tumors with orbital extension, in subtotally excised or recurrent tumors, and in other select cases.

The ocular side-effects of conventional external beam RT for nasal and periocular tumors can have a substantial impact on an animal's quality of life. Common complications include keratoconjunctivitis sicca, corneal ulceration, enophthalmia, entropion, cataracts, retinal hemorrhages, retinal detachments, and blindness. Intensity-modulated RT (IMRT), which uses conformal avoidance, significantly decreases the ocular toxicity seen in dogs treated by RT for sinonasal and orbital tumors.

Prognosis

The prognosis for most tumors involving the orbit and optic nerve is poor with conservative treatment, especially if there is bony involvement. Recurrence at the original site and involvement of adjacent or distant sites are common, often occurring within weeks to a few months. Even benign-appearing tumors such as lobular orbital adenomas and orbital meningiomas may be locally invasive and tend to recur following wide excision.

Secondary Orbital Tumors

Most feline orbital tumors are epithelial in origin, with invasive SCC being the most common. Lymphoma is another common secondary orbital tumor affecting both cats and dogs. Orbital lymphoma should be considered part of a systemic process, and further diagnostics are warranted.

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139

Cancer of the Heart

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Etiology/Pathophysiology

Cardiac neoplasia in small animals is usually associated with pericardial effusion. Most of the time, rupture of a cardiac tumor occurs which leads to hemopericardium and cardiac tamponade. In dogs, the majority of cases are secondary to malignant hemangiosarcoma. Cats most commonly have cardiac lymphoma. Diagnosis is frequently based on echocardiographic location of the mass lesion, taking into account the age and breed of the animal, and only rarely is histopathologic confirmation achieved via surgical biopsy. Given the current rate of change in treatment modalities, consultation with a veterinary oncologist is recommended.

Tumors of the heart typically arise from the myocardium, the heart base or the pericardium and are commonly associated with pericardial effusion. Pericardial effusion is a relatively common condition in the dog, much less so in the cat. Normally, there are only a few milliliters of fluid present in the pericardial space, which serves to lubricate the epicardial surface. The pericardium is a tough, fibrous membrane. The purpose of the pericardium is to stabilize the position of the heart within the thorax and provide some diastolic function. When significant amounts of fluid accumulate within the pericardial space, cardiac function may be compromised, and affected animals may start to show clinical signs as described below. The most common causes of pericardial effusion are cardiac neoplasia and idiopathic pericardial effusion.

Malignant transformation of vascular endothelial cells results in hemangiosarcoma (HSA). Cardiac HSA typically arises from the tissue of the right atrium (RA) and/or right auricle (RAu), though other regions of the heart may occasionally be affected. Spontaneous hemorrhage causes hemopericardium.

Heart-based tumors (HBTs) constitute approximately 5% of cases of cardiac neoplasia in the dog and up to 3% in cats and are commonly identified as incidental findings. Most of these are aortic body tumors (ABTs, chemodectoma or paraganglionoma). These tumors arise from chemoreceptor cells sensitive to blood oxygen and carbon dioxide tension. Most ABTs are locally invasive and up to 21% are malignant, metastasizing to lung, liver, left atrium, pericardium or kidneys. Approximately 5–10% of all heart-based tumors are ectopic thyroid carcinomas or parathyroid tumors. These are rarely secretory or functional. Hemopericardium may be present due to spontaneous hemorrhage from the mass itself. Alternatively, a hydropericardium with a modified transudate may develop secondary to obstruction of lymphatic drainage of the pericardial sac.

The myocardium may be infiltrated with neoplastic lymphocytes (LSA), occasionally causing pericardial effusion, typically a modified transudate. Cardiac lymphoma may be primary or multicentric.

Pericardial effusion may develop secondary to pericardial mesothelioma. Pleural effusion may also occur in affected animals with mesothelioma, often concomitant with pericardial effusion.

Other miscellaneous and rarely reported cardiac tumors include intrapericardial lipoma, rhabdomyosarcoma, cardiac mxymoma, and other sarcomas.

Epidemiology

The prevalence of cardiac neoplasia in the dog has been cited at 0.19% and is less than 0.03% in cats. Primary cardiac neoplasia constitutes 84% of cases, with 16% representing metastatic lesions (most commonly hemangiosarcoma and adenocarcinoma).

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Most of the information available is derived from small case series and retrospective data.

Signalment

Golden retrievers and German shepherds are predisposed to cardiac HSA. Afghan hounds, English setters, American cocker spaniels, Doberman pinschers, Labrador retrievers and miniature poodles have been reported to be at increased risk as well.

English bulldogs, Boxers, and Boston terriers are the most common breeds diagnosed with HBTs. Brachycephalic breeds are predisposed, but HBTs may develop in other breeds.

Cats of all breeds may develop cardiac lymphoma. Cardiac lymphoma is quite rare in the dog.

History and Clinical Signs

Dogs that have acute cardiac tamponade from sudden hemorrhage by RA/RAu HSA into the pericardial space typically pant, may collapse or experience hemodynamic shock. Cardiac tamponade occurs when the intrapericardial pressure exceeds the diastolic right atrial and ventricular pressures. This leads to collapse of the right ventricular outflow tract, right atrium and right ventricle (RV). Typically, the left atrial (LA) and left ventricular (LV) pressure exceeds the intrapericardial pressure, preventing collapse. Collapse of the right-sided chambers leads to impaired filling, decreased pulmonary blood flow and decreased filling of the left atrium and ventricle. Even a small amount of fluid, if it suddenly develops can result in serious hemodynamic compromise, whereas slow accumulation can lead to signs that are insidious in onset. Chronic pericardial effusion leads to hepatic venous congestion and functional right heart failure, and may result in a large, pendulous abdomen from ascites as well as dependent subcutaneous edema.

On physical examination, dogs classically have decreased or muffled heart and ventral lung sounds as well as weak pulses. Other potential findings include a fluid wave on palpation of the abdomen, hepatomegaly and pitting edema of the rear limbs. Beck's triad of clinical signs associated with cardiac tamponade is hypotension, distended jugular veins, and muffled heart sounds. Attention should be paid to the quality of femoral pulses as the pulses may noticeably get weaker with inspiration and stronger with expiration. This phenomenon, due to intrathoracic pressure changes and the subsequent effects on the pulse pressure, is termed pulsus paradoxus and is highly suggestive of pericardial effusion.

Many HBTs are discovered incidentally with no apparent clinical signs. Patients that are symptomatic typically have signs referable to pericardial effusion or outflow obstruction to the right side of the heart, either of which may result in ascites.

Patients with LSA may have weight loss or signs associated with pericardial effusion. Occasionally, the patient may present with symptoms referable to congestive heart failure. These include difficult or labored breathing, exercise intolerance, coughing, inappetence or lethargy.

Most patients with mesothelioma have symptoms associated with pericardial and/or pleural effusion. As a result, many present with dyspnea or increased respiratory rate and effort. An abdominal component to the respiratory effort may be noted.

Rhabdomyosarcoma has been reported to be associated with right-sided congestive heart failure (CHF) but not pericardial effusion, and some patients may be completely asymptomatic. Patients with intrapericardial lipomas are typically asymptomatic.

Diagnosis

Diagnosis of pericardial effusion can be made unequivocally with cardiac ultrasound (echocardiography). Hemangiosarcoma is usually diagnosed via echocardiography, revealing the presence of a mass lesion on the RA/RAu or RV junction of mixed echogenicity with irregular anechoic regions. Patients may be hypotensive. Radiographs typically reveal a globoid cardiac silhouette with pulmonary vascular underperfusion, but may be deceivingly normal or only show mild cardiomegaly.

Electrocardiography (ECG) commonly reveals sinus tachycardia. The QRS complex may be of lower amplitude (low-voltage QRS). These comprise the most common electrocardiographic abnormalities associated with pericardial effusion. The R-waves may vary in amplitude from beat to beat, a phenomenon known as electrical alternans. This occurs as a consequence of the heart swinging back and forth in the fluid-filled pericardium. The angle of the vector of LV depolarization is varied due to the positional changes, subsequently altering the amplitude of the QRS complex. This generally happens when the heart rate is between 90 and 140 bpm. Ventricular premature complexes, accelerated idioventricular rhythm, ventricular tachycardia, paroxysmal atrial flutter or atrial fibrillation, atrioventricular block, bundle branch blocks and other conduction system disturbances may occasionally be encountered on ECG in patients with cardiac neoplasia. The ECG may also be completely normal. Often, physical examination is more reliable than radiographs and ECG. Cardiac magnetic

resonance imaging (MRI) has not been shown to improve the diagnosis of cardiac neoplasia when compared to conventional echocardiography.

Testing of the pericardial effusion tends to be of limited diagnostic utility. Cytology of hemorrhagic effusions does not reliably differentiate between neoplastic and nonneoplastic disease. Neoplastic effusions have been associated with lower pH, bicarbonate and chloride levels and higher lactate, hematocrit, and urea nitrogen as compared with serum values. Serum cardiac troponin I levels have been shown to be elevated in dogs with neoplastic pericardial effusions.

On necropsy, HSA appears as a red to black, blood-filled mass on the epicardium. Histopathologic confirmation is rarely obtained antemortem but is marked by scattered, elongated plump neoplastic endothelial cells. By the time of diagnosis, most cases have associated metastasis and in general HSA should be considered a systemic/disseminated disease. The clinician should always assume that HSA is more advanced than what is evident based on imaging modalities. Cardiac troponin I levels have not been shown to be a reliable diagnostic screening tool. Definitive diagnosis requires surgical biopsy.

Heart-based tumors are most commonly diagnosed via echocardiography. Typically, these are visualized as masses of mixed or homogenous echogenicity immediately adjacent to the ascending aorta, aortic arch and proximal branch pulmonary arteries. Thoracic radiographs may show a ventral deviation of the caudal aspect of the intrathoracic trachea, resulting in a "hook-like" appearance if a large HBT is present. Cytologic evaluation of pericardial effusion when present is rarely diagnostic. Definitive diagnosis requires histopathologic evaluation of surgically obtained biopsies, often taken during palliative pericardectomy.

It is common for cats affected with LSA to have large amounts of pericardial effusion, requiring pericardiocentesis. The pericardial effusion should be submitted for fluid analysis/cytology as lymphosarcoma may be easily diagnosed. Most often, lymphosarcoma of the heart produces infiltrative myocardial lesions. Echocardiography may reveal irregular mottling and echotexture to the myocardium with focal areas of thickening, and concentric left ventricular hypertrophy may mimic hypertrophic cardiomyopathy. Grossly, white, pale lesions arise from the myocardium.

Patients affected with pericardial mesothelioma may reveal focal thickening and irregularity of the pericardial sac on echocardiography. However, normal pericardial adipose tissue may mimic infiltrative lesions. It is very common to have associated pleural effusion, and the presence of a modified transudate in the pleural and pericardial cavities for no obvious underlying reason should alert the clinician to the possibility of mesothelioma. Unfortunately, cytology of the effusion is rarely diagnostic as nonneoplastic reactive mesothelial cells are difficult if not impossible to cytologically differentiate from exfoliated neoplastic mesothelial cells. Pericardial and/or pleural biopsies are typically required for confirmation of diagnosis.

Pericardial lipomas may be diagnosed on thoracic radiographs with the appearance of an adipose density within the cardiac silhouette. Echocardiography generally reveals a homogenously echogenic mass within the pericardial sac with variable degrees of compression of the right heart chambers. Ultrasound-guided fine needle aspiration may be attempted, although definitive diagnosis generally requires surgical biopsy.

Cardiac myxomas, rhabdomyosarcomas and other cardiac sarcomas require surgical biopsy for confirmation of diagnosis.

Therapy

Once hemodynamically important pericardial effusion is confirmed, immediate pericardiocentesis is warranted. Ideally, an intravenous (IV) catheter is placed and a shock bolus of fluids is administered, but patients may require immediate pericardiocentesis and a IV catheter and fluids may need to follow.

Frequently, the fluid grossly resembles port wine which appears similar to venous blood. The presence of dark, hemorrhagic pericardial effusion is classically seen with HSA, but its presence is not pathognomonic for HSA or other cardiac neoplasia. Less commonly, the fluid may be serosanguinous from CHF or neoplasia. Rarely, it may be grossly purulent from pericarditis. Commonly, any residual fluid will leak into the pleural cavity from the hole that has been created in the pericardium. Complications associated with pericardiocentesis include puncture of a cardiac chamber, laceration of a cardiac tumor or coronary artery with subsequent intrapericardial hemorrhage. Most commonly, transient arrhythmias may occur, though they tend to be self-limiting and only rarely require antiarrhythmic therapy.

In select cases of cardiac HSA, surgical excision may be attempted (RA appendectomy +/- inflow occlusion via right thoracotomy or median sternotomy), but in the majority of cases complete surgical excision is not achieveable. Pericardectomy alone is not advised due to the risk of exsanguination and dissemination of tumor cells into the pleural cavity and has not been shown to affect recurrence of clinical signs or survival. Various chemotherapeutics (doxorubicin, dacarbazine, cyclophosphamide, vincristine) have been attempted with a positive trend in overall survival time and time to metastasis.

Metronomic chemotherapy, which is intended to prevent tumor angiogenesis, is based on more frequent and low-dose drug administration lacking a rest period compared with conventional chemotherapy. Metronomic chemotherapy lends itself to minimal toxicity and is often cost-effective and convenient.

One small study evaluating canine splenic HSA compared the use of low-dose chemotherapy in combination with piroxicam versus the standard of care chemotherapy, doxorubicin. This study found no statistical difference in survival between the groups, leading to the conclusion that low-dose orally administered chemotherapy may be an effective alternative to conventional chemotherapy. A group at Washington State University used daily dosing of an alkylating agent, lomustine, with or without nonsteroidal antiinflammatory drugs (NSAIDs) to evaluate the toxicity. The majority of the 81 dogs in this study had macroscopic tumor and/or metastasis with osteosarcoma and visceral HSA most prevalent. Thirty-six percent of dogs experienced stable or improved disease. Although minimal, mild to moderate adverse hematologic and gastrointestinal events occurred and an unexpectedly higher number experienced azotemia (13%). Currently, there are no placebo-controlled studies available for cardiac HSA. Tyrosine kinase-mediated proliferation inhibition has been observed in cell lines of canine HSA when exposed to dasitinib and imatinib alone and in conjunction with doxorubicin. The use of tyrosine kinase inhibitor therapy alone or in combination with standard or metronomic chemotherapy has yet to yield improved survival times in the treatment of cardiac HSA.

Early surgical excision is the preferred method of treatment for heart-based tumors. However, in the majority of cases complete surgical excision is not possible. Palliative pericardiocentesis and partial pericardiectomy are viable treatment options for patients with pericardial effusion secondary to HBT. A retrospective study of 6 dogs treated with stereotactic body radiation therapy (SBRT) for heart-base tumors confirmed or presumed to be chemodectomas was performed at the North Carolina State University Veterinary Hospital. Respiratory and motion management was key to the accurate delivery of a minimum of 30 Gray (Gy) delivered in three 10 Gy fractions. Four tumors were assessed after SBRT; tumor volume decreased by 30-76%. Possible treatment-related complications included cough, tachyarrhythmias, and congestive heart failure. Two dogs experienced sudden death 150 and 294 days after SBRT. Three dogs were alive at the time of the report (408 and 751 days after SBRT) and one dog died of unrelated disease 1,228 days after SBRT. While this protocol offered rapid tumor reduction, cardiac arrhythmias assumed to be tumor or treatment related and sudden death commonly occurred after SBRT. SBRT may be ideal for select patients and likely not of benefit for dogs lacking cardiovascular disturbances and/or incidentally diagnosed. As the use of SBRT evolves we will recognize appropriate candidates, and better define the survival benefit. Standard and metronomic chemotherapy alone or combined with small molecule inhibitors may be attempted, especially if metastasis is evident.

In patients affected by cardiac lymphoma with clinically significant pericardial effusion, palliative pericardiocentesis is required. Considered to be stage V, substage B, cardiac lymphoma may be treated with CHOP-based chemotherapy protocols.

Mesothelioma patients may have a palliative pericardectomy performed, but clinically significant pleural effusion typically develops, and pericardectomy has not been shown to decrease the occurrence of clinical signs or survival time. In patients affected with mesothelioma, carcinomatosis or sarcomatosis (with or without malignant effusion), short-term benefit has been obtained with intracavitary chemotherapy. Intracavitary carboplatin and/or mitoxantrone yielded a 333-day median survival time. Three dogs with pleural mesothelioma treated with intracavitary cisplatin had complete resolution of their effusions for 129, 289 and over 306 days. Resolution of effusion occurred within one or two treatments for all three dogs.

Intrapericardial lipomas may be addressed surgically if clinically important right-sided inflow obstruction of the heart is documented.

Prognosis

The prognosis for cardiac HSA is generally considered to be grave. Median survival times (MST) with palliative pericardiocentesis alone have been reported at 11 days (range 0–208 days). A MST of 43 days was achieved in eight dogs undergoing pericardiectomy and surgical resection of a RA HSA. In eight dogs with pericardiectomy and RAu masses, MST was 90 days. This difference in MST may be explained by the smaller size of auricular masses. In a separate report, 15 dogs with pericardiectomy and RA mass resection experienced a MST of 42 days. In eight postoperative patients, the addition of doxorubicin-based chemotherapy significantly improved MST to 175 days. In nonsurgical cases doxorubicin-based protocols may offer MST of 120 days. Pericardiectomy may be performed by one of two techniques: surgical (thoracotomy) or thoracoscopic-assisted pericardiectomy. However, if mass removal is intended, thoracotomy would be the ideal approach based on the experience level of the surgical team.

Heart-based tumors have a fair prognosis, but this is highly dependent on the presence or absence of pericardial effusion, secondary outflow obstruction, or other cardiac function abnormalities. Patients having undergone palliative pericardectomy had a MST of 730 days (42 days with palliative pericardiocentesis alone).

The prognosis for cardiac LSA is guarded, but variable based on response and severity. Twelve dogs with cardiac lymphoma were evaluated and dogs treated with combination chemotherapy had a MST of 157 days compared to a 22-day MST in untreated dogs. Three of the treated dogs survived >328 days. There is no evidence that primary cardiac LSA should be treated differently from other bulky aggressive lymphomas arising at other anatomic sites.

Patients suffering from pericardial mesothelioma generally have a fair to guarded prognosis. Many patients may survive months to years with palliative centesis +/- corticosteroid administration alone.

A variety of primary and secondary cardiac tumors have been reported in the veterinary literature. With technologic advancement, we will gain a more detailed picture and begin to unearth important factors regarding biologic behavior, treatments and prognosis.

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140

Cancer of the Airway and Lung

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Cancer of the Airway

Etiology/Pathophysiology

Tumors of the larynx and trachea are rare in dogs and cats. The most common primary tumors of the canine larynx are carcinomas, with squamous cell carcinoma occurring most frequently, followed by oncocytoma and rhabdomyoma. Other reported laryngeal tumors include mast cell tumor, extramedullary plasmacytoma, chondrosarcoma, osteosarcoma, melanoma, lipoma, adenocarcinomas, fibrosarcoma, and papilloma. Metastatic tumors from a distant site are rarely reported.

Feline primary laryngeal tumors include lymphoma, squamous cell carcinoma, and adenocarcinomas. Leiomyoma, basal cell carcinoma, and polyps are also reported.

Secondary invasion of the larynx can result from ingrowth of primary thyroid tumors or regional lymphoma.

The most common tracheal tumors in dogs include benign tracheal osteocartilaginous tumors, leiomyoma, adenocarcinomas, mast cell tumor, and extramedullary plasma cell tumor. In cats, adenocarcinomas, squamous cell carcinoma, and other carcinomas are the most commonly reported.

Epidemiology

There are no known etiologic or epidemiologic factors predisposing animals to developing laryngeal and tracheal tumors.

Signalment

Other than a predilection for younger dogs to develop oncocytomas, for older cats to develop malignant laryngeal tumors, and a possible overrepresentation of Siamese cats developing tracheal tumors, there is no typical age, breed, or sex predilection for laryngeal and tracheal tumors in dogs and cats. However, younger animals with active osteochondral ossification sites are at increased risk for developing benign tracheal osteocartilaginous tumors.

History and Clinical Signs

Patients with laryngeal tumors typically present with signs directly related to the primary tumor, including stridor, dyspnea, change in bark or voice, exercise intolerance, weakness, or dysphagia. Ptyalism may also be noted.

Patients with tracheal tumors present with similar symptoms as those with largyneal tumors, but are more likely to cough.

Diagnosis

The diagnosis of a laryngeal tumor is often made upon direct visualization on awake or sedated oral exam. Oral exam provides limited information regarding the extensiveness of the tumor, but the advantage is that tissue biopsy samples can be obtained in a relatively noninvasive and economical manner.

Cervical radiographs are helpful in localizing tumors of the distal portions of the larynx or trachea. Images may show a discrete soft tissue mass within the lumen of the trachea, and/or a calcified mass in cases of osteochondromas/chondromas. Thoracic radiographs are recommended to evaluate for the presence of metastatic disease and also to assess for evidence of aspiration pneumonia, which may occur secondary to laryngeal dysfunction. Cervical ultrasound and tracheoscopy may be

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helpful to determine the extent of tumors and can also be used to obtain histopathologic samples. Computed tomography (CT) and magnetic resonance imaging (MRI) provide three-dimensional localization of the tumor as well as its proximity to other vital structures within the cervical region. This detailed imaging may facilitate a diagnosis but is often required for treatment planning.

Laryngeal/tracheal lymphoma should be considered part of a systemic disease process, therefore warranting complete staging as part of a diagnostic plan.

Therapy

There is limited information regarding the treatment of laryngeal tumors in dogs and cats. In dogs, benign tumors of the larynx such as a rhabdomyoma or cyst can be removed surgically. Some cases require placement of a temporary tracheostomy tube. Smaller benign masses can be removed via a transoral approach or through a ventral laryngotomy. Postoperative inflammation and obstruction may necessitate temporary tracheostomy. For larger and/or more invasive tumors, a partial or complete laryngectomy with a permanent tracheostomy can be considered. Permanent tracheostomy, providing relief of upper airway obstruction, is a form of treatment for humans but has limited use in veterinary medicine.

Reported complications of complete laryngectomy in dogs include stomal collapse, the formation of a tracheoesophageal fistula, pharyngeal dehiscence, and ablation of the parathyroid glands. Permanent tracheostomy in cats carries a 67% complication rate with 29% in-hospital mortality. A temporary gastrostomy tube should be considered for any patient undergoing aggressive laryngotomy.

Radiation therapy is used for treating invasive or nonresectable tumors and is effective for treating lymphomas and plasma cell tumors. However, limited evidence-based information exists. Chemotherapy, with or without surgery, may also be effective.

Tumors of the trachea should be treated with surgery, which is curative for benign osteochondral tumors. Experimental evidence indicates that up to 50% of the length of the trachea can be removed with successful closure. Tension on the site of anastomosis is the limiting factor. Intraluminal stenting or bronchoscopic debulking can be palliative measures for relieving obstruction. As with laryngeal tumors, the efficacy of radiation and/or chemotherapy for non-hematologic tumors remains unproven but can be considered when surgery is not feasible.

Prognosis

Benign tumors of the larynx and trachea have a good prognosis when treated with surgical resection alone. Long-term survival is also expected with treatment of extramedullary plasmacytomas and granular cell tumors. Unfortunately, information is too limited to provide specific prognosis' for dogs with other malignancies of the airway.

Similar to dogs, little information is available regarding the prognosis for cats. In one reported study, the median survival time for 27 cats with a variety of laryngeal and tracheal tumors was only five days, with only 7% of patients alive 12 months after diagnosis.

Cancer of the Lung

Etiology/Pathophysiology

Primary lung tumors are rare in dogs and cats compared to humans. The most common primary lung tumor in dogs is bronchoalveolar carcinoma, followed by adenocarcinoma, adenosquamous carcinoma, and squamous cell carcinoma. Other primary lung tumors include histiocytic sarcoma, neuroendocrine tumors, and primary pulmonary sarcomas. Benign primary lung tumors include adenomas and fibromas. The most common primary lung tumor in cats is adenocarcinoma, followed by bronchoalveolar carcinoma, squamous cell carcinoma, and adenosquamous carcinoma.

In both cats and dogs, primary lung tumors can spread via hematogenous or lymphatic routes. This may occur regionally, to intrathoracic lymph nodes, other lung lobes, and the pleura, or distantly throughout the body. More than three-quarters of cats with pulmonary tumors will develop metastasis. Local invasion of tumors within the adjacent pulmonary parenchyma can occur.

In some cases, it is difficult to determine if a pulmonary tumor represents a primary cancer versus a metastatic lesion from a distant site. Immunohistochemical stains can be helpful in such cases, as can complete and thorough staging to evaluate for disease at distant sites.

Epidemiology

The relationship between environmental carcinogens and the development of lung tumors in dogs has been studied. One study showed that 75% of dogs with primary lung tumors live in urban environments, but the results of two other studies did not support this finding. The risk of exposure to second-hand smoke and development of lung cancer in dogs has also been evaluated with conflicting

results. The association in natural settings appears to be weak, but the risk may be increased in brachycephalic dogs compared to dolichocephalic dogs. It is hypothesized that dolichocephalic dogs possess greater surface area for filtration of inhalant carcinogens.

There are no known epidemiologic factors influencing the development of primary pulmonary tumors in cats.

Signalment

The average age of dogs with primary lung tumors is approximately 11 years (range 2–18 years). The risk of developing lung cancer rises after the age of 13. Males and females are equally susceptible. Tumors occur more frequently in larger dogs, with 60% of cancers developing in dogs weighing 20–30 kg. In cats, the average age at diagnosis is 12–13 years (range 2–20 years) with most cats being >5 years of age. No breed or sex predisposition is consistently found in felines.

History and Clinical Signs

Between 52–93% of dogs with primary lung tumors present with a chronic nonproductive cough. Other signs include dyspnea, lethargy, weight loss, tachypnea, pyrexia, inappetence, and lameness. Many dogs are diagnosed with primary lung tumors without any obvious clinical signs during routine geriatric screening tests (e.g., thoracic radiographs). Pleural effusion may occur secondary to direct invasion of the tumor into the pleura or regional pulmonary lymphatics. This may occur with primary or metastatic tumors within the lung tissue. Pneumothorax and hemoptysis may rarely occur.

Signs related to the respiratory system are detected in one-quarter to two-thirds of cats with lung tumors. Vomiting is reported in 20% of cats. Cats with lung tumors are more likely to show nonspecific signs such as lethargy, malaise, and inappetence compared with dogs.

Hypertrophic osteopathy is a known paraneoplastic syndrome associated with primary and metastatic lung tumors in dogs and cats. Animals present with lameness of one or more limbs. Radiographs will show periosteal proliferation occurring perpendicular to the shaft of the long bones. Hypertrophic osteopathy can resolve following removal of a primary lung tumor. Other known paraneoplastic effects in dogs include hypercalcemia, polyneuropathy, polymyopathy, fever, and ectopic adrenocorticotropic hormone production leading to hyperadrenocorticism.

Metastasis to the digits is a well-described clinical consequence of primary pulmonary tumors in cats and some feline patients are initially diagnosed with bony lesions within the phalanges prior to diagnosis of a pulmonary tumor. Metastasis occurs more commonly to the weight-bearing digits. Multiple digits and multiple limbs are commonly affected.

Diagnosis

Many dogs with primary and metastatic lung tumors are diagnosed via thoracic radiography. Most dogs will show a solitary pulmonary mass that is well circumscribed and located in the caudodorsal lung lobes. Diffuse and alveolar infiltrative forms are also described. Radiographs may also show regional lymphadenopathy or extension of tumor into the surrounding pulmonary parenchyma.

Computed tomography is being more frequently utilized for the diagnosis of pulmonary neoplasia in dogs and cats and is ideal for surgical planning. Thoracic CT scan is superior to thoracic radiography for the detection of tracheobronchial lymph node metastases and for detecting pulmonary metastases. The accuracy rate for thoracic CT in detecting tracheobronchial lymph node metastases was 93%, compared to 57% for radiographs. In another study, thoracic radiographs detected only 9% of CT-detected pulmonary metastases. Twenty one of 33 (64%) dogs had pulmonary nodules or masses detected on CT. Of the dogs that had positive CT findings, 17 of 21 (81%) had pulmonary nodules or masses detected on radiographs by at least one interpreter. In another study using CT as the gold standard diagnostic tool, the sensitivity of radiography for detecting pulmonary metastases ranged from 71% to 95%, and specificity ranged from 67% to 92%. Radiography had a positive predictive value of 83–94% and a negative predictive value of 65–89%. This increased accuracy of CT for detecting lesions is likely, in part, due to its higher resolution for identifying smaller lesions (e.g., thoracic CT can detect lesions of 1 mm in size) compared to radiographs (can detect lesions only when >7 mm in size). MRI of the thorax is not recommended due to excessive motion artifact.

Pleural effusion is more common in cats, and is identified in approximately one-third of patients. The diagnostic utility of cytology of pleural effusion in providing a diagnosis of pulmonary neoplasia is variable, but if effusion is detected, it is recommended to submit a sample for analysis as this is a relatively noninvasive technique that can provide significant information.

Bronchoalveolar lavage can be considered and has been found to be superior to transtracheal wash for diagnosing lung cancer in dogs.

Fine needle aspiration of lung tumors is safe, but there is a theoretical risk of seeding tumor cells within the thoracic cavity during this procedure. Studies indicate fine

needle aspirate cytology is diagnostically accurate in up to 90% and 100% of dogs and cats with pulmonary tumors, respectively. Ultrasound and/or CT-guided aspiration has been described, as well as techniques utilizing thoracoscopic or keyhole lung biopsy methods.

Therapy

Surgery is the treatment of choice for solitary pulmonary tumors in dogs and cats. For unilateral tumors, surgery can be performed through either an intercostal thoracotomy or median sternotomy approach. Thoracoscopic and keyhole techniques have also been described. Complete lung lobectomy is the preferred surgical approach, but techniques for partial lung lobectomy are described. The use of automatic stapling equipment allows for decreased surgical time with minimal complications, but is more difficult in small patients. It is important to note that biopsy of hilar lymph nodes at the time of thoracic surgery should be performed to complete staging.

Pneumonectomy is considered for lesions that have extended to all lobes of one lung while the contralateral side is unaffected. The resulting physiologic alterations are much greater than performing a single lobectomy. Dogs can survive a 50% decrease in lung volume, but not 75%. Therefore excision of all lung tissue on the left side can be tolerated since it represents less than 50% of total lung volume.

There is little information regarding the utility of chemotherapy for treating primary lung tumors in dogs and cats. In dogs, doxorubicin and mitoxantrone have been shown to provide little to no response. Two of seven dogs with measurable pulmonary tumors showed a partial response to treatment with vinorelbine. Single-agent vinorelbine was also evaluated in the microscopic disease setting in three dogs, and survival time for those patients was 112, 169, and >730 days.

Inhalational therapy has also been evaluated in dogs, resulting in complete and partial responses for dogs with metastatic tumors compared to stable to progressive disease for dogs with solitary ones.

Intracavitary chemotherapy with cisplatin, carboplatin, or mitoxatrone, as well as sclerosing agents such as talc, has been used to treat malignant effusions in dogs.

In people with non-small cell lung cancer, treatment benefits have been obtained using targeted therapy with either monoclonal antibodies or tyrosine kinase inhibitors directed against cell signaling pathways. The role of such targeted therapy in veterinary patients is unknown.

The role of radiation therapy, interventional radiology, and regional chemotherapy remains relatively unexplored for veterinary patients with pulmonary neoplasia.

Prognosis

Most information regarding prognosis for animals with pulmonary tumors is derived from the behavior of epithelial tumors.

The median survival time of 24 beagle dogs diagnosed with pulmonary carcinomas treated with symptomatic care alone was 10 months (range five days to 42 months). The prognosis for dogs with pulmonary tumors treated surgically is variable and depends on a number of factors, some of which can only be determined postoperatively (e.g., histologic grade and completeness of excision). An older study reported a median survival time of 13 months with lung lobectomy alone. For dogs with incompletely excised tumors, median survival time was only about 1–2 months compared to 11 months for completely excised tumors.

Several specific prognostic factors have been identified in dogs with pulmonary tumors (Table 140.1). Tumor stage is prognostic: T1 (solitary tumor) = median survival time of 26 months, T2 (multiple tumors) = median survival time seven months, and T3 (invasive into surrounding tissue) = median survival time of three months. The presence of metastatic disease within intrathoracic lymph nodes is a negative prognostic factor for dogs with primary lung tumors (11–15 months if no metastatic disease present; 1–2 months if metastases are detected). The presence of clinical signs at the time of tumor detection is also a negative prognostic factor: 18 months with no clinical signs compared to eight months when clinical signs are present. Tumor size and location are also prognostic. Dogs with tumors $<100\,cm^3$ and those with peripherally located tumors have longer survival times compared with dogs with tumors $>100cm^3$ or encompassing entire lung lobes.

Histologic grade is a prognostic factor for both dogs and cats. The median survival time for dogs with well-differentiated, moderately differentiated, and poorly differentiated tumors was 28 months, eight months, and five days, respectively. The median survival time for cats with well-differentiated tumors treated surgically was 23 months, compared to 2.5 months for cats with poorly differentiated tumors. Other prognostic indicators for cats include the presence of clinical signs (median survival time of 4 days if present vs. 78 days if not), pleural effusion (median survival time 2 days vs. 31 days), and the presence of metastatic disease (median survival time 3 days vs. 60 days.)

Table 140.1 Prognostic factors and associated median survival times for dogs with lung tumors

	Median survival time	
Prognostic marker for dogs with lung tumors	**Present**	**Absent**
Lymph node metastasis	1 month	15 months
Microscopic disease following surgery	1 month	11 months
Metastases	<1 month	15 months
Clinical signs at diagnosis	8 months	18.1 months
Median survival time		
Histologic grade		
Grade 1	26.3 months	
Grade 2	8.3 months	
Grade 3	<1 month	
Histologic type		
Squamous cell carcinoma	8 months	
Adenocarcinoma	19 months	
Solitary tumor	26 months	
Multifocal tumors	7 months	
Tumors invading into surrounding tissue	3 months	

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141

Cancer of the Esophagus and Stomach

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Etiology/Pathophysiology

Esophageal sarcomas have been reported secondary to infection with *Spirocerca lupi*, an esophageal worm found sporadically in the tropic warm temperate areas and throughout the United States. There is no known cause for the more commonly seen esophageal carcinomas. In cats, squamous cell carcinomas (SCC) are located in the middle third of the esophagus, just caudal to the thoracic inlet. These tumors are locally invasive and metastasis to regional lymph nodes occurs early.

No definitive etiology has been identified in the development of gastric cancer but experimentally, long-term administration of nitrosamines may induce carcinomas in dogs.

Epidemiology

Cancer of the esophagus and stomach is rare and accounts for less than 0.5% and 1% of all malignancies respectively.

Esophageal tumors can be primary or metastatic. Metastatic tumors are three times more common than primary esophageal tumors and occur through local invasion from the stomach, thymus, thyroid, and heart base as well as from mammary adenocarcinoma and lymphoma. In dogs, the most common primary esophageal tumors are SCC, osteosarcoma (OSA), fibrosarcoma (FSA), and leiomyosarcoma. Sarcomas are seen more commonly in areas where *Spirocerca lupi* is endemic. In cats, the most common primary esophageal tumor is SCC which is seen more commonly in females.

The most common gastric tumor in the dog is adenocarcinoma. Belgian shepherds, chow chows, rough-coated collies, and Staffordshire bull terriers appear predisposed to gastric adenocarcinoma, implying a genetic component. The average age of patients affected with carcinoma is 8 years with a 2.5:1 male-to-female ratio. Other tumors affecting the stomach are lymphoma (LSA), leiomyoma, leiomyosarcoma, gastrointestinal stromal cell tumor (GISTs), extramedullary plasmacytoma (EPC), mast cell tumor (MCT), and carcinoid. Leiomyomas occur in older dogs (mean age >15) as a discrete, often pedunculated lesion in the cardia or gastroesophageal junction. Recent studies utilizing immunohistochemistry to detect CD117 (c-kit protein), a transmembrane receptor with a tyrosine kinase component, have shown up to 50% of leiomyomas and leiomyosarcomas are reclassified as GISTs. Leiomyosarcomas do not express the c-kit protein.

Lymphoma is the most common gastric tumor in cats and males are more commonly affected. Gastric LSA is covered in more detail in another section. Chronic gastritis, *Helicobacter*, and common heritage have been implicated in feline gastric cancer.

Signalment

Most animals with esophageal cancer are older and no breed predilection is evident. The average age for dogs diagnosed with gastric carcinoma is 8 years. Males are diagnosed 2.5 times more often than females. Cats with gastric carcinoma are typically older with mean ages reported between 10.6 and 12.6 years.

History and Clinical Signs

Clinical signs associated with esophageal cancer are generally noted late in the course of disease. Symptoms occur when the tumor is large and has caused an obstruction or motility dysfunction. This can result in dysphagia and

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regurgitation. Other symptoms include weight loss, anorexia, halitosis, pain, and aspiration pneumonia. In some cases, respiratory signs may be the only symptom. The paraneoplastic syndrome hypertrophic osteopathy has been reported secondary to *S. lupi*-induced sarcomas.

A history of progressive vomiting, often with digested blood "coffee grounds" or tinged with fresh blood, is common in cases of gastric cancer. Weight loss, anorexia, and cachexia are often noted over a period of weeks to months. Paraneoplastic hypoglycemia can be seen secondary to leiomyomas or leiomyosarcomas and is likely due to the production of insulin-like growth factors. EPCs may be associated with hyperproteinemia, monoclonal gammopathy, and hypercalcemia. On occasion, occult blood or melena can be documented in the feces.

Diagnosis

Staging for tumors of the esophagus should include thoracic radiographs (three-view), minimum database (complete blood count [CBC], serum biochemistry profile, and urinalysis) and an abdominal ultrasound to rule out a possible primary tumor when the esophageal tumor is suspected to be metastatic.

Thoracic radiographs of the cervical region and thorax may be helpful in localization of esophageal tumors and/or secondary aspiration pneumonia. Esophageal tumors appear as a homogeneous mass in the region of the esophagus, with gas retention and dilation proximal to the lesion. Some esophageal tumors may appear calcified. Positive contrast esophagrams with barium will usually demonstrate the lesion with or without fluoroscopy. Lesions appear as a rounded or lobulated, smoothly elevated filling defect.

When available, esophagoscopy is definitive because it can locate the lesion and obtain diagnostic tissue samples for histopathology. Esophageal tumors are typically submucosal over which the mucosa is usually freely movable. Narrowing of the lumen is common, while stenosis and obstruction are rare. Computed tomography (CT) or magnetic resonance imaging (MRI) may be helpful in determining extent of involvement, location, and invasiveness. Leiomyoma can be presumptively diagnosed based on endoscopic examination and CT results that indicate a well-defined, round-to-ovoid encapsulated mass, with no ulceration of the overlying mucosa or evidence of local invasion. Endoscopic biopsies are contraindicated with leiomyomas, as they increase the risk of complications and mucosal perforation during surgery. Endoscopic fine needle aspiration is effective for obtaining a tentative diagnosis and does not affect surgical outcome. EPCs have a predilection for the terminal esophagus and cardia. A thoracotomy or cervical exploration can be performed to obtain a biopsy.

Staging for gastric tumors includes abdominal ultrasound, thoracic radiographs (three-view) and minimum database. Abdominal radiographs rarely reveal gastric tumors. Anemia is the most common laboratory abnormality. Paraneoplastic hypoglycemia can be seen with leiomyomas or leiomyosarcomas. Sporadically, elevated liver enzymes and elevated gastrin levels can be documented.

Grossly, there are three variations of gastric carcinoma that have been identified. Diffuse neoplastic infiltration of the gastric wall can produce a thickened, nondistensible stomach known as "leather bottle stomach." Gastric adenocarcinoma may also manifest as a discrete, polypoid lesion or as mucosal plaques with ulceration. Histopathologically, gastric adenocarcinomas may be classified as a diffuse type with randomly arranged, malignant epithelial cells or an intestinal type with neoplastic cells that are well organized into distinct, glandular structures. The clinical significance of these histopathologic types is not currently known.

Ultrasonography is a useful imaging modality. Carcinomas tend to be sessile and occur most commonly on the lesser curvature and gastric antrum. Benign lesions are pedunculated or well circumscribed and often occur at the cardia. Sometimes, it is easier to find gastric lymphadenopathy secondary to metastasis than the primary gastric lesion. An ultrasound-guided fine needle aspirate or Tru-Cut biopsy can be utilized to obtain a diagnostic sample.

Gastroscopy with a flexible endoscope is the most sensitive and specific noninvasive way to identify and localize lesions and obtain biopsies. When obtaining biopsies, multiple samples should be taken from multiple sites because the majority of gastric tumors have significant necrosis, ulceration and inflammation, making histopathologic examination difficult.

Barium contrast gastrograms can often document infiltrative disease of the gastric wall, but these contrast studies are cumbersome and take a relatively long time to perform. Poor motility, delayed gastric emptying time and/or prolonged adherence of contrast material to ulcerated tissue are common findings. It should be noted that it could take over 24 hours for barium to completely leave the stomach, which would delay the ability to perform gastroscopy.

Open surgical biopsy is the most definitive method of diagnosis. Leiomyoma/leiomyosarcmas should be stained with CD117 (c-kit) to differentiate GISTs.

Therapy

There are limited therapeutic options for esophageal cancer. Intrathoracic access is challenging and surgery usually results in tension on the anastomosis site and

postoperative complications. Esophageal surgery is prone to serious complications, including stricture, dehiscence, infection, regurgitation, esophagitis, and fistula formation. This has been attributed to many factors, including esophageal movement during swallowing, high wound tension, lack of a serosal layer and the presence of a segmental blood supply to the esophagus. After esophageal surgery, use of a gastrostomy tube is recommended to decrease the amount of motion occurring at the surgical site and facilitate mucosal healing. *En bloc* resection is associated with the best prognosis but submucosal resection to debulk the mass without a full resection and anastomosis can be an acceptable treatment with successful outcomes for leiomyomas/low-grade leiomyosarcomas. Short-term palliation can be achieved with placement of a gastric or percutaneous endoscopic gastrostomy tube. In people, palliation is commonly achieved by the placement of an endoluminal stent. An interventional technique to perform this procedure in veterinary patients is potentially possible.

Radiation therapy is of limited use due to the tissue tolerance of the surrounding structures. In humans, radiation therapy alone is used as a palliative treatment for esophageal tumors or following surgery. Results following radiation therapy alone are short-lived and universally poor unless done in combination with surgery and chemotherapy.

Complete surgical excision is the treatment of choice for gastric adenocarcinomas but is typically complicated due to advanced disease, predilection for the lesser curvature, antrum and pylorus, extensive gastric involvement and/or metastasis to regional lymph nodes and liver. Surgical approaches such as a Billroth I (partial gastrectomy and gastroduodenostomy) or Billroth II (partial gastrectomy and gastrojejunostomy) can provide immediate relief of gastric outflow obstruction and clinical improvement in the early postoperative period. Careful staging prior to pursuing surgery is recommended to insure the morbidity associated with the procedure can be justified.

The beneficial effects of chemotherapy alone or in the adjuvant setting for gastric adenocarcinoma are largely unknown. Reported chemotherapy protocols utilizing 5-fluorouracil, 5-fluorouracil and cyclophosphamide, 5-fluorouracil, doxorubicin and cyclophosphamide (FAC protocol) or cis-platinum appeared to provide some clinical benefit in a few cases. Comparatively, 80% of people with metastatic or nonresectable GISTs had a favorable response with the use of imatinib (Gleevec®), a selective tyrosine kinase inhibitor. This resulted in stabilization or resolution of disease for a median of 20 months. Two tyrosine kinase inhibitors are currently approved for use in veterinary medicine (Palladia™, Pfizer, and Kinavet-CA1®, AB Science) and may also prove to be effective against GISTs in dogs.

Prognosis

The prognosis for esophageal cancer is very poor. These cancers are usually not diagnosed until they are advanced, by which time they are typically difficult or impossible to resect and often are metastatic. Photodynamic therapy has been attempted, but with modest results. The median survival for dogs with esophageal sarcoma following surgery and doxorubicin chemotherapy was 267 days. Interestingly, in many cases, the cause of death was secondary to aspiration pneumonia due to abnormalities in esophageal motility.

The prognosis for gastric adenocarcinoma is poor following the onset of clinical signs. Without treatment, animals usually succumb to their disease within 1–3 months. Surgery affords the best chance for improving the long-term prognosis. Animals that survive the perioperative period have reported median survival times of 4–6 months but a small number of long-term survivals of greater than 36 months have been reported. Most patients eventually succumb due to recurrent or metastatic disease. Leiomyosarcomas and GISTs have a slightly better prognosis with reported median survival times of 6–12 months. Surgery can be curative for benign lesions that are completely resected. EPCs have an excellent prognosis with surgery and chemotherapy. Information on long-term follow-up is lacking in the literature, but a dog treated with surgery and doxorubicin chemotherapy was alive and asymptomatic 30 months post diagnosis. Less than 10% of cases of gastric MCT, regardless of treatment(s) utilized, lived beyond six months. Occasionally, there are cases of gastric MCT that appear to do significantly better than this, suggesting there may be a less aggressive variant of this disease. This supports the palliative use of systemic chemotherapy in patients with minimal clinical symptoms and a reasonable quality of life.

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142

Cancer of the Small and Large Intestine

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Etiology/Pathophysiology

The majority of canine intestinal lymphomas are primary in nature, although extension from multicentric lymphoma can occur. Most intestinal lymphomas in dogs are multifocal or diffuse throughout the intestinal tract with lesions located in the mucosa, submucosa, and lamina propria. The majority of intestinal lymphomas in dogs have been found to be of T cell origin on immunohistochemistry

Small intestinal adenocarcinoma is uncommon in dogs and the small intestine in general is an uncommon site for cancer in dogs and people. Some possible explanations for this include rapid transit times through the small intestine decreasing exposure to carcinogens, large volume of mucosal secretions diluting out carcinogens, a microbial population incapable of activating carcinogens, and microsomal enzymes in the small intestine that may detoxify some carcinogens.

Forty seven percent of intestinal adenocarcinomas expres COX-2 in the neoplastic epithelium. The presence of the COX-2 enzyme has been found to contribute to tumorigenesis in rodent models and is a potential target for nonsteroidal antiinflammatory drugs (NSAIDs).

Leiomyosarcoma is a slow-growing, locally invasive, malignant tumor originating from smooth muscle and is generally slow to metastasize. A recent study reclassified some dogs previously diagnosed with intestinal leiomyosarcomas as gastrointestinal stromal tumors (GISTs) based on the expression of the tyrosine kinase growth factor receptor, KIT. It is thought that activating mutations in c-kit are involved in the pathogenesis of these tumors. Differentiating between a leiomyosarcoma and a GIST may have implications for both biologic behavior and treatment of the neoplasia.

Both adenocarcinoma and leiomyosarcoma of the small intestine have the potential to metastasize (43.5% and 16–50%, respectively). The most common site of metastasis for an adenocarcinoma is the regional lymph node and the most common site for a leiomyosarcoma is the liver or the mesentery. Russell *et al*. reported a metastatic rate of 7% for canine GISTs based on immunohistochemical staining for CD117.

Feline intestinal lymphoma is generally not associated with feline leukemia virus (FeLV) infection. An increased incidence of feline lymphoma, specifically nasal and intestinal, was found in cats exposed to environmental tobacco smoke. Another possible cause of intestinal lymphoma is chronic inflammation, as there has been an association between low-grade or small cell intestinal lymphoma and inflammatory bowel disease. It is thought that intestinal lymphoma derives from the mucosa-associated lymphoid tissue (MALT). However, the tumor can progress and invade the submucosa and muscularis layers of the gastrointestinal (GI) tract. Lesions can be solitary, multifocal or diffuse throughout the intestinal tract. Involvement of mesenteric lymph nodes is common and dissemination to other organs such as the liver, spleen, kidneys, mediastinal lymph nodes or bone marrow can occur as the disease progresses. Intestinal lymphoma may either be small cell/lymphocytic (low-grade) or large cell/lymphoblastic (high-grade). Reports are mixed regarding the prevalence of low- versus high-grade alimentary lymphoma in cats. Earlier reports indicate that high-grade lymphomas were more common, but more recent reports indicate the low-grade lymphomas are more prevalent.

Feline small intestinal adenocarcinoma usually affects the jejunum and ileum. Approximately 50% of cats with intestinal adenocarcinoma experience metastasis. The most common sites of metastasis include the regional lymph nodes, peritoneum, omentum, mesentery, liver, and lungs. Ascites may be present secondary to carcinomatosis.

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The intestinal lesion with feline intestinal mast cell tumor can be diffuse, solitary or multifocal. The neoplasia may be either intraluminal or intramural. The small intestine is the most common location for feline intestinal mast cell tumor but colonic involvement can occur. Widespread metastasis is common at the time of diagnosis. One study found that 64% of cats with intestinal mast cell tumor had multiorgan involvement. The most common sites of metastasis include lymph nodes, liver, spleen, and rarely lung. Intestinal mast cell tumors can be difficult to diagnose because their cytoplasmic granules may not stain. This may be due to their anaplastic nature or degranulation. It has been suggested that mucosal mast cells are different from mesenchymal mast cells and require special fixation to enhance the metachromasia. Diff-Quik staining of feline mast cell tumors sometimes fails to reveal cytoplasmic granules. Circulating mast cells are uncommon with intestinal mast cell tumors, although peripheral eosinophilia has been reported.

Adenomatous polyps and carcinoma *in situ* are usually solitary. However, multiple and diffuse varieties have been identified. Furthermore, malignant transformation to invasive carcinoma has been reported.

Canine colorectal adenocarcinoma generally can be grouped into three categories based on its gross appearance: pedunculated, cobblestone, and annular. When metastasis does occur with colorectal adenocarcinoma, it usually travels via lymphatics to the local lymph nodes and may sometimes seed the peritoneum, leading to carcinomatosis. The metastatic rate for colorectal adenocarcinoma ranges from 0% to 80%. Malignant transformation from *in situ* tumors has been reported in 17–50% of dogs.

Approximately 75% of cats with colonic adenocarcinoma have metastasis. Half have distant metastasis and half are local. Metastatic sites included the colonic lymph nodes, mesenteric lymph nodes, liver, omentum, and lungs. Carcinomatosis may also occur.

Epidemiology

Small intestinal tumors are in general, uncommon in dogs. According to most reports, lymphoma is the most common specific type. The intestinal tract is the most common extranodal site for this malignancy, affecting 5–7% of all dogs diagnosed. Intestinal adenocarcinoma and leiomyosarcoma are the two most common nonlymphomatous small intestinal tumors in dogs. In particular, leiomyosarcoma is the most frequently diagnosed intestinal sarcoma and it commonly involves the jejunum and cecum.

Recently, it was found that tumors previously categorized as leiomyosarcomas were in fact derived from the interstitial cells of Cajal. Interstitial cells of Cajal are the pacemaker cells of the intestinal tract and regulate peristalsis. Tumors derived from these cells are called gastrointestinal stromal tumors (GISTs). GISTs can be distinguished from leiomyosarcomas based on the expression of c-kit (CD117). In one recent study, two-thirds of dogs diagnosed with intestinal leiomyosarcomas were reclassified as GISTs based on positive staining for CD117. In this study, GISTs were most common in the cecum and large intestine (64%) as compared to the stomach and small intestine (36%). In oposition to GISTs,leiomyosarcomas appear to develop more commonly in the stomach and small intestine (90%) and are less common in the large intestine (10%).

It is reported that up to 60% of all intestinal tumors in dogs are located in the colon and rectum. Dogs are typically middle-aged to older with males reported to be affected more frequently than females. Unlike in the small intestine, adenomatous polyps and carcinoma *in situ* are commonly identified in the large intestine. Malignant tumors, such as those that develop in the small intestine also occur.

Lymphoma is the most common intestinal neoplasia in cats. It is the most common anatomic form of lymphoma in cats since the advent of FeLV vaccine as well as routine FeLV testing and separation of FeLV-positive cats. Anatomic forms of feline lymphoma generally associated with FeLV infection, such as the mediastinal and nodal forms, are becoming less prevalent. Adenocarcinoma is the second most common small intestinal tumor in cats. Siamese may be overrepresented. Intestinal mast cell tumor is the third most common intestinal tumor in cats. Colonic adenocarcinoma (along with lymphoma) is one of the two most common neoplasias that develop in the feline large intestine.

Other less common intestinal tumors include extramedullary plasmacytoma, extraskeletal osteosarcoma, and hemangiosarcoma.

Signalment

The median age for dogs with all types of lymphoma, including intestinal, is 6–9 years. Small intestinal neoplasia should be considered a differential diagnosis in a middle-aged to older dog with signs consistent with intestinal obstruction. The median age of onset for canine intestinal leiomyosarcoma/GIST is 10.5 years. They are reportedly more common in female dogs. Dogs with colorectal polyps have a mean age of 7–8 years. Colorectal adenocarcinoma most commonly affects older male dogs. Feline intestinal lymphoma is more common in older cats with a median of age of 10–12 years. Domestic short-hairs are more commonly affected. The average age of cats with small intestinal

adenocarcinoma is 10–11 years. Siamese may be overrepresented. Feline intestinal mast cell tumors tend to affect older cats with a mean age of 13 years. Feline colonic adenocarcinoma generally affects older cats with no discernible sex or breed predilection.

History and Clinical Signs

Clinical signs for most small intestinal neoplasias in dogs and cats are similar and include one or more of the following: anorexia, vomiting, diarrhea, weight loss, melena, and lethargy. Signs may be subacute, acute or chronic in nature, depending on the underlying disease process. A patient may present with acute vomiting, anorexia, and abdominal discomfort secondary to a gastric or small intestinal obstructive lesion or with a history of chronic weight loss, decreased appetite and intermittent vomiting over the course of months if a low-grade intestinal lymphoma is the underlying problem. Therefore, the chronicity of signs should not dissuade the clinician from keeping neoplasia on the differential list for many common GI presentations. Some patients may present in shock if a GI perforation occurs secondary to underlying intestinal neoplasia. Dogs with intestinal leiomyosarcomas may present with signs secondary to paraneoplastic hypoglycemia, such as weakness, ataxia, and seizures. Some patients with intestinal tumors may present with signs referable to anemia such as weakness and lethargy secondary to gastrointestinal bleeding.

Diagnosis

A complete blood count, biochemistry profile, and urinalysis are recommended as part of a minimum database but are not helpful in establishing a definitive diagnosis. Anemia can be seen in up to ~64% of dogs with intestinal neoplasia and is associated with intestinal hemorrhage or anemia of chronic disease.

The chemistry panel can reveal a paraneoplastic hypoglycemia in dogs with intestinal leiomyosarcoma. When a dog presents primarily for signs secondary to hypoglycemia, rather than gastrointestinal signs, a serum sample should be held for simultaneous blood glucose and blood insulin levels to rule out inappropriate insulin secretion secondary to an insulinoma (beta-cell tumor of the pancreas). Hypoproteinemia is a common laboratory finding secondary to malabsorption or intestinal loss in dogs and cats with diffuse intestinal lymphoma. Cobalamin and folate should be assessed to evaluate for malabsorption and small intestinal bacterial overgrowth. Animals with intestinal extramedullary plasmacytomas should be thoroughly staged for systemic disease with serum electrophoresis, bone marrow aspiration/evaluation, abdominal ultrasound, and survey skeletal radiographs. In cats with intestinal lymphoma or intestinal carcinoma, an abdominal mass can be palpated in over 50% of cases. Abdominal radiographs may show an obstructive pattern or abdominal mass. Three-view thoracic radiographs should be performed but are usually negative for metastasis at the time of diagnosis.

The imaging test that will give the clinician the most useful information is abdominal ultrasound which provides information regarding size and location of the mass as well as evidence of metastatic spread. It also provides a means to achieve a diagnosis through less invasive procedures such as ultrasound-guided aspiration and ultrasound-guided biopsy. Ultrasound-guided aspirates and biopsies both can result in a false negative if a cystic, necrotic or inflammatory area of the tumor is sampled.

As with any neoplasia, biopsy and histopathology is the preferred method of diagnosis. Occasional misdiagnosis of neoplasia can occur with aspiration/cytology, where a tumor may be aspirated and the cytology is consistent with one type of neoplasia (i.e., carcinoma) but when a biopsy and histopathology are performed, the diagnosis changes to another tumor type (i.e., lymphoma). This can occur when the aspiration contains cells which are not representative of the underlying lesion, the tissue sampled does not exfoliate well or in order to make a correct diagnosis of neoplasia the evaluation of the tissue architecture is needed, not just evaluation of the cell type. Endoscopy and colonoscopy may be helpful in diagnosing proximal small intestinal lesions and colorectal lesions respectively. However, endoscopic biopsy may underdiagnose intestinal lymphoma in dogs and cats. Ultimately, abdominal exploratory surgery with either incisional or excisional biopsy and histopathology may be necessary to obtain a definitive diagnosis.

Immunohistochemistry for the expression of c-kit (CD117) is recommended in dogs with intestinal sarcomas to differentiate between GISTs (CD117 positive) and leiomyosarcoma (CD117 negative). The differentiation between GISTs and leiomyosarcomas can have both prognostic and therapeutic implications.

Routine immunohistochemistry has identified that T cell is the most common immunophenotype of intestinal lymphoma in dogs. Feline intestinal lymphoma can be either T cell or B cell in origin.

Therapy

Surgical excision via intestinal resection and anastomosis, with or without adjuvant chemotherapy, is the primary treatment for most animals with intestinal neoplasia. Intestinal lymphoma is the one notable exception,

where chemotherapy is the primary treatment recommendation. Surgery is only recommended in patients with intestinal lymphoma when there is evidence of intestinal perforation or obstruction. It is recommended that 5–6 cm of normal intestine on either side of the tumor be excised. For animals with colonic tumors, subtotal colectomy may be necessary. One study found that cats that had subtotal colectomy for colonic adenocarcinoma had improved survival times over cats that had just mass resection or mass biopsy. The authors of the study do not suggest that every cat with a colonic mass should receive subtotal colectomy but wide surgical margins are recommended. Biopsy of the local lymph nodes, liver, and any other abnormal-appearing abdominal organ is recommended to assess for metastasis. For dogs and cats with rectal tumors, a transanal pull-through procedure has been found to be effective. A combined abdominal-transanal approach may be necessary for tumors located at the cranial extent of the rectum extending to the descending colon.

The benefit of postoperative chemotherapy is unknown for dogs with small intestinal adenocarcinoma. However, due to the moderate to high metastatic rate, the inclusion of adjuvant chemotherapy with doxorubicin-based protocols would be logical. Approximately 50% of intestinal adenocarcinomas in dogs expres COX-2. The products of the COX-2 enzyme have been associated with protumorigenic effects such as angiogenesis, cell proliferation, and inhibition of apoptosis. Therefore, the author recommends including NSAIDs in the treatment protocol for dogs with intestinal adenocarcinomas as they have antineoplastic activity that may help improve response and survival. The metastatic rate of small intestinal carcinoma in cats is also high. Postoperative chemotherapy is recommended to help control metastasis and to prolong survival. A study evaluating cats with large intestinal carcinoma did show a survival advantage for those that received doxorubicin chemotherapy postoperatively. Whether this chemotherapy protocol is beneficial in cats with small intestinal carcinoma has yet to be determined but it is a logical choice for postoperative therapy.

As with small intestinal adenocarcinoma, the use of postoperative chemotherapy in dogs with small intestinal leiomyosarcoma has yet to be investigated in a randomized clinical trial. However, based on the moderate to high metastatic rate (16–50%), chemotherapy should be included in the treatment protocol. Surgical removal alone results in prolonged survival times (over three years) for dogs with GISTs. However, for those few cases in which GISTs are nonresectable or metastatic, adjuvant treatment with tyrosine kinase inhibitors may be useful. In humans with nonresectable or metastatic GISTs, treatment with tyrosine kinase inhibitors has been shown to result in longer survival times compared to other treatments. Therefore, the use of tyrosine kinase inhibitors in dogs with nonresectable, recurrent or metastatic GISTs is reasonable as GISTs in both species express KIT/CD117. Activating mutations have been found involving c-kit in both dogs and humans and are thought to be the driving force for GIST development. There are two oral tyrosine kinase inhibitors in veterinary medicine, toceranib phosphate (Palladia™) and masitinib mesylate (Masi). Only Palladia, is approved for use in dogs with mast cell tumors in the USA. Regardless, both inhibit KIT but their use in dogs with GISTs has yet to be investigated.

Chemotherapy is the primary treatment for intestinal lymphoma in dogs due to the multifocal or diffuse nature of the disease. Although CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)-based protocols are considered the standard of care for dogs with multicentric lymphoma, due to the poor response of dogs with intestinal lymphoma other alkylating agent-based protocols, including MOPP (mechlorethamine HCL, vincristine sulfate, procarbazine, prednisone), lomustine or DTIC/lomustine, may provide improved survival times.

In cats with intestinal lymphoma, the treatment protocol varies depending on whether they have low-grade versus intermediate to high-grade lymphoma. The treatment of low-grade lymphoma consists of the administration of prednisolone and chlorambucil. One study evaluating cats with low-grade intestinal lymphoma found that 78% were cobalamin (vitamin B12) deficient, thus requiring cobalamin supplementation. Cobalamin is absorbed exclusively in the ileum, complexed with intrinsic factor. Low cobalamin is associated with metabolic derangements and low concentrations of several amino acids. Intermediate to high-grade lymphomarequires more aggressive therapy. The best response, remission duration, and survival time is generally achieved with CHOP-based chemotherapy protocols. Eventually, most cats relapse and/or develop resistant disease. If relapsing after completing their initial CHOP chemotherapy protocol, it can be restarted. The second remission is generally about half the duration of the first. Once they fail CHOP, rescue chemotherapy can be attempted. The most successful rescue chemotherapy protocols include MOPP and lomustine.

If a solitary mass is present and there is no evidence of metastatic disease, surgical removal can be attempted in cats with intestinal mast cell tumors. Due to the high rate of disseminated disease with intestinal mast cell tumors, postoperative chemotherapy is recommended based on the likelihood of residual micrometastasis. If the intestinal mast cell tumor is not resectable or metastatic disease is present at the time of diagnosis, chemotherapy

can be attempted. A study evaluating lomustine for cats with a variety of mast cell tumors (cutaneous, splenic, intestinal) found that two cats with intestinal mast cell tumors responded. Whether lomustine would be effective in a large population of cats with intestinal mast cell tumors is unknown. Other chemotherapy agents used in dogs with mast cell tumors include vinblastine, cyclophosphamide, hydroxyurea, and prednisone. Their effectiveness in cats with mast cell tumors is unknown.

Many cat mast cell tumors have mutations in the gene c-kit leading to constitutive activation of the tyrosine kinase growth factor receptor KIT. Activating mutations of c-kit have been implicated in mast cell tumor development and progression in dogs. Small molecule targeted therapies (toceranib phosphate and masitinib meslyate) have been approved for use in dogs with mast cell tumors. As mentioned previously only toceranib phosphate is approved for use in the USA. These targeted therapies inhibit the activation of the abnormal growth factor receptor KIT, resulting in cessation of cell growth and proliferation and potentially leading to cell death through apoptosis. A recent study evaluating Palladia in cats with mast cell tumors reported a clinical benefit in 76% (13/17) of those with the gastrointestinal form. However, further studies are necessary.

Aside from definitive treatment with chemotherapy and/or a tyrosine kinase inhibitor, all patients with intestinal mast cell tumors should receive prednisolone or prednisone as well as a histamine receptor 1 and 2 antagonist.

For dogs with colorectal polyps, the use of NSAIDs has been found to be of benefit in reducing clinical signs and may be an alternative treatment to surgical excision. The author recommends placing dogs that have had surgical removal of colorectal polyps on NSAIDs postoperatively in an attempt to prevent local recurrence, development of additional polyps or malignant transformation of polyps. Although there are no clinical studies evaluating the use of NSAIDs in this particular setting, NSAIDs have been found to have various antineoplastic properties.

Surgical excision of colorectal plasmacytomas is curative in most cases. Plasmacytomas of other areas of the intestinal tract can have a high metastatic rate and if metastasis is observed, follow-up chemotherapy in the form of prednisone and melphalan is recommended. Extraskeletal osteosarcomas are both locally and systemically aggressive. Adjuvant chemotherapy has been shown to help prolong survival in dogs with extraskeletal osteosarcoma. Therefore, postoperative carboplatin is recommended for intestinal extraskeletal osteosarcoma. Visceral hemangiosarcoma is an aggressive disease with a high rate of metastasis. Adjuvant doxorubicin chemotherapy is recommended after surgical resection of intestinal hemangiosarcoma.

Many animals with intestinal neoplasia need supportive medications for nausea, decreased appetite, gastrointestinal protection, and diarrhea. The most commonly used antiemetics include maropitant, ondansentron, dolasetron, and metoclopramide. Appetite stimulants include capromorelin, mirtazapine, cyproheptadine, and megestrol acetate. Effective gastroprotectants include famotidine, omeprazole, and sucralfate. Common antidiarrheal medications include metronidazole, tylosin, sulfasalazine, and loperamide.

Prognosis

The prognosis for dogs with intestinal lymphoma is generally much worse than for dogs with multicentric lymphoma. A recent study using a CHOP-based protocol with consolidation resulted in a 56% response rate (50% complete response, 6% partial response). The median survival time for the entire study population was 2.5 months. The response rate for dogs with multicentric lymphoma is up to 90–95% with median survival times of 12–18 months. Another study evaluating dogs with intestinal lymphoma treated with multiple treatment modalities revealed very poor survival, with a median survival time of 13 days. In dogs with intestinal lymphoma, the presence of diarrhea and lack of response to chemotherapy were negative prognostic factors

In dogs treated with surgical excision for small intestinal adenocarcinoma, the presence of metastasis at the time of surgery is associated with statistically shorter survival time (median survival time three months, 20% survival at one year) when compared to dogs without metastasis (median survival time 15 months, 66.7% survival at one year).

Long-term survival has been reported in dogs with metastatic intestinal leiomyosarcoma. In one study, 50% of dogs with intestinal leiomyosarcomas had metastasis at the time of surgery. The median survival time of the entire study population was 21.3 months. Another study revealed a median survival time of 1.1 years for dogs with small intestinal leiomyosarcoma that survived the immediate postoperative period, with 29% of the dogs dying of leiomyosarcoma. The results of these historical studies should be viewed in light that some might have been GISTs that had been misdiagnosed. In one study evaluating both GISTs and leiomyosarcomas, the median survival time for dogs with GISTs that survived the perioperative period was 37.4 months, whereas the median survival time for dogs with leiomyosarcomas was only 7.8 months. Further, 7% of the dogs with GISTs developed metastasis. There were no reports of metastasis in those with leiomyosarcomas.

Recurrence of clinical signs is uncommon with removal of colorectal adenomatous polyps (17%). However, recurrence of clinical signs after removal of carcinoma *in situ* is fairly common (55%). The presence of multiple lesions was also associated with recurrence of clinical signs. Malignant transformation has been reported with rectal polyps, although more commonly with carcinoma *in situ* (17–50%).

The prognosis for dogs with colorectal adenocarcinoma has been linked to the gross appearance of the tumor. The mean survival time for those with pedunculated lesions is 32 months, cobblestone lesions 12 months, and annular lesions 1.6 months.

Cats with small cell, low-grade intestinal lymphoma treated with prednisone and chlorambucil have a good prognosis with response rates of 69–95% and median survival times of 18–24 months.

Cats with intermediate to high-grade intestinal lymphoma have a worse prognosis compared to those with the low-grade intestinal type. When compared to other anatomic sites, cats with intermediate to high-grade intestinal lymphoma tend to have the second best prognosis, after nasal lymphoma. However, the response rate, remission duration, and survival time for cats with intermediate to high-grade intestinal lymphoma are generally less than dogs with multicentric intermediate to high-grade lymphoma. The response rate for cats treated with multiagent (CHOP-based) chemotherapy is 50–86% (complete response rate of 50–70%) with a median remission duration of 4–9 months and a median survival time of up to 7–9 months. Response to therapy, FeLV status, substage, anatomic site, and chemotherapy protocols that include doxorubicin have been linked to remission duration and survival. Unlike dogs, immunophenotype (T cell vs B cell) is not a prognostic factor in cats with lymphoma.

The prognosis can be fairly good for cats with small intestinal adenocarcinoma that survive the postoperative period, with average survival times of 15 months reported. In one study, even those that had lymph node metastasis at the time of surgery and survived the perioperative period fared well (average survival time of 12 months). In the study, recurrent adenocarcinoma was the cause of death in 50% of long-term survivors.

The prognosis for intestinal mast cell tumor has historically been considered to be poor due to the high percentage of patients that present with metastatic disease. However, a recent study of cats indicated that the prognosis may be better than once thought (median survival time 531 days).

Reported cats that had subtotal colectomy for colonic adenocarcinoma had significantly longer survival times than cats with either mass resection or biopsy. Median survival time with subtotal colectomy was 138 days versus 68 days and 10 days for mass resection and biopsy respectively. In the study, the presence of metastasis was also associated with a shorter survival time (median survival time 49 days) compared to those cats that did not have metastasis (259 days). Finally, cats that receive doxorubicin chemotherapy appear to have a significantly longer survival time (median survival 280 days) compared to those that do not receive doxorubicin (56 days).

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143

Exocrine Pancreatic Cancer

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Etiology/Pathophysiology

Nearly all cancers of the exocrine pancreas are epithelial and most are adenocarcinoma arising from either the ductal or acinar epithelium. This is in contrast to insulinomas which arise from the islet cells of the endocrine pancreas. Insulinomas are covered in more detail in a different section. There are no known causes for exocrine pancreatic cancer (EPC) in veterinary medicine. Experimentally, intraductal administration of N-ethyl-N'-nitro-N-nitrosoguanidine induces EPC in dogs.

Epidemiology

Exocrine pancreatic cancer is rare and accounts for less than 0.05% of all cancers in the dog and cat. Older female dogs, spaniels, and Airedales have been described in previous publications as being at higher risk. In humans, EPC remains the fourth most common cause of cancer-related death in the United States and it occurs most commonly in people who smoke or have chronic pancreatitis or diabetes mellitus. It is not clear if this is true in veterinary medicine but recently there have been several published reports of diabetes mellitus and EPC in cats which are suggestive of a possible association. It is unknown whether diabetes mellitus develops secondary to compression of islet cells by tumor, secondary to cortisol-induced beta-cell degeneration, or secondary to decreased carbohydrate metabolism, which is common in humans with pancreatic carcinoma.

Signalment

The median age at diagnosis is 10 years for dogs and 12 years for cats. It occurs almost equally in both sexes.

History and Clinical Signs

Symptoms associated with EPC are nonspecific and may mimic pancreatitis. Anorexia, weight loss, lethargy, weakness, vomiting, maldigestion syndrome, abdominal distension, abdominal effusion, and icterus are common findings. In cats that presented with EPC, 75% had anorexia, 63% vomiting, and 38% abdominal pain, a palpable abdominal mass, and/or jaundice. Duration of clinical signs appeared to be bimodal, with 50% of cats having signs for <7 days and the other 50% having signs for >1 month.

Paraneoplastic alopecia is a rare syndrome seen in cats with pancreatic neoplasms. The pathogenesis of this dermatologic disease is unknown. Alopecia begins acutely and typically starts with loss of clumps of hair on the ventrum, and then spreads to the legs and eventually the face. Dorsal alopecia is uncommon. Other changes noted are poor, dry, thinning hair coat and focal areas of erythema. Often, there is a characteristic appearance to the skin and in areas where cats groom, the skin can appear shiny. Lesions develop rapidly over 2–10 weeks and spread over much of the body. They appear in association with the tumor and in one case resolved with tumor removal.

Histopathologically, the skin changes are characterized by loss of the stratum corneum and severe follicular atrophy with miniaturized hair bulbs. The majority of cases die or are euthanized within eight weeks of development of lesions so the presence of this condition on physical examination is highly suspicious for EPC and appears to be a poor prognostic factor.

Diagnosis

Staging for EPC includes radiographs of the thorax (three-view), abdominal radiographs (two-view), minimum

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database (complete blood count, biochemistry profile, urinalysis) and abdominal ultrasound. In cases where an aspirate is going to be obtained, a clotting profile is advisable as prolongation in partial thromboplastin time (PTT) and clotting disorders have been described in cats and people with EPC respectively. In cases where surgery is being considered, a computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen may be useful in preoperative planning and identifying metastatic disease.

Laboratory findings are generally nonspecific but can include leukocytosis, anemia, hyperglycemia, and elevations in liver enzymes. Dogs with pancreatic neoplasia may have significant elevations in serum lipase with only minimal elevations of serum amylase, implying tumor production of lipase. These findings are inconsistent, however. In a small case series of eight cats with EPC, 50% had neutrophilia, 33% had elevations in serum alkaline phosphatase activity, and 57% had increased alanine aminotransferase. Mild hyperglycemia was identified in 63% of cats.

Physical examination findings can include abdominal pain, icterus, abdominal distension, and/or ascites. In small dogs or cats, palpation of a cranial abdominal mass can occasionally be appreciated.

Survey abdominal radiographs may show decreased serosal detail or a cranial abdominal mass effect. The sensitivity for the detection of pancreatic tumors in dogs has been reported to be 19% for radiographs and 75% for ultrasound. Abdominal radiographs were helpful in identifying abdominal disease in cats with EPC. In one study, abdominal radiography was able to identify abdominal disease in all cases of pancreatic adenocarcinoma.

Ultrasonography is superior to abdominal radiographs for detecting EPC in both dogs and cats. It is a useful diagnostic tool for localization of the tumor, confirmation of ascites, and documentation of lymphadenopathy and metastasis. In cats, the ultrasound findings seen with nodular hyperplasia of the pancreas are similar to changes seen with malignant pancreatic neoplasms. There was a trend, however, for malignant masses to appear as a single, larger lesion exceeding 2 cm in at least one dimension. Hyperplastic nodules typically did not measure more than 1 cm in diameter and were numerous. Differentials for masses of the pancreas are insulinoma, gastrinoma, adenocarcinoma, adenoma, pancreatic pseudocyst, abscess, pancreatitis, and lymphoma.

When effusion is present, cytology and fluid analysis may reveal a modified transudate and neoplastic cells indicating carcinomatosis. Solitary masses can be diagnosed with cytology. Cytologic samples obtained with ultrasound guidance correctly diagnosed EPC in 92% of cases.

Therapy

The majority of EPCs are diagnosed at an advanced stage. Fifty to seventy percent of animals have metastatic disease to regional lymph nodes and distant sites documented at the time of diagnosis. In a study where necropsy findings were documented in cats with EPC, metastases to the liver, abdominal lymph nodes, lung, heart, diaphragm, tracheobronchial and cranial mediastinal lymph nodes were found. The incidence of metastasis seemed to be unrelated to the duration of clinical signs. Cats with the longest history of clinical signs were equally likely to have metastasis noted at necropsy as cats with short histories. This suggests that the duration of clinical signs prior to diagnosis is not a negative prognostic indicator.

Complete pancreatectomy or pancreaticoduodenectomy (Whipple procedure) has been described in humans and in dogs but carries a high perioperative morbidity and mortality without significant cure rates.

Chemotherapy and radiation therapy have shown limited value in humans and animals and information regarding the use of chemotherapy in veterinary medicine is scarce. In humans, external beam radiation therapy (EBRT) alone does not provide optimal tumor control and local failure rates are as high as 72%. These dismal results have spawned efforts to improve outcomes by the concurrent administration of drugs that act as radiation sensitizers, including 5-fluorouracil, gemcitabine, and, most recently, paclitaxel.

Palliative therapy to address effusions can be attempted with regular, periodic abdominocentesis and intracavitary chemotherapy. Protocols utilizing cisplatin and carboplatin have been described and appear to provide palliation for select patients. When effective, this can result in temporary relief from discomfort, slow the reaccumulation of the effusion, and possibly delay progression of the disease. Palliative responses, when seen, are generally short-lived.

Prognosis

The prognosis of EPC is generally poor, with few animals living beyond a year although a small percentage of dogs and cats have experienced long-term survival. In dogs, a unique variant of EPC described as hyalinizing pancreatic adenocarcinoma appears to be biologically less aggressive. The neoplasm is generally a solitary mass usually involving the right limb of the pancreas. Dogs without postoperative complications or concurrent life-threatening diseases survived longer than expected (four months, 16 months, and >19 months).

In a retrospective study evaluating 34 cats with EPC, metastatic disease was confirmed in 11 cats and overall median survival was 97 days. The median survival times for patients who received chemotherapy or had their masses surgically removed was 165 days. Patients with abdominal effusion present at diagnosis had a median survival of 30 days. Interestingly, however, three patients survived over one year.

A cat with metastatic EPC to the spleen treated with partial pancreatectomy and splenectomy was reported to be alive and disease free >2 years later. Therefore, the prognosis for EPC in select dogs and cats may not be as dismal as previously reported.

Comparatively, about 45 220 people develop cancer of the exocrine pancreas each year in the US, and almost all are expected to die from the disease. The median survival is 8–12 months for patients with locally advanced disease and less for those with metastatic disease at presentation. Five-year survival rates are consistently <18%. The majority of these tumors (85%) are adenocarcinomas arising from the ductal epithelium. Surgical resection offers the only chance of cure. However, only 15–20% of patients have resectable disease at diagnosis, approximately 40% have metastatic disease, and another 30–40% have locally advanced unresectable tumors.

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144

Pancreatic Endocrine Tumors

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Insulinoma

Etiology/Pathophysiology

The pancreas is made up of endocrine and exocrine tissue. The endocrine pancreas is composed of islets of Langerhans, which make up approximately 1–2% of the mass of the pancreas. Within the islets there are four cell types: alpha, beta, delta, and polypeptide cells. Beta-cells secrete various hormones, with insulin being the primary product. Approximately 60–75% of the islet cells are of beta-cell origin.

Insulin is the hormone that is primarily responsible for regulating blood glucose concentration. Insulin does not influence entry of blood glucose into beta-cells, as in other tissues. Entry of glucose into the beta-cell is proportional to the blood glucose concentration. Beta-cells are extremely sensitive to glucose concentrations and therefore the regulation of insulin secretion.

The central nervous system (CNS) has limited glycogen storage and is unable to use energy sources other than glucose. Thus, it is dependent on blood glucose to maintain its energy requirements. With hypoglycemia, cells within the cerebral cortex are affected first due to their higher metabolic rate. Counterregulatory hormones such as catecholamine, glucagon, growth hormone, and cortisol are secreted in response to hypoglycemia and aid in recovery from the hypoglycemic episode.

Insulinomas (beta-cell insulin-secreting tumor, beta-cell adenocarcinoma/adenoma) are insulin-secreting tumors of the pancreatic beta-cells. They are the most common endocrine pancreatic tumor in companion animals and are usually malignant.

Insulinomas can be found in both the right and left lobes of the pancreas with equal frequency. Occult insulinomas are most frequently found in the pancreatic body.

Epidemiology

Insulinomas are uncommon in dogs and rare in cats. One estimated report cites an incidence of 17.8/100 000 patient-years in the dog and 12.6/100 000 patient-years at risk in the cat. Insulinomas have been associated with multiple endocrine neoplasia (MEN) type I in people. This is an inherited disease that also results in parathyroid and pituitary tumors. Although we do not have a clear understanding of the epidemiology of canine insulinomas, there have been rare cases of canine MEN that involve an insulinoma.

Signalment

In dogs, middle-aged to older, medium to large breeds are predisposed. Large-breed dogs are overrepresented. Breed predispositions have not been noted in cats.

History and Clinical Signs

Clinical signs are predominantly related to hypoglycemia, resulting in neuroglycopenic manifestations and, less commonly, stimulation of the sympathoadrenal system. The degree and onset of clinical signs are related to the severity and rate of development of hypoglycemia. Gradual or chronic hypoglycemia may go unnoticed. When chronically affected by hypoglycemia, some animals adjust to blood glucose levels of 20–30 mg/dL. Clinical symptoms consistent with hypoglycemia include seizures, lethargy, weakness, coma, and ataxia. Catecholamine release can cause tachycardia, muscle fasciculations, hunger, and restlessness. Exercise causes rapid consumption of glucose and may precipitate an episode of collapse or seizure.

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Diagnosis

Differential diagnosis for other causes of hypoglycemia include hypoadrenocorticism, juvenile hypoglycemia, sepsis, growth hormone deficiency, nonpancreatic tumors, insulin overdose, hepatic disease, glycogen storage diseases, artifacts related to sample handling, and toxins. Other types of neoplasms that can lead to paraneoplastic hypoglycemia include hepatocellular carcinoma, hepatoma, leiomyosarcoma, leiomyoma, lymphoma, myeloma, and hemangiosarcoma.

A minimum database (complete blood count, serum chemistry, urinalysis) should be collected to rule out other causes of hypoglycemia. Nonspecific findings that may be associated with insulinomas include elevated liver enzymes, hypokalemia, and hypophosphatemia. Radiographs may help rule out other causes of hypoglycemia. However, radiographic changes directly related to insulinomas should not be expected. Sensitivity of identifying insulinomas with abdominal ultrasound can be as low as 36%. It may be more beneficial in identifying metastasis in the liver and local lymph nodes. Failure to identify a pancreatic mass does not rule out an insulinoma. Serum insulin concentrations that are normal to high in the presence of hypoglycemia support a diagnosis of insulinoma.

Insulin:glucose and glucose:insulin ratios have high false-positive rates and are not recommended. Rather, insulin concentration should be measured on a serum sample taken when the blood glucose is below 60 mg/dL. Insulin concentrations should be low or undetectable at this blood glucose concentration. The serum glucose and insulin are evaluated as a pair. Animals may need to be fasted in order to obtain the appropriate samples and serial samples may need to be drawn every 2–4 hours until the blood glucose concentration is below 60 mg/dL. Provocative testing is not recommended as it has not been shown to be more sensitive than paired insulin and glucose measurement and can be dangerous due to potentiation of hypoglycemia.

Additional preoperative and intraoperative methods of tumor identification may be utilized. Nuclear scintigraphy with indium 111-labeled pentetreotide has been used to image somatostatin receptors in dogs with insulinomas. Insulinomas express high-affinity somatostatin receptors of subtype sst2 (SST2), thus allowing abnormal foci of activity to be detected. Direct intraoperative ultrasonography and intravenous injection of methylene blue may also be beneficial in identifying insulinomas. Methylene blue concentrates in the neoplastic tissue. However, side-effects including Heinz body anemia and renal failure have been reported to occur.

Therapy

Surgery is the mainstay of treatment. However, even when resectable, a cure is still unlikely. Gross or occult metastasis should be expected. Debulking of gross disease may significantly assist in controlling clinical signs. The goal of surgery is to remove as much neoplastic tissue as possible. Special attention should be given to regional lymph nodes and the liver. Complications include hyperglycemia (diabetes mellitus), continued hypoglycemia, exocrine pancreatic insufficiency, and pancreatitis.

First-line medical management is glucocorticoid therapy. In particular, prednisone administered at 0.25–3 mg/kg orally twice daily can be utilized. The dose should be increased as needed to control hypoglycemia. Prednisone is used with small frequent feedings (four times daily) and limited exercise. Exercise leads to an increased peripheral demand for glucose in spite of impaired gluconeogenesis and glycogenolysis. As a result, insulin secretion continues even as blood glucose falls.

Diazoxide decreases insulin release from beta-cells and stimulates epinephrine release from adrenergic cells. The result is decreased insulin release and increased hepatic glycogenolysis and gluconeogenesis. It is effective in 64–85% of dogs. The recommended dose is 5 mg/kg every 12 hours but may be increased up to 30 mg/kg every 12 hours if necessary. Thiazide diuretics potentiate the effects of diazoxide. The most common side-effects of diazoxide are gastrointestinal in nature.

Octreotide is a somatostatin analog that activates somatostatin receptors resulting in the inhibition of synthesis and secretion of insulin. Octreotide is only effective if the malignant beta-cells are expressing somatostatin receptors (~60% in people). It is given at a starting dose of 2 µg/kg SC twice daily. The dose can be increased to three times daily. Limited studies suggest that long-term efficacy is poor. Side-effects are limited but the drug is costly.

Streptozotocin is a chemotherapeutic agent that has direct toxic effects on pancreatic beta-cells. It is nephrotoxic and therefore intravenous fluid diuresis is required. It is administered once every 2–3 weeks at a dosage of 500 mg/m^2 for five treatments. If diabetes mellitus occurs, treatment is discontinued. In one study on the use of streptozotocin in dogs with insulinoma, controls lived for 90 days. Dogs had a median duration of normoglycemia of 163 days when given streptozotocin every three weeks. In another study, streptozotocin was given every two weeks and the average return of hypoglycemia was 196 days.

Prognosis

The World Health Organization (WHO) classification for tumor staging is prognostic for insulinomas. Factors that affect prognosis include presence or absence of tumor (T0 or T1), regional nodal involvement (N0 or

N1), and distant metastasis (M0 or M1). Therefore, full staging (thoracic radiographs, abdominal ultrasound, serum chemistry, complete blood count, and urinalysis) is recommended.

Overall, the prognosis is guarded because of the high rate of metastasis and recurrence of clinical signs. Approximately 36–51% of dogs have detectable metastatic disease at the time of surgery. With surgery alone, stage I (T1N0M0), II (T1N1M0), and III (T1N0M1 or T1N1M1) dogs have an expected median survival of 19 months, nine months, and six months respectively.

Survival time for dogs treated medically is less than when surgery combined with medical management is used. In one study, medical management with prednisone and dietary change alone resulted in a median survival time (MST) of 74 days. In a separate study, the median survival time for dogs that had a partial pancreatectomy was reported at 496 days. In a subset of nine dogs that received postsurgical medical treatment (diazoxide and prednisone) at the time of relapse, the median survival time was extended to 1316 days.

Streptozotocin therapy, especially as an adjunctive to surgery, should be considered. Although data are limited, normoglycemia has been shown to be prolonged with use of streptozotocin when compared to dogs that were medically managed with diet and prednisone (163 versus 90 days respectively). In addition, reduction in metastatic lesions and resolution of hypoglycemic polyneuropathy in dogs have been reported.

Persistent postoperative hypoglycemia has also been reported to be prognostic. In one study, dogs that became normoglycemic postoperatively had a median survival of 680 days compared to those that remained hypoglycemic, which had a MST of 90 days.

Glucagonoma

Etiology/Pathophysiology

Alpha-cells secrete glucagon and constitute about 20–25% of the endocrine pancreas. Glucagon has a profound hyperglycemic effect. In people, glucagonomas are commonly associated with diabetes mellitus and severe paraneoplastic dermatologic disease. Dogs with glucagonomas can have a similar dermatologic syndrome called superficial necrolytic dermatitis, necrolytic migratory erythema, or metabolic epidermal necrosis. This dermatologic disease has been identified in multiple dogs with glucagonomas but it is more commonly associated with liver disease and is not pathognomonic for a glucagonoma.

Glucagon has catabolic effects and opposes the effects of insulin. It causes gluconeogenesis, glycogenolysis, and lipolysis that cause the conversion of glycogen to glucose, resulting in elevation of blood sugar. The catabolic effects of glucagon result in hypoaminoacidemia. Requirements for histidine and lysine-rich keratohyalin granules in the stratum granulosum make the epidermis susceptible to hypoaminoacidemia.

Epidemiology

Glucagonomas are rare in people (<250 reported) with only a few case reports in dogs. They have not been reported in cats.

Signalment

The typical signalment is an older dog. There are no reported breed dispositions.

History and Clinical Signs

Dermatologic manifestations include lesions of the footpad, pressure points, periocular area, and mucocutaneous junctions such as the perineum, genitalia, and muzzle. Hyperkeratosis of the footpads also occurs. Weight loss is associated with the catabolic effects of the glucagon. Hyperglucagonemia can cause diabetes mellitus resulting in polyuria and polydipsia.

Diagnosis

An elevated plasma glucagon level in the absence of hypoglycemia is supportive of the presence of a glucagonoma. Histopathology of skin biopsies will be consistent with superficial hydropic dermatitis and marked parakeratosis. A definitive diagnosis is obtained through histopathology of the pancreatic tumor. In animals with skin lesions, elevations in liver enzymes and hypoalbuminemia may also be present.

Therapy

Surgical debulking or resection is the treatment of choice. Octreotide may be helpful in animals that have alpha-cells that are expressing somatostatin receptors. Streptozotocin has been used with limited success in people for palliative treatment. When dermatologic lesions are present, a high-quality protein diet such, as Hill's Science Diet a/d should used in nonencephalopathic animals. Supplementation with 3–6 egg yolks per day may also be beneficial. Intravenous amino acid therapy has been useful. A 10% crystalline amino acid solution (Aminosyn®, Abbott Labs) at 25 mL/kg over 6–8 hours repeated every 7–10 days has been used to treat hypoaminoacidemia. Ideally, the hypertonic amino acid solution is administered via a central vein to decrease

risks of thrombophlebitis. Supplementation with zinc and fatty acids may also be indicated. Corticosteroids should be avoided as development of diabetes mellitus worsens the prognosis.

Prognosis

The prognosis for pancreatic glucagonomas is poor.

Gastrinoma

Etiology/Pathophysiology

Gastrinomas in dogs and cats are nonislet cell pancreatic tumors that secrete gastrin. In humans, the majority arise in the duodenum and less commonly the pancreas. There is only one report of a duodenal gastrinoma in the dog.

Parietal cells are stimulated to release acid by gastrin, acetylcholine, and histamine. The primary effect of hypergastrinemia is acid hypersecretion resulting in gastrointestinal ulceration. In humans, it is referred to as Zollinger–Ellison syndrome.

Epidemiology

Gastrinomas are rare in dogs and cats.

Signalment

Dogs are typically middle aged and cats are typically older. No breed dispositions have reported.

History and Clinical Signs

Common clinical signs are vomiting and weight loss. Other clinical signs may include hematemesis, diarrhea or melena, lethargy, and pale mucous membranes. Prolonged elevation of circulating gastrin can cause gastric antral hypertrophy. Perforated ulcers can result in shock and peritonitis.

Diagnosis

A minimum database should be collected. Abnormalities are typically associated with gastrointestinal bleeding, vomiting, and liver metastasis. Biochemical abnormalities may include anemia, hypokalemia, hypochloremia, hypoalbuminemia, hypoproteinemia, and increases in liver enzymes and hyperbilirubinemia.

Unless a perforated ulcer is present, abdominal radiographs are of limited use. Contrast may be useful in identifying areas of thickened gastric wall.

Transabdominal ultrasonography is of limited use because the tumors are typically small in size. Abnormalities that may be identified include a primary pancreatic tumor, evidence of metastasis in the liver and regional lymph nodes and a thickened gastric wall.

Endoscopic evaluation of the upper gastrointestinal tract may reveal esophagitis, esophageal and gastroduodenal ulcerations, and a thickened pylorus. Biopsies may reveal inflammation, gastric mucosal hypertrophy, and loss of the mucosal barrier.

Serum gastrin concentrations are typically three times the upper normal range. However, they can be in the normal range. In cases of suspected gastrinoma with normal gastrin levels, provocative testing can be used. Intravenous secretin or calcium infusion can stimulate gastrin release.

A definitive diagnosis is obtained via biopsy. Histopathology and immunohistochemistry will confirm a gastrinoma.

Therapy

Surgery is typically only palliative due to the high metastatic rate. Surgical treatment may be limited by the small size of the tumor making identification difficult. The techniques used to identify the mass are similar to those used for identification of insulinomas and include transabdominal and intraoperative ultrasound, magnetic resonance imaging, and computed tomography. Most gastrinomas express somatostatin receptors on the cell surface. Therefore, indium 111-labeled octreotide nuclear scintigraphy has been used. Methylene blue injection has been used for tumor identification in humans.

The goal of medical management is gastric acid reduction and treatment of gastroduodenal ulceration. Histamine receptor antagonists and proton pump inhibitors are used. Proton pump inhibitors block all three gastric acid secretory pathways. Octreotide has two beneficial effects: it suppresses tumor gastrin release and inhibits gastrin from stimulating the parietal cells.

Prognosis

The prognosis is guarded to poor as approximately 76% of cases have metastatic disease at the time of diagnosis. In animals that receive both surgical and medical management, survival times range from one week to 18 months.

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145

Liver and Biliary Tract Tumors

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Etiology/Pathophysiology

The etiology of hepatobiliary tumors in dogs and cats is largely unknown although human cases are often linked to infection with the hepatitis virus (B and C) and cirrhosis. Cirrhosis, which may be secondary to chronic disease or alcohol consumption in people, is rare in dogs and a viral etiology has not been documented in dogs or cats. Other theories behind the development of hepatocellular carcinoma (HCC) and other hepatobiliary tumors include exposure to chemical carcinogens (aflatoxins or nitrosamines, for example) and chronic infections or inflammatory diseases of the liver. Trematodes are thought to be involved in the development of bile duct carcinomas in people and this link has also been explored in dogs and cats but seems unlikely to be a major cause or concern. More recently, somatic genetic alterations are thought to likely play a role in tumor development, such as mutations in p53, PIK3CA, beta-catenin, and others which have been documented in people.

There are four main histologic categories of primary hepatobiliary tumors in both dogs and cats: hepatocellular, bile duct, neuroendocrine (carcinoid), and mesenchymal (sarcoma). Within in each individual category is an array of both malignant and benign tumors. In general, dogs are thought to be more likely affected by malignant tumors whereas cats more often have benign tumors.

Primary hepatobiliary neoplasms can also be described using three morphologic subtypes: massive, nodular, or diffuse. The definition of a massive liver tumor is a large, solitary mass confined to a single liver lobe; nodular tumors have discrete nodules scattered throughout multiple liver lobes; diffuse tumors consist of coalescing nodules within all liver lobes or widespread infiltration of the hepatic parenchyma by neoplastic cells. As we will discuss further, the histologic and morphologic features of hepatobiliary tract tumors help us to make determinations about prognosis for both dogs and cats.

Hepatocellular Tumors

Hepatocellular tumors develop from the hepatocyte. These tumors include hepatocellular adenomas and hepatocellular carcinomas. Hepatocellular adenomas are benign tumors and while they can be found in both dogs and cats, they are more common in the cat. Hepatocellular adenomas are typically considered incidental findings and rarely cause clinical signs in affected patients. Adenomas can, however, reach a large size, necessitating surgical removal. These tumors are also difficult to clinically distinguish from a massive HCC without the aid of a biopsy.

Hepatocellular carcinoma is the most common primary liver tumor in the dog and the second most common in the cat. The majority of HCCs are morphologically massive (53–84%) followed by nodular (16–25%) and diffuse (0–19%) presentations. The left side of the liver is more commonly affected than the right, with over two-thirds of tumors arising from the left lateral, medial, and papillary process of the caudate lobe. HCCs have the ability to metastasize but the likelihood of metastasis is largely based on the morphologic subtype. Massive HCC have a low reported rate of metastasis (0–37%) whereas the nodular and diffuse subtypes have dramatically higher metastatic rates of 93% and 100% respectively. Metastasis is most commonly reported to the regional lymph nodes, peritoneum, and lungs.

Bile Duct Tumors

There are two primary tumors that can arise from the bile duct epithelium in dogs and cats: bile duct adenomas and biliary carcinomas. Bile duct adenomas are also called

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biliary cystadenomas or hepatobiliary cystoadenomas. These are considered benign tumors and are the most common hepatobiliary tumor found in the cat (accounting for 50% of all feline hepatobiliary tumors). Similar to hepatocellular adenomas, biliary adenomas typically do not cause clinical signs in affected patients unless they reach a large enough size to cause abdominal discomfort, necessitating surgical removal. Male cats are thought to be overrepresented.

Bile duct carcinomas (also called cholangiocarcinomas) are malignant tumors in both dogs and cats. They have an aggressive clinical course with metastasis detected in 60–80% of affected patients. Metastasis to the local lymph nodes and lungs is most common but other intraabdominal sites have been reported. In cats, metastasis resulting in diffuse carcinomatosis can occur in 67–80% of cases. Bile duct carcinomas can be intrahepatic, extrahepatic, or occasionally within the gallbladder itself. Morphologically, bile duct carcinomas are similar to HCC in that 37–46% are massive, 0–46% are nodular and 17–54% are diffuse. In dogs, females and Labrador retrievers are thought to be predisposed whereas there is no sex or breed predisposition yet confirmed in cats.

Neuroendocrine Tumors

These tumors arise from the neuroectodermal cells. They are considered rare tumors in both the dog and cat and are often referred to as carcinoids. Carcinoids have a tendency to occur in younger animals compared to other hepatobiliary tumors. They have an aggressive clinical course and carry a poor prognosis, primarily due to the fact that early metastasis is found in >90% of patients diagnosed. The most common sites of metastasis were the peritoneum and lymph nodes. These tumors are typically intrahepatic and have a predilection for a nodular or diffuse presentation, making surgical resection often difficult or impossible. A small number of extrahepatic neuroendocrine tumors of the gallbladder have been reported for which surgical resection was performed but long-term follow-up is unavailable.

Mesenchymal Tumors (Sarcomas)

Mesenchymal tumors, also called sarcomas, arise from the stromal cells of the liver. They are considered rare, making up less than 15% of all primary hepatic tumors. There are several different subtypes of sarcomas that have been reported in the canine and feline liver including hemangiosarcoma (most common in the dog), leiomyosarcoma (most common in the cat), fibrosarcoma, osteosarcoma, rhabdomyosarcoma, and liposarcoma. Primary hepatic sarcomas carry a poor prognosis due to their aggressive clinical course and high rate of metastasis. Metastasis to the lungs and spleen is most common and is reported in 86–100% of cases. Morphologically, approximately 36% of mesenchymal tumors are massive and 64% are nodular. Bear in mind that the liver is also a common site for secondary sarcomas including metastatic hemangiosarcoma and disseminated histiocytic sarcoma.

Epidemiology

As discussed earlier, liver tumors in the dog and cat can be of either primary or secondary origin. In the dog, retrospective studies have indicated that the prevalence of primary hepatic neoplasia is low (0.6–1.5% of all canine tumors). Secondary neoplasia, the result of metastasis to the liver, is a much more common occurrence. Tumors originating in the spleen, pancreas, and gastrointestinal tract are the most likely to result in metastasis to the liver. However, other systemic neoplasms such as lymphosarcoma, malignant histiocytosis or systemic mastocytosis often involve the liver as part of their widespread clinical course.

In cats, the prevalence is similar, with 1.0–2.9% of all feline tumors being of primary hepatic origin. However, when one study excluded hematopoietic neoplasms, the prevalence increased to 6.9%. There are currently no studies documenting the frequency of metastatic disease to the liver in cats.

Signalment

Hepatobiliary tumors are most common in older animals (over the age of 10), the exception to this being carcinoids which are typically found in younger animals (71% of dogs were under the age of 10). Some studies indicate that miniature schnauzers may be overrepresented for the development of HCC and Labrador retrievers may be predisposed to bile duct carcinomas but there are no other known breed propensities in either species. One study documented a male predilection for canine HCC and a female predilection for bile duct carcinoma. In cats, some studies have indicated a male predominance for carcinoids and bile duct tumors.

History and Clinical Signs

In dogs with hepatobiliary tumors, clinical signs are often lacking or will be somewhat vague. These may include things such as anorexia, weight loss, lethargy, and vomiting. Less frequently, symptoms such as abdominal

discomfort, polyuria, polydipsia, diarrhea, seizures, weakness, ataxia, dyspnea, hematochezia or melena may be observed. If neurologic symptoms do occur in an affected patient, they may be caused by secondary hepatic encephalopathy or paraneoplastic hypoglycemia.

Physical examination may reveal the presence of a cranial abdominal mass affect in up to 75% of patients. However, some massive tumors or nodular and diffuse tumors may not cause any obvious physical exam changes and can be easily missed. Occasionally, a patient may become jaundiced secondary to a hepatobiliary tumor or develop ascites. Overall, dogs and cats with malignant tumors are more likely to become symptomatic than those patients with benign tumors.

Diagnosis

Laboratory Tests

There are no distinguishing complete blood count abnormalities found in patients with hepatobiliary tumors. Hematologic profiles most often show mild and nonspecific changes such as anemia, leukocytosis, and thrombocytosis. A mild, nonregenerative anemia is most common (present in 20–53% of patients). The cause is largely unknown but speculated to be secondary to anemia of chronic disease, red blood cell sequestration, microangiopathic destruction through torturous tumor vessels, or iron deficiency. A leukocytosis may also be present and can be caused by inflammation or necrosis of any large tumor. Thrombocytosis has been reported in approximately 50% of dogs diagnosed with a massive HCC. The cause of this is not fully understood but is speculated to be secondary to anemia, inflammatory cytokine production, chronic iron deficiency, or a paraneoplastic process.

Similarly, serum biochemical profiles often show nonspecific changes. Liver enzyme elevations are commonly found in dogs with hepatobiliary tumors but there is no association with the magnitude of elevation and the severity of disease. These abnormalities are also in no way specific to hepatobiliary neoplasia as many other clinical conditions can affect these values. There are, however, some trends that may be helpful. Alkaline phosphatase (ALP) and alanine aminotransferase (ALT) are the most common values to be elevated in dogs with primary hepatic neoplasia whereas aspartate aminotransferase (AST) and bilirubin are more commonly elevated in metastatic neoplasia, with >90% of dogs having elevations in more than one liver enzyme. In cats, one study showed that ALT, AST, and bilirubin were higher in cats with malignant tumors compared to benign tumors The ratio of liver values to one another has also been examined. An AST:ALT ratio of less than 1 is most common with HCC or bile duct carcinoma whereas a ratio greater than 1 is more likely with a neuroendocrine or mesenchymal tumor.

Other biochemical abnormalities commonly seen with hepatobiliary neoplasia include hypoalbuminemia, hyperglobulinemia, hypoglycemia, and elevated bile acids. In cats, azotemia has been reported as the most common biochemical abnormality. Studies have not clarified the cause of the azotemia though it may represent concurrent and unrelated chronic renal disease.

Imaging

Abdominal radiographs may be helpful at confirming the presence of a large hepatobiliary mass but can easily miss small, nodular or diffuse tumors. In some cases, radiographs may show the presence of mineralization within the biliary tree of dogs with bile duct carcinoma although this is a rare and nonspecific finding. Therefore, ultrasound is the recommended method of imaging for both dogs and cats. Ultrasound also allows for the detection of intraabdominal metastasis, ascites, and the location of the disease and its relationship to other anatomic structures. Most importantly, ultrasound will allow us to determine the morphologic features (massive, nodular, or diffuse) of the tumor and help guide whether surgical resection should be attempted.

Ultrasound images alone, however, are not adequate to diagnose histologic tumor type. An ultrasound-guided fine needle aspiration (FNA) or needle biopsy is recommended, and is especially useful in cases of nodular or diffuse disease. An accurate diagnosis is possible using these techniques in approximately 60% of FNA samples and 90% of needle biopsy samples. Both of these procedures are considered minimally invasive. In some cases, laparoscopic biopsy may be considered more appropriate and is also an excellent means of determining histologic tumor type. In cases of massive tumors, it may not be clinically warranted to know the histologic diagnosis of a particular tumor prior to proceeding with exploratory surgery since the mass will most likely be fully removed and biopsied postoperatively anyway. Advanced imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) are the primary imaging modalities utilized in human medicine for hepatobiliary tumors but have not been fully evaluated in veterinary medicine.

Therapy and Prognosis

Hepatocellular Carcinoma

The prognosis for patients with HCC is dependent primarily on the morphologic subtype. Massive HCC generally carries a good prognosis as it is confined to one

liver lobe and is therefore amenable to surgical resection. In addition to surgical resectability, other prognostic factors for massive HCC include the side of the liver affected (right side worse than left side), pretreatment ALT and AST elevations, and ratio of ALP:AST and ALT:AST. In a paper evaluating surgery in 42 dogs with massive HCC, the median survival time after liver lobectomy was 1460 days versus 270 days for dogs managed medically only. Many of the dogs that underwent liver lobectomy were lost to follow-up as they were still alive or went on to die of other unrelated causes at the end of the study period. Right-sided liver tumors are considered to have a worse prognosis because of their proximity to the caudal vena cava, resulting in an increased risk of intraoperative death. Massive HCC has a low metastatic potential (0–37%) and a low recurrence rate (0–13%) after surgical resection.

In contrast, the prognosis for dogs with nodular or diffuse HCC is poor. This is primarily because that these tumors are not typically surgically resectable due to the involvement of multiple liver lobes and they have a high metastatic rate (93% and 100%, respectively). It is often not possible to clinically determine if nodular and diffuse types of HCC are secondary to intrahepatic metastasis prior to diagnosis or represent multiple foci of disease.

There is little information in the veterinary field about chemotherapy for the treatment of nonresectable HCC. In general, HCC is thought to represent a chemoresistant cancer as response rates of less than 20% are reported in the human literature. This is thought to be secondary to the development of drug resistance within the hepatocytes, owing to their role in detoxification, or through the expression of P-glycoprotein. A recent paper evaluated the chemotherapy agent gemcitabine (2',2'-difluorodeoxycytidine), which has been used in human medicine for the treatment of solid tumors, including HCC. This study did not find a statistical improvement in survival time for those patients with nodular, diffuse or nonresectable massive HCC with the use of gemcitabine but the overall survival time of this small patient population was 983 days. Other treatment techniques that have been explored more recently include arterial chemoembolization, immunotherapy, and antiangiogenic medications.

Bile Duct Tumors

Initial treatment for bile duct tumors should be surgical resection if they are confined to one (or two) liver lobes with no evidence of distant metastatic disease. The prognosis for surgically excised adenomas is excellent with no reports of local recurrence of metastasis. On the other hand, bile duct carcinomas carry a guarded prognosis even when surgically excised due to their high rate of metastasis and local recurrence. The median survival time for patients with bile duct carcinoma is less than six months despite surgical removal. Chemotherapy can be considered to slow disease progression but specific chemotherapy protocols and recommendations have not been effectively evaluated to date in veterinary medicine. There is also no known effective treatment for nodular or diffuse tumors which cannot be surgically excised.

Neuroendocrine Tumors

Neuroendocrine tumors carry a poor prognosis. Metastatic disease is documented in greater than 90% of patients at the time of diagnosis. These tumors are often morphologically nodular or diffuse, limiting the ability to surgically excise them. There is currently no known effective treatment or chemotherapy protocol and the role of these treatments is largely unknown.

Hepatic Sarcomas

Liver lobectomy is recommended if tumors are confined to a single liver lobe. Hepatic sarcomas, however, carry a poor prognosis despite surgical resection due to their high metastatic rate (86–100%). The role of chemotherapy is still under investigation but protocols utilizing doxorubicin and ifosfamide as well as antiangiogenic protocols should be considered to slow disease progression based on their use in sarcomas in other locations such as the spleen.

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146

Tumors of the Urinary Tract

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Tumors of the Urinary Bladder

Etiology/Pathophysiology

Tumors of the urinary bladder are uncommon in dogs and rare in cats. Transitional cell carcinoma (TCC) is the most common primary tumor of the urinary bladder in both species. Other tumors reported include squamous cell carcinoma, leiomyosarcoma, leiomyoma, undifferentiated carcinoma, lymphoma, hemangiosarcoma, rhabdomyosarcoma, fibroma, and other mesenchymal tumors.

Transitional cell carcinoma is most often located in the trigone region of the bladder in dogs and at the apex in cats. Mass lesions and thickening of the bladder wall can lead to partial or complete urinary tract obstruction. Urethral and prostatic involvement has been reported in 56% and 29% of cases respectively. At the time of diagnosis, lymph node involvement is reported in 16% of cases, with 14% demonstrating spread to distant sites. The overall metastatic rate is 50%.

Epidemiology

The overall incidence of bladder tumors is 2% of all reported malignancies in the dog. In cats, bladder cancer is rarely reported. Risk factors associated with the development of TCC include exposure to older-generation topical flea and tick control products (i.e., flea and tick dips), lawn herbicides and pesticides, obesity, female sex, and a strong breed-associated risk. The female:male ratio of dogs with TCC has been reported to range from 1.71:1 to 1.95:1. The risk is higher in neutered dogs than in intact dogs of both sexes. New-generation spot-on flea control products do not appear to be associated with TCC.

Signalment

Affected dogs and cats are usually older, with an average age of 11 years and 13 years respectively. The most commonly affected breeds include West Highland white terriers, beagles, dachshunds, Shetland sheepdogs, and Scottish terriers which have an 18-fold risk of developing TCC.

History and Clinical Signs

The most common clinical signs associated with TCC are stranguria, pollakiuria, hematuria, dysuria, and urinary incontinence. Urinary tract signs may present for weeks to months prior to diagnosis. Temporary relief of these signs may be associated with the use of antibiotics. In more severe cases, abdominal palpation may reveal a palpable caudal abdominal mass. Rectal examination abnormalities include urethral thickening or sublumbar lymphadenopathy. TCC can also metastasize to the inguinal lymph nodes, so palpation of the inguinal fat pads may reveal firm masses. Other lower urinary tract conditions resembling bladder TCC include other types of neoplasia, cystitis, polypoid cystitis, polyps, granulomatous cystitis/urethritis, and cystic calculi. Rarely, dogs have shifting leg lameness or warm, swollen, and painful limbs due to paraneoplastic hypertrophic osteopathy.

Diagnosis

Diagnostic evaluation of a patient with suspected TCC should include deep abdominal palpation and rectal evaluation. Rectal examination may reveal thickening of the urethra and enlargement of internal lymph nodes. The complete blood count and serum biochemical panel may reveal signs of renal involvement. Urine sediment

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reveals malignant cells in only 30% of cases. In cases with high index of suspicion for a bladder mass, cystocentesis should be avoided to decrease the chance of tumor transplantation or bladder rupture. Concurrent urinary tract infection is prevalent in TCC cases, therefore urine culture is recommended.

Diagnostic imaging is essential for documentation of a bladder mass. Abdominal radiographs are usually unrewarding unless the lesion is mineralized. However, radiographs may show sublumbar lymphadenopathy, prostatomegaly, a caudal abdominal mass or bony metastases. Thoracic radiographs demonstrate pulmonary metastasis in 17% of cases at the time of diagnosis. Pulmonary changes may include nodular interstitial or lobar interstitial opacities and alveolar infiltrates.

Ultrasonography is a sensitive diagnostic tool to evaluate the urinary tract and has largely replaced the use of double-contrast cystography. Ultrasonography can also confirm ureteral obstruction when there is dilation of the renal pelvis alone or accompanied by hydronephrosis.

Histopathology is the gold standard for the diagnosis of TCC. However, cytology can also be utilized. There are multiple methods for obtaining bladder tissue samples such as cystotomy, cystoscopy, and traumatic catheterization. Due to sampling size, multiple tissue samples should be submitted to increase the diagnostic yield. Most recently, A DNA based assay to detect genetic mutations specifically in the *BRAF* gene has proven to be highly sensitive and specific for the diagnosis of TCC (CADET® *BRAF, Sentinel Biomedical*). The test evaluates malignant cells naturally shed and is therefore performed on voided urine samples. However, the assay is limited TCC and experimentally it has been found that up to 15% do not have the mutation.

Therapy

Because the trigone and urethra are most commonly involved in dogs, complete removal of the tumor is usually not possible. In addition, many dogs develop multifocal bladder lesions. As a result, most dogs with bladder tumors are managed medically, with chemotherapy, radiation and/or photodynamic therapy.

If a patient is suffering from urinary obstruction, surgery may be considered to reestablish urine flow or place a cystostomy tube. The most common disadvantages of tube cystostomy are recurrent urinary tract infections and premature removal of the tube by the patient. Urethral stents are gaining favor over cystostomy tubes. Stents are placed surgically and nonsurgically using fluoroscopy. The most common indication for urethral stenting is luminal obstruction secondary to tumor infiltration. In a series of 12 cases, urethral stents relieved obstruction in all cases. The outcome was fair to excellent in 10/12 cases. Urinary incontinence is the most common complication.

The use of radiation therapy for the treatment of TCC of the bladder is limited. The reported one- and two-year survival rates following intraoperative radiation therapy were 69% and 23%, respectively. Therapy-related complications include urinary incontinence, pollakiuria, and stranguria, all of which affect the patient's quality of life. A report of weekly course fractional external beam radiation therapy in combination with mitoxantrone and piroxicam was well tolerated but results were no better when compared to medical therapy alone. However, 90% of the dogs had amelioration of their clinical signs.

The mainstay treatment of TCC in dogs is systemic medical therapy with cyclooxygenase (COX) inhibitors alone or in combination with chemotherapy. Cure rates are relatively low but several different drugs can lead to remission or stable disease. In dogs, single-agent therapy with piroxicam or cisplatin has shown a response rate of 20% with a median survival time of approximately six months. Although the concurrent use of cisplatin and piroxicam combination therapy has shown a response rate of 70%, the high incidences of renal failure lead to early termination of the protocol.

The most commonly used chemotherapy combination in dogs is mitoxantrone (5 mg/m^2 IV q3 weeks) and piroxicam (0.3 mg/kg once a day). This combination has a documented response rate of 35% and median survival of 291 days. Indications to continue therapy include positive response such as complete or partial remission. Stable disease is considered a positive response as long as the patient has no detrimental effects associated with chemotherapy administration and a good quality of life.

Deracoxib (Dermaxx®, Novartis), a COX-2 inhibitor, at a dose of 3 mg/kg/day, has shown positive responses, with 17% of dogs having a partial response and 71% of dogs having stable disease.

Prognosis

The prognosis for TCC in dogs will largely depend on tumor size, location, and metastasis at the time of diagnosis. Multiple different treatments have been identified that result in remission and stable disease for several months. Most of these patients will have an excellent quality of life while on treatment. Prognostic factors for survival are tumor stage at the time of diagnosis (Box 146.1), younger age (increased risk of distant metastasis), prostate involvement (increased risk of distant metastasis), and higher T stage (increased risk of nodal and distant metastasis). Information regarding prognostic factors in other bladder tumors is limited. Prognostic factors for bladder tumor in cats have not been well

Box 146.1 TNM clinical staging system for canine bladder cancer

T – primary tumor

Tis	Carcinoma *in situ*
T0	No evidence of a primary tumor
T1	Superficial papillary tumor
T2	Tumor invading the bladder wall, with induration
T3	Tumor invading neighboring organs (prostate, uterus, vagina, and pelvic canal)

N – Regional lymph node (internal and external iliac lymph node)

N0	No regional lymph node involvement
N1	Regional lymph node involved
N2	Regional lymph node and juxtaregional lymph node involved

M – Distant metastases

M0	No evidence of metastasis
M1	Distant metastases present

defined. The reported median survival of cats treated with surgery and adjunctive therapy (i.e., chemotherapy or NSAIDs) was 269 days.

Urethral Tumors

Most tumors affecting the urethra are malignant. Transitional cell carcinoma and squamous cell carcinoma are the most commonly reported tumor types. Smooth muscle tumors (e.g., leiomyosarcoma) have been reported less frequently. Granulomatous urethritis, a benign condition of the urethra, must be differentiated from malignant tumors due to the different treatment approaches and prognosis. Treatment recommendations and response rates for urethral tumors are similar to those of the bladder.

Renal Tumors

Etiology/Pathophysiology

Primary renal tumors are uncommon in dogs and cats. The majority of these tumors are malignant and more than half are epithelial in origin. In cats, lymphoma is the most common renal tumor and can affect both kidneys. In a report of 54 dogs with renal tumors, the most common was renal cell carcinoma. Other tumors that can occur in the kidney include TCC, nephroblastoma, hemangiosarcoma, other sarcomas, and lymphomas. An unusual syndrome in female German shepherd dogs consists of slow-growing dermal fibrosis and fibromas, concomitant renal cystadenocarcinoma, and uterine tumors. This syndrome is similar to Birt–Hogg–Dubé syndrome in humans.

Pulmonary metastases have been detected radiographically in 16–34% of dogs with primary renal tumors at the time of diagnosis. At death, metastases were detected in 69% of dogs with carcinomas, 88% of dogs with sarcomas, and 75% of dogs with nephroblastomas.

Epidemiology

The etiology of renal tumors in dogs and cats is unknown. The previously mentioned syndrome in German shepherd dogs is the result of a dominantly inherited missense mutation of a tumor suppressor gene. In cats, feline leukemia virus (FeLV) is strongly associated with development of renal lymphoma.

Signalment

Most renal tumors occur in older dogs (mean age 8 years) but nephroblastoma may occur at any age. The male to female ratio of dogs with epithelial renal tumors has been reported to be 1.2:1. In cats, the median age at diagnosis was 11 years with a similar number of male and female cats.

History and Clinical Signs

Clinical signs associated with renal tumors are not specific. Presenting complaints may include weight loss, polyuria, lethargy, hematuria, abdominal pain or signs suggestive of renal failure (vomiting, anorexia). Physical examination may reveal a midabdominal mass and occasionally bilateral renal enlargement.

Diagnosis

Clinicopathologic findings include mild anemia alone or accompanied with marked neutrophilia, or abnormalities consistent with renal azotemia. Paraneoplastic syndromes such as polycythemia, neutrophilia, and hypertrophic osteopathy have been reported.

Ultrasonography is highly sensitive for the diagnosis of renal neoplasia. Tissue samples can be obtained by ultrasound-guided percutaneous biopsy or at the time of surgery.

Therapy and Prognosis

Nephrectomy is the treatment of choice for dogs with unilateral renal tumors without evidence of azotemia or distant metastasis. Excretory urography, computed tomography (CT), and evaluation of glomerular filtration rate (GFR) via scintigraphy may also be useful,

especially for surgical planning. Evaluation of possible tumor extension into the vena cava is important if surgery is considered.

The reported median survival time for dogs with renal cell carcinoma treated with nephrectomy is eight months. Standardized chemotherapy as an adjunct or in the metastatic setting for renal carcinoma has not been well defined. In humans, sunitinib, a multikinase receptor inhibitor, has shown antitumor activity against metastatic renal cell carcinoma. At this time, controlled studies using tyrosine kinase inhibitors against renal carcinoma in veterinary patients are lacking. Toceranib phosphate, a multikinase receptor inhibitor similar to sunitinib, is approved for mast cell neoplasia in veterinary patients and may be considered for the treatment of metastatic renal carcinoma.

Chemotherapy treatment for renal lymphoma is similar to protocols used to treat lymphoma in other organs. Approximately 60% of cats achieve complete remission. Negative prognostic factors included involvement of other organ system (CNS), FeLV infection, and severity of renal failure.

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147

Tumors of the Male Reproductive System

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Testicular Tumors

Etiology/Pathophysiology

Testicular tumors are the most common cancer found in the male reproductive tract and are typically considered nonaggressive. Primary testicular neoplasia commonly arises from three separate areas of the testis: the sustentacular cells of Sertoli (Sertoli cell tumors), interstitial cells (Leydig cell tumors), and germinal epithelium (seminoma). A recent study evaluated 345 testicular tumors; seminomas (33.9%) were the most common followed by interstitial cell tumors (33%), and lastly Sertoli cell tumors (26.4%). Although less frequently seen, other tumor types can be found such as lymphoma, hemangiosarcoma, and others.

Epidemiology

The prevalence of testicular tumors in dogs is 27%, which has increased from previous years. A cryptorchid testicle has an approximately 10 times increased risk of developing cancer compared to a descended testicle. This effect may be in part due to the higher temperature of the retained testis within the body. Of retained testes tumors, 34% are seminomas and 54% are Sertoli cell tumors. Other risk factors are age, breed, and exposure to environmental carcinogens. In one study, intact dogs over 6 years of age had an increased incidence of testicular tumors. Collies and Shetland sheepdogs were five times more likely to develop testicular tumors, specifically Sertoli cell tumors. Environmental carcinogen exposure has also been a proven risk factor.

Military working dogs in the Far East that were exposed to chemical sprays like Agent Orange, herbicides, and dioxin demonstrated an increased risk of seminomas.

Signalment

Testicular tumors are diagnosed in older dogs, with a median age of approximately 10 years. No specific breed predilection has been consistently described.

History and Clinical Signs

Sertoli cell tumors are often large (1–5 cm). Atrophy of the contralateral testicle is common. Dogs with Sertoli cell tumors can present with bilateral dorsal alopecia, hyperpigmentation of the skin or scrotum, enlarged nipples, squamous metaplasia of the prostate, gynecomastia, and thinning of the skin. Many of these clinical signs are associated with hyperestrogenism which causes signs of feminization and is found in approximately 20% of cases. Severe bone marrow hypoplasia leading to life-threatening pancytopenia can result from the excessive endogenous estrogen production from the tumor.

Leydig cell tumors are relatively small (usually under 2 cm) in size, and can be found as either solitary or multiple and unilateral or bilateral.

Seminomas are larger tumors (can be greater than 5 cm) and often appear as nodules. They can occur along with interstitial and Sertoli cell tumors. Hyperestrogenism is rarely seen with this tumor type although a recent case study described a 5-year-old Yorkshire terrier with confirmed hyperestrogenemia and secondary alopecia.

Diagnosis

Staging with full blood analysis, urinalysis, thoracic radiographs, and abdominal ultrasound should be performed in all patients with testicular tumors. Results typically reveal no abnormalities unless the presence of hyperestrogenemia results in blood dyscrasias or pancytopenia.

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The metastatic rate for seminomas and Sertoli tumors is approximately 10%. Metastasis occurs through lymphatic invasion. Therefore, evaluation for regional metastasis is warranted prior to surgery. There are reports of aggressive seminomas in dogs with distant metastasis to the spleen, lungs, meninges, eyes, and skin. Testicular ultrasound is recommended in dogs with clinical signs of testicular neoplasia and nonpalpable disease. For dogs with signs of feminization, obtaining serum levels of estradiol-17-beta may help support a diagnosis of functional testicular tumor. Paraneoplastic hypertrophic osteopathy, although rare, has been reported in a dog with a Sertoli cell tumor. Therefore, extremity radiographs should be performed in dogs with Sertoli cell tumors with concomitant lameness.

Therapy

Castration, including scrotal ablation, is considered the treatment of choice for testicular tumors and is curative for dogs with nonmetastatic disease. However, when metastatic disease is present, adjunctive chemotherapy or radiation therapy is necessary. The use of cesium-137 external beam radiation therapy for regional lymph node metastasis in four dogs with seminoma has been described and shown to be 100% effective. There is limited information regarding the usefulness of chemotherapy, but there is suggested efficacy with both cisplatin and bleomycin. There is recent evidence that seminomas and Leydig cell tumors express kit (CD117), making the use of a tyrosine kinase inhibitor (such as Palladia™, or Gleevec®) a reasonable treatment option for cases with metastatic disease. The use of metronomic chemotherapy for high-grade seminomas is also a valid treatment option, as one study found that seminomas demonstrated increased angiogenesis.

Prognosis

The prognosis is excellent for nonmetastatic testicular tumors and guarded for metastatic tumors or dogs that have blood dyscrasia secondary to hyperestrogenism. Also, seminomas with high mitotic index and increased numbers of agyrophilic nucleolar organizer regions (AgNORs) had increased risk of metastasis.

Prostate Tumors

Etiology/Pathophysiology

Carcinomas are the most common prostatic tumor, with transitional cell carcinoma and adenocarcinoma being the most frequent types. Other types such as squamous cell carcinoma, undifferentiated carcinoma, and sarcomas are rarely found. In dogs, most prostatic carcinomas are suspected to be ductal or urothelial in origin, rather than acinar, as in humans. The absence of androgen receptors in ductal epithelial cells suggests that canine prostatic carcinoma formation is likely androgen independent. Controversy still exists regarding the effects of castration on the development of canine prostatic carcinoma. Regardless, three studies did reveal that castrated dogs were at increased risk for developing prostatic carcinoma with odds ratios ranging from 3.86 to 4.34.

Epidemiology

Prostate tumors are rare neoplasms in dogs, having a prevalence of less than 1% of all canine cancers. These tumors are extremely uncommon in cats with only a few reported cases.

Signalment

There is no known breed predilection and prostatic carcinoma typically affects older dogs, median age 10 years. Although exceedingly rare, prostatic carcinoma can occur in older cats.

History and Clinical Signs

The most common presenting clinical sign in a dog with a prostate tumor is either tenesmus or dysuria, including hematuria, stranguria or pollakiuria. Older, castrated, male dogs presenting with any of the above clinical signs should be evaluated for urogenital cancer as few other diseases cause such signs. Other possible presenting signs are anorexia, weight loss, acute lameness or back pain which may indicate metastasis to the pelvis or lumbar spine.

In cats, clinical signs vary but include dysuria, urethral obstruction, and obstipation. Physical exam findings and diagnostics are similar to those for prostate tumors in dogs.

Diagnosis

Physical exam findings are variable but the most common abnormality is prostatomegaly that can be palpated as irregular, firm, and painful and/or demonstrates loss of the median raphe. Complete blood count and serum biochemistry rarely reveal any specific changes. Urinalysis often indicates pyuria or bacteriuria as secondary bacterial infection is commonly associated with this neoplasia. Many owners report improvement of clinical signs if treated with antibiotic therapy, but this improvement is often short-lived. Three-view thoracic radiographs are

recommended, although pulmonary metastasis occurs in <10% of dogs at the time of diagnosis. Abdominal radiographs are helpful in identifying prostatomegaly, mineralization of the prostate, sublumbar lymphadenopathy, and/or bony lesions of the lumbar spine or pelvis (typically osteoblastic [proliferative] in nature).

Metastatic, hormone-refractory, androgen-independent prostate cancer in men is similar in biologic behavior to canine prostatic carcinoma. Eighty five to ninety percent of those diagnosed with this form of prostate cancer will have evidence of skeletal metastasis during the course of disease. Skeletal metastasis has been reported to occur in 22% of dogs, with the majority of these lesions found in the axial skeleton.

Abdominal ultrasound is the most useful of all imaging modalities as it can help confirm regional metastasis which occurs in approximately 50% of dogs at presentation. Definitive diagnosis requires cytology or histopathology. Fine needle aspiration, via ultrasound guidance, has been shown to be 80% accurate in confirming a diagnosis of carcinoma. As an alternative, a prostatic wash can be performed. Although less invasive, it is also less sensitive.

In the published feline cases, metastatic disease varied in location, but included pulmonary, pancreatic, renal, and myocardial.

Therapy

There is limited information regarding treatment efficacy for dogs with prostate tumors. Androgen ablation therapy is ineffective in dogs, as tumors arise from androgen-independent regions. For tumors confined to the prostate, total or partial prostatectomy can be considered. Due to persistent incontinence and recurrent urinary tract infections, patient morbidity is high while owner satisfaction is expectedly low. Radiation therapy, an alternate local treatment option, was not found to be useful in one series of dogs which received a palliative protocol. However, a more recent study indicated a 60% response rate and an extended survival time (median survival time 645 days) when intensity-modulated and image-guided radiation therapy (IM/IGRT) were utilized.

Due to the high metastatic rate in dogs, local treatment alone is not effective. Cyclooxygenase (COX) inhibitor therapy is reported to be successful in treating various types of urogenital carcinomas. Two studies indicated that approximately 75–88% of canine prostate carcinomas express COX-2. A previous publication indicated that COX inhibitors were effective in the treatment of canine prostatic carcinoma (MST 6.9 versus 0.7 months). In a separate study, the addition of mitoxantrone chemotherapy to piroxicam did not increase survival.

Palliative irradiation, urethral stenting, laser ablation or cystostomy tube placement can be considered in dogs with urethral obstruction. These options are palliative and may only increase survival time minimally.

Treatment for cats with prostatic carcinoma is unknown. One reported cat underwent a prostatectomy and received doxorubicin (30 mg/m^2) and cyclophosphamide (300 mg/m^2) and was euthanized 10 months later due to recurrent disease.

Prognosis

The overall prognosis for prostate cancer is guarded to grave as this tumor is both locally and distantly aggressive. The rate of metastasis at the time of death is approximately 80%, with the most common sites being the lungs, regional lymph nodes, liver, and bone. Prognostic indicators that have been found to be negatively associated with survival include the presence of metastasis at diagnosis, presence of clinical signs at diagnosis, and the lack of nonsteroidal antiinflammatory drug (NSAID) therapy.

It is difficult to confirm treatment and prognostic information for cats based on the limited reports available. However, it would be reasonable to consider that these tumors have a similar prognosis to their canine counterparts as they also tend to be aggressive.

Penis, Prepuce, and Scrotum Tumors

Etiology/Pathophysiology

Tumors of the penis, prepuce, and scrotum are rare in dogs and even rarer in cats. The most common tumors of the penis are transmissible venereal tumor (TVT) and squamous cell carcinoma (SCC). The prepuce can also be affected by TVT. Most tumors of the prepuce and scrotum are those associated with skin, specifically SCC, melanoma, and mast cell tumor (MCT). Other reported tumors that can affect all three areas include hemangiosarcoma, lymphoma, lipoma, plasmacytoma, soft tissue sarcoma, ossifying fibroma, chondrosarcoma, and osteosarcoma of the os penis.

Epidemiology

Limited information is available for this group of tumors. See the section on epidemiology for transmissible venereal tumors below and the respective chapters for specific tumor types.

Signalment

With the exception of TVT, tumors of the penis, prepuce, and scrotum are generally diagnosed in older dogs.

For TVT, young, sexually active dogs are most commonly affected.

History and Clinical Signs

Presenting signs are dependent on tumor location and include stranguria, hematuria, discharge, foul odor, constant licking, and a large mass.

Diagnosis

Complete staging including abdominal ultrasound to evaluate for regional lymphadenopathy and three-view thoracic radiography is recommended. Fine needle aspiration or preferably biopsy is recommended to obtain a definitive diagnosis.

Therapy

Surgery is the treatment of choice for the majority of tumors in this group. The exception is TVT (see section on TVT below). Penile amputation may be required when tumors are invasive or when extensive prepuce removal is performed. For scrotal tumors, castration with scrotal ablation is recommended. Adjunctive therapy relevant to the tumor type is warranted when metastasis or recurrence occurs.

Prognosis

The reader is encouraged to refer to the specific tumor type chapters for a more in-depth review. Overall, the prognosis for nonmetastatic tumors, that can be completely excised, is good to excellent. However, for metastatic or recurrent tumors the prognosis is guarded to poor. Osteosarcoma of the os penis may have a guarded prognosis as this tumor has the potential to metastasize similar to other axial forms.

Transmissible Venereal Tumor

Etiology/Pathophysiology

Transmissible venereal tumor is often transmitted through coitus but can also spread through close contact such as sniffing or licking of the genitalia. The exact origin of this tumor is unclear but evaluation of antigen expression suggests that TVT expresses similar markers to histiocytes. Canine TVT can be observed in leishmaniotic dogs, and amastigotes can be harbored in canine TVT cells.

Transmissible venereal tumors can affect other members of the canine family such as foxes, coyotes, and wolves. When evaluating the karyotype of TVTs, worldwide, they are similar and are characterized by 59 chromosomes (versus 78 in normal dogs).

Epidemiology

There is a higher prevalence of TVT in warm climates and in rural areas where there are large numbers of free-roaming, reproductively unaltered dogs.

Signalment

Transmissible venereal tumor affects both female and male dogs. There is an increased risk in young, sexually active dogs.

History and Clinical Signs

Transmissible venereal tumor can present as solitary or multiple nodules on the external genitalia that appear as pedunculated or cauliflower-like masses. In males, it usually occurs on the bulbus glandis but can be seen on the penis or prepuce. In female dogs, the lesions develop in or around the vagina. Infected dogs can present with a few weeks (or months) history of bloody discharge, deformed external genitalia, ulceration or swelling of the affected area. Differential diagnosis may include urinary tract infections, prostatitis, other causes of paraphimosis or phimosis or other malignancies (urogenital carcinomas, sarcomas, or other round cell tumors).

Rarely, dogs can have extragenital lesions without a primary lesion. These ulcerative, hemorrhagic lesions can occur in the mouth, nose, eyes or skin caused by biting or rubbing which can predispose the skin to implantation of the TVT.

Diagnosis

Transmissible venereal tumor should be suspected if the geographic location, history, lifestyle, and clinical signs fit the diagnosis. To obtain a definitive diagnosis, either cytologic or histopathologic confirmation is required. Microscopically, the cells are large, discrete (round cells) with abundant blue cytoplasm containing distinct clear vacuoles. Single or multiple nucleoli and mitotic figures may be seen (Figure 147.1).

Transmissible venereal tumors have the immunohistochemical staining characteristics of histiocytes. They stain positive to antibodies against vimentin, lysozyme, macrophage-specific immunostain (ACM)1, and alpha-1-antitrypsin (AAT). Therefore, the use of immunohistochemistry may be helpful in cases where it is difficult to confirm a diagnosis or if there are atypical metastatic sites present.

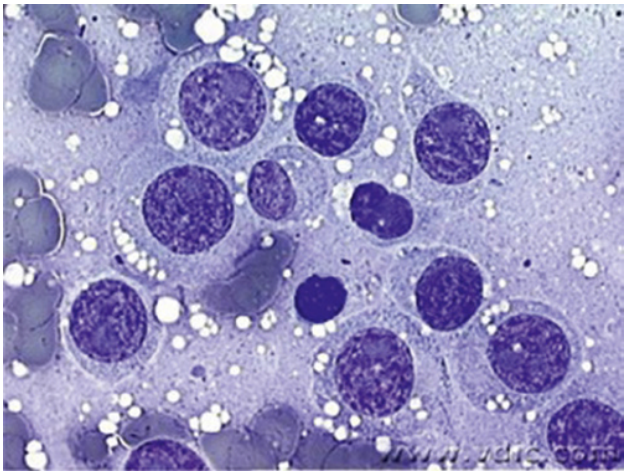


Figure 147.1 Fine needle aspirate of a canine TVT. Note the homogeneous population of discrete round cells with mild anisocytosis and anisokaryosis. The cells have a moderate amount of cytoplasm with multiple discrete clear cytoplasmic vacuoles.

Any dog with suspected TVT should undergo full staging, including urinalysis, as there is evidence that dogs with TVT are at high risk of developing urinary tract infections. Although metastatic disease occurs in less than 10% of reported cases, evaluating for local metastasis with abdominal ultrasound and three-view thoracic radiographs is recommended. A differential for suspected metastasis is transplantation (autologous or allogeneic) of TVT from the primary genital lesion.

Therapy

There are multiple treatment options for TVT. The least invasive, least expensive and most effective option is the use of single-agent vincristine chemotherapy. Administering vincristine at the recommended dose of 0.5–0.7 mg/m^2 IV once weekly for 3–6 treatments elicits a complete response in over 90% of dogs. Other protocols involving cyclophosphamide, vinblastine, doxorubicin, and methotrexate have been used with less success. However, for vincristine-resistant tumors, doxorubicin given at 30 mg/m^2 IV every three weeks can be effective.

Radiation therapy is an effective treatment modality for TVT. Orthovoltage radiation was evaluated in 18 dogs with solitary primary genital and cutaneous lesions. All lesions were treated with a total dose of 10–30 Gy. Seven dogs had a complete response to a single fraction of 10 Gy. The remaining patients required an additional 2–3 fractions to achieve a complete response. In a separate study, 15 dogs with primary genital TVT received cobalt irradiation. A 100% complete response rate was reported.

Surgery can be used in cases of primary or metastatic lesions, but it is not typically recommended as the recurrence rate can be up to 70%.

Lastly, the use of immunotherapy with intralesional bacillus Calmette–Guérin (BCG) has been shown to be effective as a single agent and in combination with vincristine therapy.

Prognosis

The prognosis for TVT is good to excellent as some dogs can experience spontaneous regression. The majority of dogs that receive single-agent vincristine therapy or radiation therapy will be cured of their disease. The prognosis is, however, guarded for dogs that have ocular or central nervous system invasion or evidence of disseminated metastasis. An increase in the AgNOR area in the nucleus was found to be a negative prognostic indicator in dogs with TVT.

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148

Gynecologic Cancers

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Uterine Tumors

Etiology/Pathophysiology

Uterine cancer is extremely rare in dogs and cats. This is in part because the overwhelming majority of pets are spayed. Leiomyoma is the most common uterine tumor in the dog, followed by leiomyosarcoma. Other types of tumors have been reported such as fibroma, lipoma, hemangiosarcoma, fibrosarcoma, angiolipoleiomyoma, adenoma, adenocarcinoma, and extramedullary plasmacytoma. In women, estrogen is considered to be the primary factor in the development of uterine carcinoma. It is believed that both endogenous and exogenous estrogen can result in endometrial hyperplasia. It also potentiates the transformation of endometrial hyperplasia to endometrial carcinoma. Estrogen is not the underlying hormone responsible for endometrial changes in dogs. In fact, it is progesterone that plays a large role in both neoplastic and nonneoplastic gynecologic diseases of the dog. Dogs develop cystic endometrial hyperplasia which is much less likely to transform into carcinoma.

The most common uterine tumor in the cat is adenocarcinoma which arises from the endometrium. Although much rarer, leiomyoma, leiomyosarcoma, hemangioma, squamous cell carcinoma, and carcinosarcoma have been reported. An association of feline leukemia virus (FeLV) and the development of uterine adenocarcinoma in cats have been reported.

Birt–Hogg–Dubé (BHD) syndrome is a rare inherited condition that occurs in German shepherd dogs resulting from a mutation in the canine orthologue (folliculin) tumor suppresser gene. It manifests in multiple uterine leiomyomas, bilateral renal cystadenocarcinomas, and nodular dermatofibrosis. A similar BHD syndrome has been noted to occur in humans.

Epidemiology

The incidence of uterine tumors is less than 0.5% in dogs and approximately 1% in cats. BHD is inherited through an autosomal dominant pattern.

Signalment

Uterine tumors typically occur in middle-aged to older dogs and cats, but there are reports in dogs under 1 year of age. These tumors are overwhelmingly more common in intact females, but there are reports of uterine stump carcinomas in spayed females. There is no specific breed predilection.

History and Clinical Signs

Most dogs and cats with uterine tumors are asymptomatic. However, purulent to hemorrhagic vaginal discharge, lethargy, anorexia, constipation, and pyometra can occur. Other signs may be associated with the metastatic lesions themselves.

Diagnosis

A minimum database including complete blood count, biochemistry, and urinalysis is recommended for any animal with potential gynecologic cancer. Abdominal radiographs may reveal a mass effect in the caudal abdomen. To thoroughly evaluate the extent of disease or for the presence of regional metastasis, an abdominal ultrasound is required. Although the majority of uterine tumors are benign in the dog, three-view thoracic radiographs should be performed. In cats, thoracic radiographs and abdominal ultrasound are mandatory as malignant uterine tumors are associated with a high

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metastatic rate (up to 50%). Definitive diagnosis requires histology and is easily obtained at the time of hysterectomy.

Therapy

Ovariohysterectomy is the treatment of choice in all cases of uterine tumors, except in the setting of distant metastasis or carcinomatosis. Surgical excision of any regional metastatic foci is also recommended.

In women, adjunctive chemotherapy has been shown to have a mild to modest benefit for metastatic leiomyosarcomas and carcinosarcomas when compared to surgery or radiation alone. Although there are no veterinary reports on the use of chemotherapy for uterine tumors, it is highly recommended in cases of malignant or metastatic tumors. Based on human data, it would be reasonable to consider chemotherapeutics such as cisplatin, carboplatin, doxorubicin, cyclophosphamide, gemcitabine, and ifosfamide as viable therapeutic options.

A 2007 study evaluated the presence of estrogen and progresterone receptors in smooth muscle genital tumors. Estrogen receptor alpha (ERalpha) was found in 56.3% and progesterone receptor (PR) in 84.4% of canine tumors. This finding makes hormone receptor antagonist therapy a reasonable treatment option.

Prognosis

The prognosis is excellent for dogs and cats with benign tumors following complete ovariohysterectomy. For malignant tumors localized to the uterus, the prognosis can be good as many of these dogs can still be cured with surgery. However, the prognosis is guarded for metastatic tumors. In cats with uterine adenocarcinomas, the prognosis is guarded to poor as they often metastasize.

Vaginal Tumors

Etiology/Pathophysiology

Vaginal tumors are the second most common tumor of the female reproductive system. The most common histologic type is leiomyoma. These tumors, similar to the uterine leiomyomas, are slow growing and do not metastasize. Other less common tumors include fibroma, polyp, lipoma, myxoma, lymphoma, liposarcoma, mast cell tumor, adenocarcinoma, squamous cell carcinoma, fibrosarcoma, leiomyosarcoma, osteosarcoma, hemangiosarcoma, and TVT.

One study found that all pedunculated masses were benign. And of the sessile, broad-based masses, all were malignant (with the majority being TVT).

Feline vaginal tumors are extremely rare, with most being benign.

Epidemiology

In dogs, there is some evidence that vaginal neoplasia may be associated with a history of mammary tumors, ovarian cysts, pyometra or previous treatment with reproductive hormones. One study found that the majority of dogs with vaginal cancer are sexually intact and nulliparous.

Signalment

The mean age for dogs with vaginal cancer is 10.8 years. Although there is no breed predilection, both boxers and poodles have been reported to have an increased risk.

History and Clinical Signs

Common clinical signs reported include purulent to hemorrhagic vaginal discharge, swelling of the vulva or perineal region, a vulvar mass, constant licking of the vulva, dysuria or tenesmus. Tumors typically arise from the vulva, vestibule, or vaginal roof. There is no correlation between the location of the mass and histologic tumor type.

Diagnosis

Definitive diagnosis of malignancy requires histology. However, the presence of a vaginal mass is often easily determined based on history, clinical signs, and physical exam findings (including a digital vaginal exam). For small lesions, vaginoscopy may be required. Full staging is recommended for all animals with vaginal tumors: complete blood count, biochemistry, three-view thoracic radiographs, and an abdominal ultrasound. Paraneoplastic hypercalcemia has been infrequently reported to be associated with older basset hounds with clitoral adenocarcinoma.

Treatment

Surgical excision with dorsal episiotomy is the treatment of choice. Concurrent ovariohysterectomy is also recommended as some malignancies such as leiomyomas may be hormone dependent. For highly invasive vaginal tumors, either subtotal vaginectomy or a complete vulvovaginectomy and perineal urethrostomy can be performed. It is advised that any metastatic foci should be removed at the same time.

Adjunctive radiation therapy and chemotherapy can be considered for animals that have incompletely excised

malignant tumors or metastatic/high-grade tumors, respectively.

The use of carbon dioxide laser ablation in conjunction with doxorubicin chemotherapy(at 30 mg/m^2 intravenously) every four weeks for a total of two treatments has been shown to provide long-term control in one case report of a poodle with vaginal fibrosarcoma.

Another potential treatment is the use of the progesterone receptor antagonist aglepristone, as neoadjuvant therapy prior to surgery for large benign vaginal tumors.

Prognosis

Surgery is often curative for benign tumors and the prognosis is guarded for malignant tumors as they have the potential to metastasize and recur.

Ovarian Tumors

Etiology/Pathophysiology

Ovarian tumors can arise from different locations within the ovary and are classified based on their origin, such as epithelial cells, sex cord stromal elements of the ovary and germ cells. Epithelial tumors are further characterized as adenoma, cystadenoma, adenocarcinoma, and undifferentiated carcinoma. Tumors referred to as sex cord stromal tumors are granulosa cell tumors, luteomas, and thecomas. Although more common in the male, this group also includes Sertoli, Leydig and Sertoli-Leydig cell tumors. Lastly, the germ cell tumors include dysgerminoma, teratocarcinoma, teratoma, and choriocarcinoma. Other rare tumor types include hemangiosarcoma, rhabdomyosarcoma, fibrosarcoma, and carcinosarcoma.

The majority of ovarian tumors, regardless of their histologic subtype, are unilateral. However, adenocarcinomas and mixed sex cord stromal tumors (specifically Sertoli-Leydig cell tumor) can occur bilaterally in about 30% of cases. The rates of occurrence for each type varies depending on the study, but granulosa cell tumors and epithelial tumors account for most ovarian tumors in dogs and granulosa cell tumors are the most common ovarian tumor found in cats.

The overall metastatic rate for ovarian tumors in dogs is approximately 25%, with a higher incidence, approximately 50%, in both adenocarcinomas and teratomas. Sex cord tumors are the only histologic type that has the potential of being hormonally active, as they arise from gonadal tissue of the ovary and can produce steroid hormones.

In cats, the most common ovarian tumor is granulosa cell tumor, followed by dysgerminomas. They are typically unilateral but can be found bilaterally. Similar to dogs, granulosa cell tumors in cats can metastasize and are hormonally active. Although there are few reports of teratomas in cats, they have been noted to occur in young animals and rarely metastasize.

Epidemiology

As ovarian tumors are extremely rare in both dogs and cats, the true prevalence is unknown.

Signalment

The majority of ovarian tumors affect older dogs, with the exception of teratomas. One study found pointers had an increased risk of developing epithelial tumors while English bulldogs were at higher risk for granulosa cell tumors. German shepherds and poodles were also reported to have a higher occurrence of ovarian tumors.

History and Clinical Signs

The clinical signs reported are variable but may include vaginal discharge, distended abdomen, pyometra, and an abnormal estrus cycle. If metastasis occurs, clinical signs may be associated with the location of involvement, such as ascites secondary to tumor effusion. As sex cord tumors can cause hormonal dysfunction, signs associated with excess sex hormones (both estrogen and progesterone) can be observed. Examples of such changes include bilateral alopecia, vulvar enlargement, vaginal bleeding, pyometra, and endometrial hyperplasia. Granulosa cell tumors rarely produce enough sex hormone to cause bone marrow aplasia, but rare examples of sepsis or bleeding secondary to neutropenia and thrombocytopenia have been reported.

Diagnosis

Although the metastatic rate for ovarian tumors is relatively low, it is still recommended that thorough staging is performed including complete blood count, biochemistry, three-view thoracic radiographs, and abdominal ultrasound. An ultrasound is especially important to help evaluate for local metastasis to regional lymph nodes, surrounding organs, and peritoneum. It is not recommended that ultrasound-guided cytology/biopsy be performed. If the tumor is malignant, seeding or translocation of the tumor cells can occur. If histopathology cannot differentiate tumor type, the use of immunohistochemistry may be helpful. HBME-1 (and cytokeratin 7) and inhibin-alpha are useful markers to confirm epithelial and sex cord stromal tumor origin, respectively.

Many dogs with metastatic ovarian carcinoma can present with secondary ascites. One study found that the overall accuracy of using cytology to differentiate ovarian carcinoma effusions from other types is approximately 95%.

Therapy

A complete ovariohysterectomy is the treatment of choice for dogs with ovarian tumors that have no evidence of metastasis and typically results in a cure. There are limited reports of dogs with metastatic tumors. In one report, a dog was treated with cisplatin 50 mg/m^2 intraperitoneally for ovarian carcinomatosis, resulting in long-term control. In humans, platinum drugs, taxanes, and monoclonal antibodies are considered first-line therapies. Based on human research and success with chemotherapy, platinum agents should be considered for metastatic ovarian tumors. In a recent study, cyclooxygenase 2 (COX-2) was found to play a potential role in carcinogenesis and was expressed in 81% of canine ovarian carcinomas. Therefore, the use of NSAID therapy, similar to what has been found in other urogenital tumors, should be considered for ovarian carcinomas.

Prognosis

The prognosis is excellent for solitary ovarian tumors that are completely excised with no evidence of metastasis. If metastatic disease is present, the prognosis is guarded to poor, depending on the response to chemotherapy. The use of platinum drugs and COX-2 inhibitors is recommended.

Treatment and prognosis are similar in cats. Surgery is the treatment of choice, and if metastatic disease is present, carboplatin (intravenous or intraperitoneal) and/or COX-2 inhibitors are recommended.

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149

Mammary Cancer

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Canine Mammary Cancer

Etiology/Pathophysiology

Mammary tumors occur most commonly in intact female dogs and in female dogs spayed later in life. Hormone exposure, primarily during development of the mammary glands, is the most significant risk factor. Increasing age and breed are also consistently reported risk factors. Obesity at 9–12 months of age and diets high in red meat have also been associated with increased risk of tumor development. These factors may influence the level of estrogen and progestin in the body or augment the effect of these hormones on mammary tissue.

Estrogens and progestins stimulate growth and development of mammary tissue and may contribute to tumorigenesis through direct growth factor activity. Secondary increases in growth hormone and insulin-like growth factor 1 may also contribute. In humans, estrogen and progestin also increase DNA and chromosomal damage.

Early ovariohysterectomy is protective against mammary tumor development. Dogs spayed before their first estrus have 0.5% lifetime risk. Dogs spayed before the second estrus have 8% risk and those spayed before the third estrus 26% risk. The benefit of ovariohysterectomy beyond the third heat appears slight, if any, though ovariohysterectomy once a mammary mass has been diagnosed may be of some benefit. The age of first pregnancy and parity does not appear to influence tumor development. Exposure to exogenous progestins and estrogens increases the risk, and has also been linked to tumor development at younger age. Hormone exposure was confirmed or suspected in most male dogs diagnosed with mammary tumors.

The entire mammary chain is exposed to the same hormones and growth factors, which is known as field effect carcinogenesis. As such, dogs are at risk for multiple mammary masses. Up to 66% of dogs have more than one mass. There is histologic and chronologic evidence that mammary masses may progress through benign, *in situ*, and noninvasive stages before developing into invasive carcinoma. Estrogen and progesterone receptor levels appear to decrease as tumors become larger, less differentiated, and more invasive.

Epidemiology

Mammary gland tumors are the most common tumors in intact females, though the overall incidence depends on the population in question. The lifetime risk of intact female dogs has been reported to be as high as 26%. The incidence in North America is lower than many other regions due to the more common practice of early ovariohysterectomy. Evaluation of several European registries showed that mammary tumors account for 50–70% of tumors in intact female dogs. Approximately 1% of mammary tumors occur in males.

Signalment

Mammary masses occur most frequently in older female dogs. The risk increases with age from 7 to 13 years, and dogs with malignant masses tend to be older than those with benign tumors. Increased risk is reported for poodles, Chihuahuas, dachshunds, Yorkshire terriers, Maltese, cocker spaniels, English springer spaniels, Brittany spaniels, German shepherd dogs, German shorthair pointers, English setters, and Doberman pinschers.

History and Clinical Signs

Most dogs with mammary tumors are otherwise healthy. Dogs usually present for a palpable mass or a mammary mass may be an incidental finding. Careful palpation of the other glands, inguinal and axillary

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nodes is imperative. Some studies have found that the two caudal mammary glands are more commonly affected.

Inflammatory mammary carcinomas account for approximately 8% of mammary masses. Dogs are often systemically ill, with painful, edematous mammary glands. Dogs may also be inappetent, lethargic, and febrile. Inflammatory mammary carcinomas may be misdiagnosed as mastitis, severe dermatitis or vasculitis.

Diagnosis

Evaluation of the mammary chain should be part of a routine examination. The size, mobility, and appearance may increase suspicion for malignancy. A minimum database, including complete blood count, chemistry profile, urinalysis, and thoracic radiographs, should be completed. An abdominal ultrasound to assess visceral lymph nodes is indicated and regional lymph nodes should be aspirated when possible. The lymphatic drainage is unpredictable, but axillary, sternal, and inguinal lymph nodes should be assessed.

Tumor stage has important prognostic and treatment implications, and most clinicians use a modified five-tier World Health Organization (WHO) tumor, node, metastasis (TNM) staging scheme (Table 149.1). The original WHO staging scheme has four stages. Tumor size has been found to be prognostic, and so this delineates the first three stages. The presence of lymph node metastases determines stage 4 disease regardless of tumor size, and dogs with distant metastases have stage 5 disease.

Surgical resection and histopathology provide a definitive diagnosis in most cases. Cytology can be performed if presurgical diagnosis is desired. Cytology has been reported to be 67.5–93% accurate at differentiating benign from malignant masses, with sensitivity of 86–96% and 88–100% specificity for malignancy. Cytologic diagnosis of malignancy also correlated well with survival.

Table 149.1 Canine mammary tumor staging. Modified World Health Organization Tumor, Node, Metastasis (TNM) staging scheme

Stage	Tumor size	Lymph node metastasis	Distant metastasis
1	T1 (T <3 cm)	N0 (none)	M0 (none)
2	T2 (T 3–5 cm)	N0 (none)	M0 (none)
3	T3 (T >5 cm)	N0 (none)	M0 (none)
4	Any T	N1 (positive)	M0 (none)
5	Any T	Any N	M1 (positive)

Forty to fifty percent of canine mammary masses are benign. Both benign and malignant tumors may be simple or complex. Simple tumors are composed of only one cell type whereas complex masses have both luminal and myoepithelial components. In complex carcinomas, the epithelial cells are neoplastic while the myoepithelium is benign.

The most common benign masses include ductal ectasia, lobular and fibroepithelial hyperplasia, adenomatous masses, and benign mixed tumors. Most malignant tumors are carcinomas. Simple mammary carcinomas are most often tubular, tubulopapillary, cystic, papillary, cribriform or solid. Mucinous carcinoma, squamous cell carcinoma, and malignant mixed tumors are less common. A histopathologic grading system for mammary carcinomas exists, and has been found to be prognostic in several studies. Criteria include the extent of tubule formation, nuclear pleomorphism, and mitotic rate. Mammary sarcomas are also reported, with extraskeletal osteosarcoma being most common.

Therapy

Surgery is an integral part of therapy for mammary tumors, with the exception of inflammatory carcinomas and those with widespread metastases. In dogs, it is unclear whether the extent of surgery is prognostic. Most studies suggest that for a single mass, the outcome is the same for mass resection and radical mastectomy as long as excision is complete. However, given the prevalence of multiple tumors, unilateral radical mastectomy has also been advocated. In a 2008 study, 58% of dogs developed a second tumor which would have been prevented by unilateral mastectomy. However, in the same study, had all dogs received unilateral mastectomies, 42% would have had unnecessarily aggressive surgeries. If multiple mammary masses are present, a regional, unilateral or staged bilateral mastectomy is indicated.

One study found that ovariohysterectomy at the time of mass resection or within two years of developing mammary carcinoma improved two-year survival. This may be because tumors in intact females retain some hormone responsiveness. Hormone therapy with agents like tamoxifen (estrogen receptor blocker) is not commonplace, in part because of the ease of sterilization and also because of the significant risk of pyometra in intact females. If the dog is to be spayed at the time of mass removal, ovariohysterectomy should be performed first to avoid tumor seeding.

For large, high-grade, or metastatic tumors, surgery alone is unlikely to be curative. However, the role of chemotherapy for canine mammary carcinoma is unclear. Adequately powered, randomized, controlled trials are lacking. Chemotherapy is often recommended

for masses larger than 3 cm in diameter, when aggressive behavior is predicted histologically, or when metastasis is present. It is also advised for mammary sarcomas.

In a small, nonrandomized clinical trial, adjuvant 5-fluorouracil and cyclophosphamide improved survival. After two years, the median survival time of treated dogs was not reached compared to six-month median survival for those treated with surgery only. A 2012 study evaluating carboplatin alone and in combination with nonsteroidal antiinflammatory agents postoperatively also found significant benefit. A benefit for doxorubicin, docetaxol, and gemcitabine has not been shown. Simon *et al.* (2006) showed a trend towards increased local control and improved survival when doxorubicin or docetaxol was administered postoperatively but the results did not reach statistical significance. Larger, randomized, controlled studies are needed to better evaluate the role of chemotherapy and the most effective agents.

Prognosis

The most significant prognostic factors are tumor size, stage, and histologic grade. Several studies have found that tumors less than 3 cm carry the best prognosis, while others have shown that tumors up to 5 cm carry a similar prognosis. The median survival time for dogs with stage 1 and 2 disease exceeds two years in most studies. One study found that tumor size in the absence of lymph node metastasis was not prognostic. However, 86% of dogs with lymph node metastases had primary tumors larger than 5 cm. Dogs with lymph node and distant metastases generally survive less than six months when treated with surgery alone.

Inflammatory carcinomas and sarcomas carry a poor prognosis. The reported survival time of dogs with inflammatory carcinomas is 25–30 days. The prevalence of metastases is extremely variable between studies, with 8–100% metastases reported at diagnosis. A recent study found improved survival of 183 days when dogs with inflammatory mammary carcinomas were treated with piroxicam.

Feline Mammary Cancer

Etiology/Pathophysiology

Exposure to estrogen and progesterone during mammary development plays the most significant role in tumor development. As in dogs, estrogen and progesterone serve as trophic factors for mammary tissue. Cats spayed before 6 months of age have 91% reduced risk, those spayed before 12 months 86% reduced risk and those spayed between 12 and 24 months have 11% reduction in risk. Ovariohysterectomy later in life has not been found protective. Exposure to exogenous progestins is also associated with increased risk. Female cats exposed to exogenous hormones have 3.4 times the risk of unexposed cats. Over one-third of affected male cats had a known history of progestin exposure. Benign changes are commonly associated with pregnancy, pseudopregnancy, and progestin administration.

Epidemiology

Mammary tumors are the third most common tumor type in female cats, accounting for 12–25% of tumors in female cats in North America. In Europe, the incidence has been reported to be 25–40%. The three main risk factors are hormone exposure, age, and breed, with intact females having seven times the risk of spayed female cats. Eighty to ninety-five percent of feline mammary masses are malignant.

Signalment

Mammary tumors most commonly affect intact females and those spayed as adults. The risk of developing mammary tumors increases from 6 to 14 years of age, with peak incidence at 10–12 years. Male cats account for 1–5% of malignant masses. Siamese cats are at increased risk and also tend to be younger when diagnosed.

History and Clinical Signs

Most cats with mammary tumors present for a palpable mass within the mammary chain and are otherwise healthy. Large, adherent or ulcerated masses may be painful. The caudal glands have been reported to be affected more often although some studies have shown equal occurrence. Multiple masses occur in up to 60% of cats. Inflammatory mammary carcinomas are rare in cats but present with systemic signs and edematous, painful mammae as in the dog.

Diagnosis

As most feline mammary tumors are malignant, initial diagnostic tests should include thorough screening for metastatic disease. This includes a complete blood count, chemistry profile, serum thyroxine level, urinalysis, thoracic radiographs, and abdominal ultrasound. Regional lymph nodes should be aspirated when possible. Lymphatic drainage is unpredictable and so axillary, sternal, and inguinal nodes should be assessed. Cytology may be helpful to rule out cutaneous or lymphoid tumors.

Benign masses do occur in cats, accounting for 10–20% of masses. The most common benign diseases are fibroadenomas, mammary duct ectasia, and fibroadenomatous hyperplasia. Fibroadenomatous hyperplasia usually occurs in young females during pregnancy or pseudopregnancy but can be seen in male or altered cats due to exogenous progestins.

Tubular, papillary, tubulopapillary, cribriform, and solid carcinomas are the most common malignancies. Sixty percent of mammary carcinomas are deemed moderately differentiated, 27.3% are poorly differentiated, and only 12.7% are well differentiated. Feline mammary sarcomas and inflammatory carcinomas have been rarely reported. Metastatic disease occurs in 50–90% of cats, with up to 83% showing lymph node or pulmonary metastasis. Visceral metastasis and carcinomatosis also occur.

Tumor stage has been found to be prognostic. The most commonly used system is a modified WHO four-stage system (Table 149.2). The original staging system was also four tier but criteria included whether a metastatic lymph node was fixed or mobile, which has not been found prognostic.

Therapy

For most solitary tumors, a unilateral radical mastectomy is recommended. For multiple tumors involving both mammary chains, staged bilateral radical mastectomies should be performed. Unlike in dogs, the extent of surgery is prognostic, with cats undergoing radical mastectomies having longer disease-free intervals. One study found a trend towards increased survival, but a more recent report did not show survival advantage. Most mammary carcinomas are estrogen and progesterone receptor negative and so the role of concurrent ovariohysterectomy is unclear. For benign masses, ovariohysterectomy or withdrawal of exogenous hormones can induce regression.

Table 149.2 Feline mammary tumor staging. Modified World Health Organization Tumor, Node, Metastasis (TNM) staging scheme

Stage	Tumor size	Lymph node metastasis	Distant metastasis
1	T1 (T <2 cm)	N0 (none)	M0 (none)
2	T2 (T 2–3 cm)	N0 (none)	M0 (none)
3	T3 (T >3 cm)	Any N	M0 (none)
	Any T	N1 (positive)	M0 (none)
4	Any T	Any N	M1 (positive)

While surgery alone can result in long-term survival for cats with stage 1 or 2 disease, the median survival for cats with more advanced stages is 4–6 months. The benefit of chemotherapy is unproven but is advocated by most clinicians for cats with negative prognostic factors. The use of doxorubicin and cyclophosphamide in the setting of gross disease has been associated with a 45–50% overall response rate. Two studies, which lacked control groups, found no overall benefit to postoperative doxorubicin therapy, but did report survival times for cats with stage 3 tumors which were longer than historical controls. In these reports, cats with stage 3 tumors survived a median of 448 and 460 days. McNeill *et al.* (2009) did not find a benefit of adjuvant doxorubicin chemotherapy over surgery alone. Within the population of cats in the study, 47% had stage 1 tumors which are expected to have long-term survival with or without chemotherapy. The authors comment that the study had 12% power to detect a difference between the groups. Most clinicians advocate chemotherapy for cats with tumors greater than 3 cm diameter, lymphatic invasion or lymph node metastasis.

Prognosis

Median survival time is well correlated with tumor size and stage. Reported survival times for cats with tumors less than 2 cm range from 12 to 54 months. The median survival times for cats with stage 2 disease range between 9-24 months. Cats with tumors larger than 3 cm or more advanced disease survive a median of 4–6 months when treated with surgery only. As noted above, the addition of chemotherapy may improve the outcome for these cats, but clear benefit has not yet been shown.

One study showed that tumor differentiation was also prognostic, with 100% of cats with well-differentiated tumors being alive at one year, 57% with moderately differentiated tumors alive at one year, and no cats with poorly differentiated tumors surviving to one year. As most cats have moderately differentiated tumors, the prognostic benefit of this information is limited. Age, breed, percent necrosis, completeness of surgical excision, proliferative indices, and hormone receptor status may also be prognostic.

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150

Tumors of Bone and Joint

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Etiology/Pathophysiology

Primary tumors of bone are most commonly diagnosed in the appendicular skeleton, with osteosarcoma (OSA) being the most common tumor type. Other neoplasms, such as chondrosarcoma (CSA), fibrosarcoma (FSA), hemangiosarcoma (HSA), and histiocytic sarcoma, are less frequently identified. The metaphyseal region of long bones is the typical location for appendicular OSA, with the distal radius and proximal humerus being the two most common sites. The proximal tibia and distal femur may also be affected, with proximal femur, distal tibia, distal humerus, and ulna being less common sites.

While many possible contributing factors have been suggested, the precise etiology of OSA remains unknown. Suspected risk factors include previous radiation therapy, fracture, and metal surgical implants. There is also some evidence that the timing of spay/neuter may affect the incidence of OSA, but a clear causal effect has not been demonstrated.

Osteosarcoma is characterized by proliferation of endosteal cells, which results in the tumor arising within the medullary canal. This is responsible for the typical radiographic appearance of bony lysis and periosteal reaction. Two less common OSA variants, periosteal and parosteal, exist. Periosteal OSA arises from cortical bone but may invade the medullary canal; in contrast, parosteal OSA is characterized by the development of tumor external to the cortex, which does not invade into deeper structures. While extremely rare, parosteal OSA likely represents a less aggressive form of OSA.

Other neoplastic processes that can affect bone include hematopoietic tumors (such as lymphoma, histiocytic sarcoma, or multiple myeloma) and metastasis from a solid tumor. Primary bone tumors such as osteosarcoma often metastasize to other bony sites; however, metastatic bony lesions secondary to other cancers are also common. Many carcinomas, particularly those arising from the urogenital tract, often demonstrate a propensity for bony metastasis. While not absolute, metastases are commonly found in the diaphysis, whereas primary bone tumors generally occupy the metaphyseal region.

Axial skeletal neoplasia may be caused by any of the sarcoma types that affect the appendicular skeleton. OSA remains the most common tumor in axial locations as well, although it only accounts for about 25% of all cases of axial skeletal neoplasia. The mandible and maxilla are the sites most often affected, but other bones of the skull, the scapula, ribs, sternum, vertebrae, and pelvis may also be affected. Multilobular osteochondrosarcoma (MLO, also known as multilobular tumor of bone) typically affects the flat bones of the skull and is a slow-growing, locally invasive tumor. The metastatic propensity of MLO is largely dependent upon grade. In general, mortality from axial skeletal neoplasia occurs from local disease rather than metastasis, likely due to the challenging nature of surgical resection in these areas. Mandibular OSA appears to have a better prognosis than OSA in appendicular or other axial locations. Improved prognosis may result from less aggressive biologic behavior when compared with appendicular sites and from the relative ease of complete surgical excision compared with other axial sites.

Synovial cell sarcoma has been reported to be the most common canine joint tumor; however, other reports also describe a high incidence of histiocytic sarcoma affecting synovial surfaces. These tumors most commonly affect large joints of the appendicular skeleton (e.g., stifle, elbow), and have biologic behavior similar to these tumor types in other locations. Suspicion of a joint tumor

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should be high for bony lesions where more than one articular surface is involved.

Epidemiology

Large- and giant-breed dogs are most often affected with appendicular OSA, and a genetic component to the disease has long been suspected based on observed breed predilections. It should be noted that while small-breed dogs have a lower likelihood of developing OSA, they are more likely to develop axial OSA than their large-breed counterparts.

Skeletal neoplasia is much less common in the cat, where it is infrequently reported. OSA is the most common bone tumor in cats and, while locally invasive, carries a better prognosis than canine OSA due to the overall lower incidence of metastasis and a protracted course of disease in cats that do develop metastases. Like dogs, appendicular OSA in cats occurs more frequently than axial, but axial OSA is relatively more common compared to the distribution in dogs.

Signalment

Tumors of bone and joints typically affect dogs and cats that are middle aged to older. A bimodal age distribution, however, has been documented for canine OSA, with two specific peaks at 1–2 years and 7–9 years of age. Although the vast majority of dogs with OSA fall within the older group, a young age should not preclude consideration of OSA as a diagnosis.

Large-breed dogs are overrepresented, with breeds such as the Great Dane, Rottweiler, golden retriever, German shepherd, greyhound, Saint Bernard, Irish wolfhound, Scottish deerhound, borzoi, and Doberman pinscher commonly diagnosed with bone tumors. No important sex predilection between male and female dogs exists, but neutered animals are potentially at greater risk.

History and Clinical Signs

Dogs with appendicular bone or joint tumors typically present for evaluation of lameness or swelling of a limb. In many cases, the history may be that of a chronic, progressive lameness that has only been partially responsive to analgesics. An animal may also present with an acute onset of severe, nonweight-bearing lameness, sometimes due to pathologic fracture. It is not uncommon for owners to associate the acute onset with a nontraumatic event such as running, jumping, etc. Axial lesions may go longer without detection, but animals are often evaluated for swelling or mass lesions. Site-specific signs can occur depending on the tumor location and systemic signs such as lethargy or inappetence may occur from paraneoplastic syndromes or simply result from pain associated with the primary or metastatic tumors.

Diagnosis

A complete physical examination should be performed in all cases. Variable degrees of swelling, pain, and instability may be associated with the primary tumor. Each patient should also be carefully assessed for any evidence of metastasis, either to bone or to local lymph nodes. Complete orthopedic and neurologic examinations should be performed, particularly in cases of appendicular neoplasia where amputation may be considered as the surgical treatment of choice. The presence of orthopedic or neurologic co-morbidities does not preclude amputation, but knowledge of these is essential for planning and owner education.

Routine laboratory evaluation by means of complete blood count, chemistry panel, and urinalysis should be performed. These tests serve to evaluate the patient's systemic health prior to anesthesia, surgery, and chemotherapy. In addition, elevated total alkaline phosphatase (ALP) has been shown to be associated with a worse prognosis in canine OSA.

The first step in attaining a bone tumor diagnosis is orthogonal view radiographs of the affected limb or region. OSA has a characteristic mixed osteolytic and osteoproductive appearance, which when combined with a metaphyseal location is highly suggestive of this disease entity (Figure 150.1). As previously mentioned, particular sites are more common for OSA, are often described by the phrase "away from the elbow, towards the knee," with the thoracic limb being more commonly affected. OSA does not generally cross an articular surface; this trait is more characteristic of a primary joint tumor, or fungal or bacterial osteomyelitis. Metastatic lesions are often diaphyseal and predominantly lytic, although a spectrum of lytic versus productive disease is possible with OSA. When radiographs demonstrate an uncharacteristic lesion, other diagnostics, such as culture and biopsy, can be performed to obtain a definitive diagnosis. Radiographs may also be evaluated for the presence or absence of pathologic fracture.

Although classic radiographic findings may be sufficient to proceed with surgical treatment, many cases may benefit from presurgical confirmation of neoplasia and/or tumor type, particularly in patients that live or have a travel history to fungal endemic areas. Ultrasound-guided fine needle aspiration and cytologic evaluation is a relatively noninvasive means of obtaining a diagnosis of



Figure 150.1 Orthogonal view radiographs (cranial-caudal (a), lateral (b)) of the right radius and ulna. An expansile and lytic lesion of the distal radial metaphysis is identified with associated soft tissue swelling. Cytologic aspirate of this lesion was consistent with osteosarcoma.

neoplasia, although differentiation between types of cancer is often not possible with cytology alone. ALP staining of cytologic samples may allow for more conclusive identification of OSA in some cases. When indicated or desired, bone biopsy can be performed which typically results in a specific tumor diagnosis in about 80% of cases.

Bone biopsy may be performed using an incisional technique, Michele trephine, or Jamshidi needle. Jamshidi needles yield a smaller biopsy but provide a diagnosis in the vast majority of cases. Bone biopsies should be planned in order to minimize the size of the surgical site and provide for appropriate tumor excision at the time of definitive surgery. Samples should always be taken from the center of the lesion, as a peripheral biopsy is more likely to yield reactive bone rather than the true disease process. In addition to using the smallest sampling tool thought likely to provide a diagnostic sample, it is also recommended to avoid penetration of both cortices to minimize the likelihood of pathologic fracture.

While micrometastatic disease is thought to be present in nearly all dogs diagnosed with appendicular OSA, gross metastasis is only identified in about 10% of cases at the time of initial diagnosis. Pulmonary and bony metastases occur with approximately equal frequency at the time of initial diagnosis, although metastasis to other locations is possible.

Staging of patients is performed due to its relevance in estimating survival time. Little distinction is made in osteosarcoma regarding histologic grade due to the biologic aggressiveness of these tumors in nearly all cases; however, the presence of gross metastasis (stage III disease) is associated with shorter survival times. Median survival times (MST) in dogs with stage III appendicular OSA are still highly variable, however, and are affected by treatment provided. Grading of non-OSA sarcomas is generally thought to be associated with prognosis, with grade III tumors much more likely to metastasize and associated with a shorter survival time.

Staging in all cases should include three-view thoracic radiographs to evaluate for pulmonary metastasis. Abdominal ultrasound may also be performed to check for metastatic disease, particularly in cases with pelvic limb neoplasia, lymphadenopathy, atypical presentation/clinical findings, or in patients with histiocytic disease. Similarly, lymph node aspirates should be performed when lymphadenopathy is noted on physical examination or imaging studies or if the regional lymph node is readily accessible.

Nuclear scintigraphy, performed with an intravenous injection of technetium-99m, allows for identification of skeletal abnormalities with increased metabolic, particularly osteoblastic, activity. This diagnostic tool is highly sensitive but lacks specificity; areas of increased uptake may be due to neoplastic disease, infection, fracture, or other orthopedic co-morbidities. The input of an experienced radiologist, as well as follow-up radiographs to evaluate abnormal areas, can help to distinguish between these differentials.

Computed tomography (CT) is being increasingly used, both to evaluate for thoracic metastases and for evaluation of the local tumor site. While traditional, high-quality radiography is able to detect pulmonary metastases that are approximately 7–9 mm in size, CT has a reported sensitivity for detection of lesions as small as 1 mm. Despite this improved detection of disease, the clinical relevance of smaller metastatic lesions with regard to survival times is uncertain.

Assessment of the local tumor site in appendicular OSA with CT is generally nonessential when the chosen treatment is amputation. CT may help to evaluate the extent of disease if alternative surgical treatments such as limb-sparing surgery are to be considered. In addition, CT is often highly valuable for surgical planning in cases

of proximal appendicular tumors or disease affecting the axial skeleton. Magnetic resonance imaging (MRI) is generally less useful than CT for imaging bone, making CT the imaging modality of choice in most cases. MRI may be useful, however, in evaluating the local extent of disease prior to limb-sparing surgery, or to assess the proximity of neoplasia to neurovascular structures.

Therapy

Surgical margins around bone and joint tumors generally fall into the categories of wide or radical excision. Wide excision is defined as complete removal of disease with a margin of normal tissue, and radical excision includes the excision of a body part, such as limb amputation for cases of appendicular neoplasia. Limb amputation followed by chemotherapy is the recommended treatment for appendicular OSA, and amputation is often indicated for CSA, FSA, HSA, and for excision of other appendicular tumors in which local excision with adequate margins is not possible (Table 150.1). The decision to pursue limb amputation is typically difficult for owners to make; however, these dogs generally recover well from surgery and owner satisfaction is quite high. Videos of amputee dogs can sometimes be helpful to owners and are now commonly posted for public viewing on numerous websites. Dogs that are obese or have concurrent musculoskeletal or neurologic disease may have a prolonged recovery compared to the average patient and may benefit from physical rehabilitation after surgery.

Tumors of the thoracic limb are preferably treated by forequarter amputation. Forequarter amputation including excision of the scapula is preferred due to the ease of the surgical procedure, the likelihood of wide margins around disease, and improved cosmetic appearance when the scapula is removed, as muscle atrophy over this bone can be unsightly. Tumors of the scapula may be treated by partial or total scapulectomy with preservation of the limb; however, CT is recommended in these cases to ensure adequate margins around the extent of disease. Tumors of the ulna alone may be treated by ulnectomy; CT is again recommended to evaluate local disease for surgical planning.

Pelvic limb tumors are most commonly treated with coxofemoral disarticulation; similarly, this surgical technique is generally preferred over a midshaft femoral amputation due to ease of technique and wider surgical margins. Tumors of the proximal femur may be treated by *en bloc* excision of the acetabulum in addition to amputation or hemipelvectomy. Pelvic tumors can also be treated by partial or total hemipelvectomy. When performing hemipelvectomy, a detailed knowledge of anatomy is important to avoid trauma to intrapelvic structures such as the rectum and urethra. Preoperative CT scan is indicated before hemipelvectomy, and if incomplete or narrow surgical margins are likely, consultation with a radiation oncologist prior to surgery is strongly recommended.

Recovery after amputation surgery is generally rapid, with most dogs ambulating within a few days of surgery. Perioperative analgesia is essential, and may be provided with a wound soaker catheter or with systemically administered medications. Recovery after hemipelvectomy surgery is similar to amputation. Complications of these surgeries include seroma formation and, less commonly dehiscence, hemorrhage, and infection.

Limb-sparing surgery is described for appendicular bone tumors, but appropriate case selection and client education are essential. Limb-spare may be indicated for cases in which the dog is unable to tolerate amputation due to orthopedic or neurologic co-morbidities, or when owners have declined amputation. In general, limb-sparing surgery is considered only for tumors of the

Table 150.1 Treatment options for canine appendicular osteosarcoma

Treatment type	Effectiveness	Other considerations
Amputation + chemotherapy	Gold standard; MST ~1 year	Amputation generally well tolerated
Limb-spare (SRS/SBRT or surgical) + chemotherapy	Comparably effective to amputation + chemotherapy; infection associated with limb spare surgery improves survival	Limited availability due to highly trained personnel required and availability of SRS equipment
Amputation alone	MST <6 months	Death due to progression of metastatic disease
Palliative radiation	Pain relief for 2–3 months	>50% response rate
Aminobisphosphonates (often recommended in conjunction with radiation)	Four months of pain relief with pamidronate in 28% of dogs	Zoledronate more effective, may be cost-prohibitive

MST, median survival time; SRS, stereotactic radiosurgery.

distal radius. The presence of a pathologic fracture is considered a relative contraindication for limb-sparing, as fracture may predispose to spread of tumor cells and subsequent local recurrence. Significant complications associated with limb-sparing surgery include infection, implant failure, and local recurrence. Infection rates associated with limb-sparing surgery are high, and have been described as ranging between 30% and 70%. This high rate of infection is likely due to a variety of factors such as impaired vascular supply, minimal soft tissue coverage, implants, and subsequent delivery of chemotherapeutics. Infection, however, has been associated with a prolonged survival time compared to dogs that do not experience infection; dogs with surgical site infection have been shown to have median survival times approximately twice as long (an average of 250 days longer) as dogs that did not develop postoperative infections. Several different limb-sparing options are available, but a detailed explanation of the many techniques is beyond the scope of this chapter.

Radiation therapy can also be used to treat local disease in canine OSA cases. Full course curative intent radiation therapy is not routinely pursued due to the cost, side-effects to adjacent tissue, and lack of benefit when compared with standard surgical treatment. Developing techniques such as stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT), in which 1 to 5, high dose radiation treatments are delivered to the precise tumor location are showing promise. SRS/SBRT have been shown to have comparable success in some cases when compared to traditional surgical treatment; however, they continue to have limited availability due to the need for specialized equipment and highly trained personnel.

Palliative radiation therapy may also be pursued for pain relief in cases where surgery is not possible or owners do not elect for aggressive therapy. Generally, palliative radiation therapy involves the delivery of several large doses of radiation in 2–4 fractions. Decrease in inflammation, slowing of osteolysis, and reduction in tumor size are all benefits associated with palliative radiation therapy. Over 50% of patients respond to therapy, with onset of pain relief in 1–2 weeks and improvement lasting approximately 2–3 months on average.

While it is reported that only approximately 10% of dogs will have documented metastasis at the time of diagnosis, it should be noted that this number originates from dogs presenting to referral hospitals. It is therefore possible that the incidence in primary care veterinary clinics could be higher since thoracic radiographs are often performed at the time of diagnosis, and referrals are probably less likely in dogs that have detectable metastases. Even though 90% of dogs will have no detectable pulmonary metastasis, with rare exceptions, appendicular OSA in the dog is assumed to be metastatic at the time of diagnosis. The extremely high likelihood of microscopic metastases is supported by studies evaluating survival of dogs undergoing amputation alone. In dogs with OSA that receive amputation alone, the one- and two-year survival rates are only 11.5% and 2% respectively. Systemic therapy to control the outgrowth of micrometastasis is therefore recommended.

Many chemotherapy drugs and combination protocols have been attempted, but a clear benefit of any one particular protocol has not been clearly documented; preferred protocols often vary by doctor or institution. In general, chemotherapy with single-agent carboplatin, doxorubicin or alternating carboplatin and doxorubicin seems currently most favored and generally results in median survival times of 8–12 months. In the authors' opinion, the literature does not provide convincing evidence that any protocol is superior to single-agent therapy with carboplatin. Combined with the fact that carboplatin is generally well tolerated and is not associated with cardiotoxicity, the authors routinely recommend single-agent carboplatin. Additional prospective studies are needed to determine whether either of these protocols is superior and to determine the optimal number of doses. Cisplatin has shown significant efficacy and is considered standard of care for human osteosarcoma, but technical aspects and toxicity associated with administration coupled with the potential for renal toxicity have made this protocol less often utilized in veterinary patients. The administration of chemotherapy in the face of gross metastasis is generally unrewarding, with median survival times most often ranging from 30 to 90 days. Preliminary data support further studies to examine the potential of toceranib phosphate (Palladia™) to slow disease progression but no definitive conclusions can be made to date.

Multiple immunotherapy agents have shown some efficacy either alone or in combination with chemotherapy. These include liposomal muramyl tripeptide phosphatidyl ethanolamine (LMTPPE) and various delivery methods of interleukin (IL)-2. However, these agents are not commercially available and therefore are not routinely used.

Aminobisphosphonates (ABPs) are a group of synthetic analogs of organic pyrophosphate which possesses multiple potential benefits for patients with bone tumors or bony metastasis. Generally, this class of drugs is considered palliative in that they can induce apoptosis of osteoclasts (inhibiting bone osteolysis), reduce pain, improve quality of life, and may delay progression of bony metastasis. In addition, *in vitro* studies have found that this class also exhibits direct cytotoxic effects on osteosarcoma cell lines. While oral ABP formulations are available, this route of administration does not reach

levels believed to be required for the beneficial effects of ABPs against neoplastic bony lesions. Pamidronate is the most commonly used ABP in veterinary medicine as it is the most reasonably priced. Infusions of pamidronate were shown to be well tolerated in dogs and resulted in increased tumor bone mineral density and pain reduction for four months in 28% of dogs with osteosarcoma. When used in combination with palliative radiation therapy, pamidronate also appeared to improve limb function when compared with radiation therapy alone. Another ABP, zoledronate, is much more expensive at this time; zoledronate appears superior to pamidronate in that 50% of dogs achieved pain alleviation for greater than four months in one study.

Prognosis

For dogs with appendicular osteosarcoma that are treated with amputation alone, the MST is less than six months. Amputation followed with chemotherapy significantly improves prognosis, with MST approximately twice as long and between 25% and 62% of dogs alive at one year. Longer survival times are associated with periosteal or parosteal OSA, small stature, and dogs developing surgical site infections after a limb-sparing surgery. Negative prognostic indicators include elevated serum ALP, dogs developing OSA when they are less than 5 years old, metastatic disease (bone, lymph node or lung), increased tumor necrosis, proximal humeral location, and larger tumor size. Amputation for cats with appendicular osteosarcoma is often curative, although metastasis can occur.

Chondrosarcoma has better survival times compared to OSA, with histologic grade the most important prognostic factor. After amputation alone, dogs with grade I CSA had a MST of six years, grade II MST approximately half as long, and grade III CSA only associated with a MST of 0.9 years. Metastatic rate was similarly dependent upon grade, with 0%, 31%, and 50% of grade I, II, and III dogs developing pulmonary metastasis. Prognosis for appendicular HSA is less favorable than other diseases, due to the extremely high metastatic potential.

Variable prognoses have been described for axial OSA based on location and type of treatment. Overall, small dogs have a more favorable prognosis than large dogs, irrespective of location. Mandibular OSA has a better prognosis than other locations; when complete surgical margins are achieved after surgical excision, a 70% one-year survival rate is reported. Negative prognostic indicators include incomplete surgical resection, larger dogs, elevated ALP, and large tumors. Maxillary OSA has a reported MST of approximately five months.

As with appendicular tumors, CSA of the axial skeleton has a significantly better prognosis than OSA. Nasal CSA has a low metastatic rate and reported MST of 210–580 days. Rib CSA treated with surgical excision has a MST of 1080 days. Grade, location, and completeness of surgical excision have all been noted as possible prognostic indicators; however, only small case numbers have been evaluated. Similarly, MLO has moderate metastatic potential but improved overall survival times when compared to OSA. Mandibular location, low histologic grade, and complete surgical excision were positive prognostic factors. MST after surgery ranges from 630 to 797 days, with median time to metastasis between 420 and 542 days.

Prognosis associated with joint tumors is variable depending on type of tumor and whether complete excision is possible. Synovial cell sarcomas treated with complete excision may have a MST of greater than two years with surgery alone. Histiocytic disease typically exhibits a much more aggressive clinical course.

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151

Soft Tissue Sarcomas

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Etiology/Pathophysiology

Soft tissue sarcomas (STS) are a group of tumors that arise from mesenchymal tissues. Tumors within this group tend to have different morphologic and histologic features, but the biologic behavior is similar; therefore, they are often treated as one. Several important biologic features have been described:

- ability to arise from any anatomic site
- appear pseudoencapsulated but tend to infiltrate through and along fascial planes
- metastasize hematogenously in up to 20% cases, but regional lymph node metastasis is unusual
- local recurrence after conservative surgery is common
- gross tumors generally have a poor response to chemotherapy and radiation therapy.

Not all lesions arising from the subcutaneous space are malignant, and many are often benign or inflammatory. Though histologic distinction is not clinically important in the treatment of these tumors, the nomenclature is determined by the connective tissue (muscle, adipose, fascial, fibrous, and neurovascular) from which they arise. Tumors classified as STS include fibrosarcoma, peripheral nerve sheath tumor, myxosarcoma, liposarcoma, undifferentiated sarcoma, and malignant fibrous histiocytoma. Soft tissue tumors such as osteosarcoma, chondrosarcoma, hemangiosarcoma, rhabdomyosarcoma, histiocytic sarcoma, nerve root/brachial plexus, oral sarcomas, and synovial cell sarcoma are not classified as STS as they have a higher propensity for metastasis and/or local recurrence.

Epidemiology

Soft tissue sarcomas comprise approximately 15% of all skin and subcutaneous tumors in dogs and 7–9% in cats. In dogs, sarcomas have been associated with radiation, trauma, foreign bodies, implants, and the parasite *Spirocerca lupi*. In cats, three different types of sarcomas are seen: vaccine-associated sarcomas (also referred to as injection site sarcomas), viral-induced sarcomas, and nonviral nonvaccine sarcomas.

Vaccine-associated sarcomas have been shown to be linked to the administration of inactivated vaccines, such as feline leukemia virus (FeLV) and rabies. The development of sarcomas at sites of vaccine administration with FeLV or rabies is believed to be between 1/1000 to 1/10 000 cases. Some reports have shown an increased risk with increasing number of vaccinations and with repeated vaccination at the same site. The time to tumor development at the site of vaccination has been reported to be four weeks to 10 years but most commonly occurs between two and 10 months post vaccination. The majority of injection site sarcomas in cats arise from vaccines, but it is important to keep in mind that there have been reports of tumor development at the site of lufenuron and microchip injections. It is hypothesized that the formation of these tumors is related to inflammation created secondary to the injection. This is supported by the similar histologic appearance of injection site sarcomas to tumors arising in the eyes of cats after trauma.

Viral-induced sarcomas are rare. Typically, these multicentric tumors are seen in young cats that are positive for FeLV. FeLV can serve as a natural vector and transduce nonviral genetic elements from cat cellular DNA. This can result in the formation of a recombinant virus, termed feline sarcoma virus (FeSV), which exhibits altered oncogenicity. FeSV has been isolated from naturally occurring fibrosarcomas of FeLV-infected cats, supporting the theory that FeSV can cause the transformation of cells and induce sarcoma formation in FeLV-positive cats.

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Signalment

Soft tissue sarcomas tend to occur in middle-aged to older dogs and cats. No specific breed or sex predilection has been identified but medium and large-breed dogs seem to be overrepresented.

History and Clinical Signs

Soft tissue sarcomas present as firm, fixed, often slow-growing masses most commonly affecting the trunk, extremities, or oral cavity. Many times, they are initially noted when they are small but go untreated as they are assumed to be benign. The skin overlying these tumors is often moveable. When tumors are small, they are nonpainful but as they grow, they invade into the tissues which can result in the tumor becoming fixed or ulcerated and infected. Clinical signs manifested from the tumor are dependent on the site from which it originates; for example, tumors on a limb may result in lameness.

Diagnosis

A fine needle aspirate (FNA) is always warranted on detection of any new mass or lesion. Cytology can be beneficial in helping to rule out cysts or other tumor types (mast cell tumors), but it is always important to keep in mind that cytology is not sufficient for a definitive diagnosis of a STS. These tumors do not readily exfoliate and can contain areas of inflammation and necrosis. The presence of inflammatory cells and necrosis in the absence of neoplastic cells on cytology does not rule out a STS. A study conducted on FNAs of 40 STSs reported that only 62.5% of the cases yielded an accurate diagnosis, while 15% were incorrectly diagnosed.

Biopsy and histopathology are needed for a definitive diagnosis of a STS. There are two types of tumor biopsy commonly employed: pretreatment and posttreatment biopsy. Pretreatment biopsy is the preferred method and includes needle core (Tru-Cut), wedge or incisional, and punch biopsy. All biopsies should be positioned so that the biopsy tract can be included in the curative intent treatment field. Posttreatment biopsy refers to an excisional biopsy, where the diagnosis is made after removal of the gross tumor. Often, this method is attractive to pet owners as it allows for treatment and diagnosis in one step but unfortunately, posttreatment biopsies are rarely curative. An excisional biopsy should only be performed when it is possible to take a 2–3 cm margin around the tumor and even then it may not be necessary as lesions may prove to be benign.

Once a diagnosis of STS has been made, it is important to determine the clinical stage or extent of disease. Knowledge of the clinical stage will help determine the appropriate treatment. Diagnostic tests that should be performed prior to beginning definitive treatment include three-view thoracic radiographs, as the lungs are the most common site of metastasis. Careful palpation of regional lymph nodes with FNA or biopsy if accessible and/or abnormal. Careful palpation of the mass is necessary to determine tumor size and fixation to surrounding tissues. Advanced imaging with the use of computed tomography (CT) or magnetic resonance imaging (MRI) can be helpful to evaluate the extent and invasiveness of larger tumors, tumors in the head or neck, or tumors within a body cavity.

Therapy

Dogs

Surgery

Local tumor control accomplished with wide, surgical excision is considered the treatment of choice, and advances in reconstructive techniques have significantly expanded surgical options for aggressive resection with good functional and cosmetic outcomes.

The surgical approach is classified according to the extent of the wound margins as intracapsular (when the tumor is surgically penetrated); marginal (when the tumor is excised just outside, or at, the pseudocapsule); wide (when a portion of normal tissue is left around the tumor); and radical (when an entire anatomic segment is removed, for example, amputation). The minimum recommended margins for gross surgical resection are 3 cm lateral to the tumor and one fascial plane deep. However, if the tumor is attached to the muscle or fascial layer, the entire layer may be compromised and should not be considered a clean margin. Additionally, adipose and connective tissue are not tumor barriers. Biopsy tracts and any areas of fixation to surrounding tissue require *en bloc* resection with the tumor, as these areas are considered contaminated.

Soft tissue sarcomas are typically surrounded by a pseudocapsule, which allows the tumor to be "shelled out" and submitted for histologic evaluation. Unfortunately, this type of marginal excision commonly results in tumor cells extending to the edges of the resected tissue. Any surgical procedure involving margins less than 3 cm and one fascial plane deep must be considered an incomplete excision even if no macroscopic tumor is evident after removal.

Histopathology of the tumor and surrounding tissue following surgery is important as it provides surgical

margins and tumor grade. Both are necessary in determining whether further treatment, including additional surgery or radiation therapy, is necessary. Following removal of the tumor, surgical margins should be clearly marked on the specimen and completeness of excision should be evaluated. The resected tumor should be pinned out to the original dimensions to prevent shrinkage during formalin fixation. The following terminology is commonly used when evaluating surgical margins and considering additional treatment:

- *incomplete margins* – neoplastic cells are continuous with at least one surgical margin in any plane
- *narrow margins* – distance between surgically created tissue edge and neoplastic cells is less than 5 mm
- *adequate margins* – distance between surgically created tissue edge and neoplastic cells is ≥ 5 mm and <10 mm
- *ideal margins* – distance between surgically created tissue edge and neoplastic cells is at least ≥ 10 mm.

Marginal and incomplete resection is associated with a higher risk of local recurrence (26–60%). Further, dogs with incomplete margins are 10.5 times more likely to develop local recurrence than dogs with complete margins. Studies have also shown that the first surgery provides the best opportunity for local tumor control. Subsequent surgeries increase morbidity, treatment costs, and the risk of further local recurrences, while decreasing survival time. If a second surgery is performed after inadequate resection, a margin of healthy tissue of 3 cm in all directions surrounding the scar is recommended, including the removal of normal-appearing subcutaneous fat and underlying fascia. In a study evaluating scar reexcisions, local recurrence was reported in 15% of dogs and residual tumor was identified in 22% of the resected scars.

Prior to the routine availability of radiation treatment, radical and often disfiguring surgery was the mainstay of treatment and resulted in one-year control rates of 70–80%. Although STS have historically been considered radiation resistant compared to other tumor types, the multimodality approach of combining surgery with radiation has been proven to help prevent local recurrence.

Surgery and Radiation Therapy

The sequencing of radiation and surgery is based on multiple factors and should be determined on an individual basis. There are several advantages and disadvantages to both preoperative and postoperative radiation therapy. The rationale for administering postoperative radiation therapy is that the radiation kills or prevents the multiplication of any microscopic tumor cells left behind. Some advantages of postoperative radiation include the following:

- wound complications are rare in tissues that are irradiated after the first inflammatory phase of wound healing
- removal of a larger tumor with necrotic regions or infections may make the patient and patient's family more comfortable
- postoperative treatment planning may be simpler than preoperative planning in patients in which the size or shape of a tumor creates difficulty in achieving a uniform dose distribution.

Disadvantages of postoperative radiation include increased radiation field size, damage to vasculature, that may lead to local tissue hypoxia which decreases the effectiveness of radiation, and potential delays if post-surgical wound complications occur. Postoperative radiation is generally started within 7–14 days after surgery.

The rationale behind preoperative radiation therapy is to decrease the number of tumor cells, thus reducing contamination of the surgical site. Advantages include a smaller radiation field, reduction in the size of the tumor, making surgical excision with wide margins less difficult, and undisturbed tumor bed and blood supply, which increases the effectiveness of radiation. Disadvantages include the possibility of poor or delayed wound healing in the irradiated field.

Radiation therapy is commonly used as an adjunct to surgery. Radiation seems to have the greatest efficacy when it is used to treat remaining microscopic disease following surgical cytoreduction and is less effective when used to treat bulky, gross disease. Marginal surgical resection combined with radiation therapy is an attractive alternative to limb amputation for a STS on an extremity. It can also be used following a planned marginal resection when wide surgical resection is not possible, such as with tumors of the head or neck. In these cases, removal of all grossly visible tumor is advised. Radiopaque clips are often placed during surgery to mark the lateral, proximal, and distal extent of the tumor to aid in radiation planning.

Several studies have evaluated radiation therapy for incompletely excised soft tissue sarcomas in dogs. They have shown that similar local control and survival rates are attained with a better functional and cosmetic outcome by performing marginal surgical excisions plus adjuvant radiotherapy compared to radical surgery alone. A prospective study evaluated 48 dogs with soft tissue sarcomas treated with surgery to decrease tumor size to <3 cm. This was followed by conventionally fractionated, full course radiation therapy to a total dose of 63 Gy. The result was a five-year survival rate of 76% and a recurrence rate of 16%. The median time to recurrence

was 23.3 months. Another study evaluating 35 dogs with soft tissue sarcomas that were excised to microscopic disease followed by daily radiation to a total dose of 42–57 Gy reported an overall median survival of 61.7 months.

Interestingly, a recent study evaluated intentional marginal excision of canine STS of the limb followed by a coarsely fractionated radiation protocol consisting of four, once weekly, 8–9 Gy fractions. Fifty-six dogs were included. The results compared favorably to studies using more fractionated "definitive" protocols, as the one-, two-, and three-year disease-free intervals were 82%, 74%, and 70%, respectively, with a local recurrence rate of 18%. The main disadvantages of using coarsely fractionated protocols are reduced efficacy and the increased risk of late radiation toxicity, which may be significant and include bone necrosis and radiation-induced tumors at the site. In the study, the risk of developing late radiation side-effects was low when the fraction size did not exceed 8 Gy.

Radiation Therapy

If surgical excision of a soft tissue sarcoma is impossible because of tumor location or size, radiation therapy can be applied; however, measurable and bulky tumors tend to have a poor long-term response to primary radiotherapy. Tumor control with conventional doses of radiation alone (40–48 Gy) are difficult to obtain because of their low growth fraction, relatively long doubling time, and tendency to develop hypoxic regions within the tumor parenchyma. Reported one-year control rates are 30% at 35 Gy (10 × 3.5 Gy), 35% at 40 Gy (10 × 4 Gy), 48% at 45 Gy (10 × 4.5 Gy) and 67% at 50 Gy (10 × 5 Gy). At two years, control rates vary from 12% at 40 Gy to 33% at 50 Gy.

As a single modality, radiation has generally been considered palliative for STS with control defined as a slowly regressing or stable tumor mass. The goal of palliative or coarsely fractionated radiation therapy is to alleviate pain, swelling, and inflammation associated with the tumor, in the hope of improving quality of life. Typical palliative protocols involve fewer fractions of larger radiation doses (4–10 Gy), often given on a weekly basis. The delivery of a small fraction size once per week is unlikely to lead to a durable response because tumor cells have a significant amount of time to repair damage and proliferate between treatments. Therefore, larger doses of radiation are often delivered to optimize killing of tumor cells, with the increased risk of late radiation toxicity accepted as part of the treatment. Since palliative radiation therapy is administered to improve quality of life, not to prolong it, patients likely will not live long enough to experience permanent late effects. A study evaluating nonresectable STS treated with a palliative protocol (3 × 8 Gy) reported stable disease in 87% of the tumors treated with a median time to progression of 8.7 months.

As an alternative to once weekly fractionation, a retrospective study evaluated a palliative radiation protocol consisting of 4 Gy fractions given over five consecutive days. In this study, 10 soft tissue sarcomas were treated. A measurable overall response rate of 80% was reported, with tumor control achieved in 100% of patients and a median progression-free survival of 5.7 months. With this protocol, the risk for late side-effects is about half that of the traditional 8 Gy × 4 fraction protocol.

Many advancements have been made in the field of radiation oncology, and with these advancements and improved technology, stereotactic radiation can now be used to treat STSs. Stereotactic radiation consists of high doses of radiation precisely targeted at the tumor with rapid dose fall-off outside the tumor to help spare normal tissues and limit side-effects. Stereotactic protocols generally consist of 1–3 fractions of radiation given on a consecutive-day basis. The goal of stereotactic radiation is to deliver an ablative dose of radiation to the tumor and achieve long-term control of the disease. Currently, there are no published veterinary studies on stereotactic radiation and STS, but it is expected that this will be a very viable treatment option for nonresectable STS.

Chemotherapy

Adjuvant chemotherapy at times is useful in the treatment of STS. It is best utilized when combined with radiation therapy and/or surgery. Chemotherapy alone does not seem to be effective, with the exception of providing palliation in some cases. Doxorubicin-based protocols, either alone or in combination with cyclophosphamide, have shown the most promise with an overall response rate of 23%.

Despite the fact that STS are slow to metastasize, the metastatic rate for cutaneous STS is grade dependent and varies from less than 15% (grade I and II) to 41% (grade III). Due to the higher metastatic rate of grade III soft tissue sarcomas, postoperative chemotherapy should be considered as it may prevent or delay metastasis. Single-agent doxorubicin, mitoxantrone, or combination protocols are most commonly used.

Metronomic chemotherapy (continuous administration of chemotherapy drugs at doses that are significantly lower than conventional maximally tolerated dose therapy) has been evaluated in canine STS. A retrospective study evaluated 85 dogs with incompletely resected STSs. Thirty dogs received continuous cyclophosphamide (10 mg/m^2) and standard-dose piroxicam therapy (0.3 mg/kg). Fifty-five control dogs did not receive additional therapy. When comparing these two groups, treated dogs had a disease-free interval of 13.7 months which was significantly longer compared to 7.0 months

for untreated dogs. Another study evaluated low-dose cyclophosphamide and its effects on T-regulatory cells and tumor angiogenesis in dogs with STS. This study found that dogs receiving 15 mg/m^2/day of cyclophosphamide had significant decreases in the number and percent of T-regulatory cells as well as microvessel density, further supporting that metronomic therapy may provide antitumor effects.

Cats

Surgery and Radiation Therapy

Injection-associated sarcomas are poorly encapsulated tumors with extension and infiltration along fascial planes. Surgically, 3 cm margins laterally and one fascial plane deep to tumor have been utilized for the treatment of vaccine-associated sarcoma. However, this is not adequate considering the reported high rates of local recurrence which range from 35% to 59%. In response to this, surgical margins of >3 cm laterally and two fascial planes deep to the tumor, along with partial scapulectomy, osteotomy of spinous processes or hemipelvectomy when indicated, are now recommended. Despite attempting aggressive surgical margins, complete resection is achieved in less than 50% of cats, and overall one- and two-year disease-free intervals are only 35% and 9%. A retrospective study evaluated radical excision for treatment of 91 STSs. Radical excision was defined as 5 cm of tissue beyond the palpable edges of the tumor and two fascial planes or bone deep to the tumor. With this approach, surgery resulted in complete margins in 97% of cases and a local recurrence rate of 14%.

Due to the high rate of local recurrence following wide surgical resection, full-course radiation is considered essential in the management of cats with vaccine-associated sarcomas. The timing of the radiation therapy is controversial, and there are pros and cons to preoperative versus postoperative approaches. The time to recurrence when the combination of surgery and radiation therapy is used ranges from 13.5 months to 19.5 months. In studies investigating preoperative radiation therapy, complete resection significantly improved time to local recurrence with a disease-free interval for completely excised tumors of 33 months versus 10 months for incompletely excised tumors. Unfortunately, even with combination therapy, recurrence rates still range from 40% to 45%.

Chemotherapy

The most common chemotherapy drugs used to treat vaccine-associated sarcomas are doxorubicin, carboplatin, and cyclophosphamide. Postoperative chemotherapy has been shown to have only a minimal effect on survival in cats treated with curative-intent surgery and radiation therapy. Chemotherapy, however, may have beneficial effects on local tumor control. The effect of doxorubicin alone was evaluated in 12 nonresectable vaccine-associated sarcomas. An initial reduction of >50% in tumor volume was seen in 50% of the animals. Unfortunately, the response was not durable, and all cats showed progressive disease. However, the median overall survival was significantly longer for cats that did respond. More recently, tyrosine kinase inhibitors have been shown to block the PDGF/PDGF receptor signaling pathway in vaccine-associated cell lines and to inhibit vaccine-associated growth in a murine model. These drugs are currently being evaluated for treatment of these tumors.

Prognosis

Dogs

The overall prognosis for dogs with STS is good, but the range of biologic behavior for these tumors can be broad. The median survival time for dogs ranges from 3.9 years following surgery alone to 6.2 years with surgery and adjunctive radiation. Overall, up to 33% of dogs eventually die of tumor-related causes.

Research has identified valuable prognostic information including histologic grade, mitotic index, and completeness of surgical margins. A complete histologic margin predicts nonrecurrence and recurrence appears to increase with grade. The metastatic rate for dogs with grade I or grade II is less than 15% compared to 41% for grade III STS. High mitotic index (>9 mitotic figures per 10 high-power fields) is prognostic for recurrence, metastais, and survival. Other factors, including markers of cellular proliferation, tumor dimension, tumor location, histologic type, invasiveness, and cytogenetic profile, may be useful indicators of prognosis but presently require further investigation.

Cats

The prognosis for vaccine-associated sarcomas treated with surgery alone, using traditional recommendations of 3 cm margins and one fascial plane deep to the tumor bed, is poor. Multimodal treatment (extensive surgery, radiotherapy, chemotherapy) is recommended and the use of sophisticated imaging techniques can improve diagnosis and help in surgical planning. The combination of radiation therapy either pre- or postoperatively has improved the disease-free interval and overall survival time in cats with vaccine-associated sarcomas. Median survival time with combination therapy is 23 months compared to 19 months with surgery alone.

Vaccine-associated sarcomas are graded from I (least) to III (most aggressive) depending on mitotic index, differentiation, and necrosis. Approximately 15–24% of vaccine-associated sarcomas will metastasize to the lungs or other sites, and evidence has suggested that a higher grade is associated with an increased risk of metastasis. In cats, it appears that completeness of excision is one of the most important prognostic factors. Hence, it is very important that everything is done to ensure the greatest possibility of obtaining complete margins when recommending treatment for these tumors in cats.

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152

Hemangiosarcoma

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Etiology and Pathophysiology

Etiology

Hemangiosarcoma (HSA) is a malignant cancer of vascular endothelial cells. Although ionizing radiation has been associated with cutaneous HSA, there is no clear etiology for the visceral and subcutaneous forms. Vascular endothelial growth factor (VEGF) and other growth factors such as basic fibroblast growth factor (bFGF) and angiopoietin-1 are found in above normal levels in hemangiosarcoma. It is therefore hypothesized that dysregulation of angiogenesis may play a key role. Experimentally, it has been shown that overexpression of VEGF can lead to malignant transformation of vascular endothelial cells.

In humans, this disease is known as angiosarcoma and has been related to arsenicals, vinyl chloride exposure, and androgens as well as radiation exposure. These may induce a mutation in the von Hippel–Lindau tumor suppressor gene leading to an increased synthesis of hypoxia-inducible factor-1 (a transcription factor for angiogenic proteins such as VEGF). Mutations in other tumor suppressor genes such as p53 and PTEN have also been found but studies are limited.

The etiology of dermal hemangiosarcoma differs from visceral, myocardial, and other less common primary forms. Dogs with repeated, prolonged exposure to direct ionizing ultraviolet (UV) radiation have been documented to have an increased risk. The predisposition for dogs to develop dermal HSA regionally on the ventral abdomen supports solar induction, as well as field cancerization (a term used to describe the increased risk for regional tumor development after exposure to carcinogens).

Pathophysiology

Location

Hemangiosarcoma as a primary tumor has been reported to arise in the liver, kidney, bladder, prostate, peritoneum, lung, right auricle, muscle, bone, oral cavity, central nervous system (CNS) and integument, but can arise from any vascular site in the body. In the dog, the spleen is the most commonly affected organ (28–50%), followed by the right atrium and auricle (3–50%) and skin/subcutaneous tissue (13–14%). Multiple unrelated primary tumors can occur as has been speculated in dogs with concurrent splenic and myocardial forms.

Dermal hemangiosarcoma is a much less aggressive disease than visceral hemangiosarcoma. It has been proposed that there are two dermal forms: the solar-induced form, affecting thin-coat predisposed breeds with a good prognosis, and a nonsolar-induced, more aggressive form seen in nonventral locations in thicker coated, non-predisposed breeds. Dermal hemangiosarcoma (both solar and nonsolar) has a low metastatic rate. Common sites of metastasis include lungs, oral or nasal tissue, bone, heart, and CNS. The solar-induced form historically carries the best prognosis. Hypodermal (subcutaneous) HSA is characterized as being aggressive with higher local tumor invasion and a higher metastatic rate than dermal forms.

Hemangiosarcoma is much less common in cats than in dogs. In contrast to dogs, integumentary HSA (subcutaneous and dermal) is more common than the visceral or myocardial form. Seventy-seven percent of all reported feline cases arise from the integument. The most common locations in decreasing order are head/face, pinna, and ventral abdomen/inguinal region.

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Metastasis

With few exceptions, hemangiosarcoma is a highly metastatic malignancy. The multistep process involved in metastasis is shared by all solid tumors and includes the creation of new blood vessels (angiogenesis), mobility and invasion into surrounding tissue, embolism into circulation, evasion of host immune defenses, lodging into capillary beds, and extravasation into a new environment. A detailed description of this cascade is beyond the scope of this chapter.

Due to its intimate relationship with blood vessels, HSA is readily able to mobilize and metastasize. The most common route is via the vascular system but spread can occur by tumor seeding onto the local organ parenchyma and within body cavities after rupture.

Although the metastatic rate of hemangiosarcoma is regarded as high, the rate can vary depending on site of origin. The visceral and myocardial forms of HSA are characterized by an extremely high metastatic rate (80–90%) to local (liver, omentum, other intraabdominal organs) as well as distant locations (lungs, CNS). Other less common primary sites such as renal, retroperitoneal, and lingual demonstrate metastatic rates of 75%, 88%, and 45% respectively. Primary integumentary forms have a metastatic rate of 30% for dermal, 35–50% for subcutaneous, and 75–90% for intramuscular locations.

Epidemiology

Hemangiosarcoma accounts for 2–5% of cancers in the dog, and between 0.5% and 2% in the cat. It is more common in the dog than in any other species, and has an extremely high mortality. The dermal forms represents <1% of all skin tumors in dogs and cats. Breeds such as whippets, Italian greyhounds, greyhounds, English pointers, Dalmations, and Staffordshire terriers are at higher risk due to their thin coat and light complexion. Lightly pigmented cats do not carry the same risk for dermal HSA as dogs. However, they are prone to other solar-induced neoplasms such as squamous cell carcinoma. For dermal forms, there are no other known risk factors in the dog and cat. The strong breed association with the visceral and myocardial forms suggests an inherited predisposition for dogs. There is no known predisposition for cats.

Signalment

Dog

Hemangiosarcoma can arise in any breed at any age. The visceral and myocardial forms predominantly affect larger, middle-aged to geriatric dogs such as golden retrievers, Labrador retrievers, and German shepherds. Dermal hemangiosarcoma is most common in older dogs, median age 9 years. Dogs predisposed include thin-coated, lightly pigmented breeds. Hypodermal HSA appears in 9–10-year-old dogs, with no sex or breed predilection. Primary renal and retroperitoneal hemangiosarcoma are extremely rare. The median age for both forms is 10 years, with larger nonspecific breeds most commonly affected. With the renal form, there appears to be a predilection for males. Other primary sites such as the tongue have no specific sex, breed or age predilection.

Cat

The mean age for cats with HSA is 10 years. There is no sex or breed predilection in this species.

History and Clinical Signs

Dog

Visceral Nonmyocardial

Dogs with the visceral form of hemangiosarcoma can present with a variety of symptoms, ranging from lethargy to acute death from hemorrhagic shock. The most common presenting complaints are weakness, lethargy, collapse, and gastrointestinal changes such as anorexia, vomiting, and diarrhea.

Patients often present with pale mucous membranes, delayed capillary refill time, tachycardia and/or arrhythmias, poor pulse quality, and a palpable fluid wave in the abdomen. If no rupture has occurred, findings may be limited to a large cranial abdominal mass or organomegaly.

Myocardial

Dogs with primary myocardial hemangiosarcoma present with symptoms of pericardial effusion such as exercise intolerance, collapse, arrhythmias, and dyspnea. They are at a higher risk for acute death due to the added danger of tamponade. Physical exam findings may include extreme weakness, tachycardia, muffled heart sounds, and pulsus paradoxus.

Integument

Dogs with dermal HSA are often asymptomatic. Symptoms of the hypodermal and intramuscular forms vary greatly. Most patients present for lameness, pain, bruising, swelling or a palpable mass that can range from firm to soft and fluctuant. All forms of integument hemangiosarcoma can demonstrate ulceration.

Compared to dermal HSA which has a predisposition for the ventral abdomen, subcutaneous and intramuscular HSA have no predilection for location.

Uncommon Primary Locations

Unlike the above forms, renal hemangiosarcoma may carry a more prolonged history of vague symptoms, with a delay of 1–2 months between onset of clinical signs and diagnosis. Some dogs will have hemoperitoneum. The majority present with stage I disease (nonrupture, localized). Presenting complaints include lethargy, anorexia, and abdominal pain. The left kidney is more commonly affected.

Clinical signs of retroperitoneal HSA are similar to patients with the renal form. However, time to diagnosis is often shorter as acute hemorrhage is more common.

Dogs with HSA arising from the tongue may be asymptomatic. Diagnosis often occurs as an incidental finding identified during routine physical exam or dental prophylaxis. One-third of these dogs will have clinical signs related to an oral mass, including bleeding from the mouth, difficulty swallowing or difficulty eating. Lesions on physical exam are small (<2 cm) and commonly located on the ventral surface but can arise from the dorsal aspect as well. Up to one-quarter of dogs can have multiple lingual tumors.

Cat

Due to the most common location being the integument, most symptoms include a red or bruised raised swelling or mass. However, for visceral and myocardial forms, similar symptoms as seen in the dog can be expected.

Diagnosis

Complete blood count (CBC), serum biochemistry, urinalysis (UA), abdominal ultrasound, echocardiogram, three-view thoracic radiographs, and coagulation testing are recommended for most forms of HSA. With the myocardial form or if an arrhythmia is present, an electrocardiogram (ECG) should also be pursued. The exception to the above is with the dermal form. Because of the lower metastatic rate, abdominal ultrasound, echocardiogram and ECG may not be necessary. The reader is cautioned to approach each patient on an individual basis.

A high level of suspicion for HSA can be formulated based on ultrasonography findings (70% of splenic masses will be malignant and approximately 70% of those will be HSA). Additionally, HSA often, but not always, appears hypoechoic, cavitated, and nonhomogeneous. Nonetheless, caution must be exercised as other nonmalignant lesions such as hematoma or hemangioma may have a similar appearance.

Effusions are typically serosanguinous to hemorrhagic and samples characteristically lack clot formation.

Hematologic abnormalities may include anemia, thrombocytopenia, schistocytes, acanthocytes, prolonged prothrombin time, prolonged activated partial thromboplastin time, and increased fibrin degradation products. Approximately 50% of all dogs with splenic hemangiosarcoma meet disseminated intravascular coagulation (DIC) criteria.

Dogs with myocardial hemangiosarcoma may demonstrate a decreased amplitude of the QRS complex and electrical alternans on ECG. A visible tumor can be detected with echocardiography in 65–90% of cases.

With renal hemangiosarcoma, over half of patients are anemic. Patients may present with hematuria, proteinuria, hypoproteinemia, and thrombocytopenia. Ultrasonography often reveals a unilaterally, irregular, enlarged kidney.

With all forms, cytologic or histologic analysis is required for a definitive diagnosis. Ultrasound-guided fine needle aspiration for visceral forms can be attempted but is associated with a significant risk of hemorrhage and low sensitivity (38%). Therefore, most cases will require surgical biopsy. If necessary, immunochemical analysis for factor VIII-related antigen (von Willebrand factor), CD31, CD34, and vimentin can be performed.

In cats, full testing, including abdominal ultrasound, three-view thoracic radiographs, CBC, serum biochemistry and UA, is recommended regardless of primary location. Echocardiography in cats may not be warranted as cardiac HSA is extremely uncommon. The value of this and other diagnostics should be determined on a case-by-case basis.

Staging System

Staging describes the severity of cancer based on its size, local behavior, and presence of metastasis. This information is utilized in treatment planning and in assessing prognosis. Unfortunately, no standard staging system has been established for the cat. For the dog, a modified World Health Organization (WHO) tumor, node, metastasis (TNM) system is commonly used (Table 152.1). In this classification, there are three established stages. For visceral HSA, stage I (T0 or T1, N0, M0) describes a tumor <5 cm in diameter or microscopic with no evidence of nodal or distant metastasis and no evidence of rupture. Stage II (T1 or T2, N0 or N1, M0) describes no invasion into adjacent structures with or without tumor capsule rupture, no measurable distant metastasis with or without regional lymph node involvement.

Table 152.1 Modified World Health Organization TNM staging system

Stage	0	I	II	III
T = primary tumor	No evidence of tumor	Tumor less than 5 cm; confined to primary site	Tumor 5 cm or greater or ruptured; invading subcutaneous tissue	Tumor invading adjacent structures, including muscle
N = lymph nodes	No lymph node involvement	Regional lymph node involvement	Distant lymph node involvement	
M = metastasis	No distant metastasis	Distant metastasis		

Table 152.2 Chemotherapeutics commonly used for the treatment of hemangiosarcoma

Drug	Dose	Frequency/days given (every 3 weeks = 1 cycle)	Use	Route	Unique side-effects
Doxorubicin	30 mg/m^2	Every 2–3 weeks (day 1 and day 14 or 21)	Single agent or combined with cyclophosphamide +/- vincristine	Intravenous	Cardiotoxicity
Vincristine	0.75 mg/m^2	Days 8 and 15	Combined with doxorubicin	Intravenous	
Cyclophosphamide	100 mg/m^2	Day 1 (when with vincristine and doxorubicin), days 3–6 (with doxorubicin alone)	Combined with doxorubicin alone or vincristine and doxorubicin	Intravenous or oral	Sterile hemorrhagic cystitis
Dacarbazine	800 mg/m^2	Day 1 (same day as doxorubicin)	With doxorubicin	Intravenous (constant rate infusion)	
Temozolomide	100–125 mg/m^2	Days 1–5	With doxorubicin	Oral	

Stage III (T2 or T3, N1 or N2, M1) describes a tumor invading adjacent structures, lymph node involvement (regional or distant), and/or distant metastasis.

When applied to the integumentary system, the TNM classification can be utilized with the following additional location-specific parameters: stage I, tumor confined to the dermis; stage II, tumor extends into subcutaneous tissue, rupture not a consideration; stage III, muscular invasion has occurred.

Therapy

Surgery

Regardless of species and primary location, surgery along with adjunctive doxorubicin-based chemotherapy (Table 152.2) is the treatment of choice. Notable exceptions include small dermal lesions (stage I) and conjunctival forms; these presentations may not require adjunctive chemotherapy as they carry a much lower risk of metastasis.

Surgical mass removal is vital to minimize the risk of fatal hemorrhage with splenic hemanigosarcoma. Intraoperatively, arrhythmias are common, so continuous ECG monitoring for a minimum of 24 hours postoperatively is recommended. Ventricular tachycardia, sustained tachycardia (180 beats per minute) with paroxysmal runs of ventricular premature complexes (VPCs) or patients that are symptomatic for ventricular arrhythmias can be treated with lidocaine boluses or constant rate infusions. Most arrhythmias will resolve within 24–48 hours.

Patients with splenic hemangiosarcoma commonly have evidence of liver metastasis at the time of diagnosis. However, all hepatic nodules identified at surgery should not be assumed to be malignant as benign conditions such as nodular hyperplasia are also commonly found in the aged animal. It is necessary to perform a biopsy of any suspicious lesion when removing an abdominal mass.

Surgical excision of myocardial HSA is rarely performed. Tumors in this location are a significant technical challenge and are seldom completely removed. For most patients, laparoscopic or open thorax pericardiectomy may be the only surgical option. Pericardiectomy may provide palliation and short-term survival gains as it minimizes risk of pericardial tamponade. Owners should be warned about sudden death from tamponade if removal or pericardectomy is not pursued.

Complete surgical excision of dermal hemangiosarcoma is strongly recommended. If the mass is small and no evidence of subcutaneous invasion is found, adjunctive chemotherapy may not be warranted as the risk of metastasis for this form is low.

Unlike dermal tumors, where surgical excision alone may be adequate, hypodermal and intramuscular tumors require multimodal therapy. HSA in this location is associated with a high local recurrence and metastatic rate. Therefore, wide surgical excision (3 cm minimum margin) +/- adjunctive radiotherapy is recommended. To address the risk of metastasis, systemic chemotherapy (doxorubicin based) is always recommended.

In cats, complete histopathologic excision with wide surgical margins is likewise recommended for all dermal forms of hemangiosarcoma. As in dogs, subcutaneous and other nondermal hemangiosarcoma forms have a higher risk of metastasis. Hence adjunctive chemotherapy should be considered.

Doxorubicin-Based Chemotherapy

Doxorubicin is the most active chemotherapeutic for hemangiosarcoma. It can be used alone or as part of a multiple agent protocol (see Table 152.2). Regardless of which is utilized, chemotherapy is regarded as well tolerated by most animals. Gastrointestinal toxicity (vomiting, diarrhea, anorexia) is often self-limiting and is seen in up to 20% of patients, but requires hospitalization far less often. Like most chemotherapeutics, the most common hematologic side-effects are neutropenia and thrombocytopenia, and, less likely, anemia. Doxorubicin-based protocols that incorporate dacarbazine result in a response rate of 47% but have more significant hematologic and gastrointestinal side-effects. Oral temozolomide in place of dacarbazine has recently been evaluated. The response rate was found to be similar but with less hematologic toxicity.

Doxorubicin, like all anthracyclines, is cardiotoxic. An irreversible, dilated type cardiomyopathy can occur at cumulative doses at or above 180–240 mg/m^2. A more cardioprotective anthracycline is epirubicin. Adverse cardiac effects can be seen with its use but at doses more than double that of doxorubicin. In one study, it was shown to be equally effective as doxorubicin, but more gastrointestinal side-effects (vomiting, diarrhea) occurred. Other formulations of doxorubicin such as pegylated, liposome-encapsulated (PL-DOX) are available. Encapsulation into liposomes leads to decreased cardiotoxicity and decreased drug uptake by phagocytes, thereby prolonging exposure to the drug. Comparison of response and survival time between pegylated and nonpegylated forms has revealed no differences. Of unique concern, PL-DOX may induce palmar-plantar erythrodysesthesia (PPES), a painful desquamation dermatitis. Adjunctive therapy with pyridoxine may minimize symptoms and lessen risk.

Other notable toxicities of anthracyclines include anaphylactic type reactions during infusion and tissue necrosis if extravasated. Proper administration requires accurate intravenous catheter placement, patient sedation when appropriate, and avoiding bolus administration.

In the cat, adjunctive chemotherapy with a doxorubicin-based protocol is recommended following surgical excision for all forms of HSA except small dermal lesions. Single-agent doxorubicin dosed at 25 mg/m^2 every three weeks, or a combination protocol with cyclophosphamide and vincristine, should be considered.

Immunotherapy

Immunotherapy modifies a biologic response by enhancing a preexisting immune response, inducing an immune response or suppressing an immune response. When given in conjunction with chemotherapy, immunomodulatory agents may enhance efficacy and improve prognosis. One such immunomodulatory agent is muramyl tripeptide-phosphatidylethanolamine (L-MTP-PE), a lipophilic derivative of muramyl dipeptide (MDP), a molecule resembling the cell wall of bacteria. L-MTP-PE stimulates cells of macrophage lineage to become tumoricidal. When a doxorubicin-based protocol was used in conjunction with L-MTP-PE (given twice weekly for eight weeks), the median survival time was significantly improved (277 days versus 143 days with chemotherapy alone). L-MTP-PE is not presently available in the United States.

Antiangiogenic Therapy

Angiogenesis is a normal process involved in fetal development, wound healing, and the female reproductive cycle. In health, it is controlled by inhibitory regulators. In the cancer patient, this process becomes abnormally activated and unregulated and is involved in tumor growth and metastasis.

Newer cancer treatment strategies focus on the inhibition of angiogenesis. Growth factors monitor and activate endothelial cell growth and development. As examples, VEGF and bFGF act directly on endothelial cells; Transforming growth factor (TGF) and platelet-derived growth factor (PDGF) attract and activate inflammatory cells and connective tissue, which thereby promotes angiogenesis. Antiangiogenic agents are directed towards inhibition of one or more growth factors or their receptors, thereby preventing further angiogenesis, growth and metastasis of a tumor.

Angiogenesis inhibitors are an attractive antineoplastic treatment as they are not limited to cytotoxic therapy and may be more acceptable and tolerable by both the owner and the patient. Further, they do not induce multidrug resistance as they do not target tumor cells directly.

Metronomic Chemotherapy

Metronomic or continuous low-dose oral chemotherapy has been demonstrated to have antiangiogenic and immune-modulating effects. Its use has been shown to improve survival in dogs undergoing splenectomy. Cyclophosphamide, the most commonly prescribed, also suppresses T-regulatory cells, thereby improving host antineoplastic immune function. In one study, cyclophosphamide (12.5–25 mg/m^2 PO) and etoposide (50 mg/m^2 PO) were administered daily on alternating three-week cycles with piroxicam (0.3 mg/kg/day PO). Results revealed a median survival of 178 days, which was significantly better than historical controls undergoing surgery alone. Although low doses of chemotherapy are used, owner compliance and care are required to minimize risks for sterile hemorrhagic cystitis.

To date, very few metronomic protocols have been evaluated in patients with hemangiosarcoma. Further studies need to be done to determine efficacious drugs, dosages, and timing.

Tyrosine Kinase Inhibitors

Palladia™ (toceranib phosphate) is a receptor tyrosine kinase inhibitor that affects the activities of multiple receptors, including VEGF and PDGF-alpha. Similar to metronomic chemotherapy, it also has immunomodulatory effects against myeloid-derived suppressor cells. Masitinib mesylate (Masivet®), another receptor tyrosine kinase inhibitor approved for use in dogs in Europe, was shown to decrease T-regulatory lymphocytes in the bloodstream of dogs and was well tolerated when combined with a metronomic dosage of cyclophosphamide. However, neither Palladia nor Masivet has been shown to lead to survival benefits for HSA. Imatinib mesylate (Gleevec®), a human receptor tyrosine kinase inhibitor, has been shown to induce apoptosis in hemangiosarcoma cell lines with a dose-dependent killing effect *in vitro*. It is associated with hepatotoxicity in the dog and for most, is cost-prohibitive.

Other Agents

Interferons are cytokines that have been used for antiangiogenic therapy in humans; interferon-alpha 2a inhibits angiogenesis by suppressing bFGF and VEGF production. Daily injections are required, making it less practical for the veterinary patient. Neutralizing antibodies may also eventually be produced, making the use of escalating doses necessary.

Matrix metalloproteinases (MMPs) are another potential target for therapy. These enzymes degrade components of the extracellular matrix, and play an important role in wound healing and tissue remodeling. In the cancer patient, MMPs are involved in tumor invasion, proliferation, and fostering a local environment to enhance tumor growth. Minocycline is a synthetic agent that inhibits MMPs. However, its use has not been shown to significantly prolong survival in dogs with HSA when combined with a doxorubicin-containing protocol.

Complementary Treatment

Nutraceuticals or homeopathic remedies have been explored as adjuncts to standard therapy for hemangiosarcoma in an effort to improve quality of life. Yun-Zhi PSP is the active ingredient in I'm-Yunity (an extract of *Coriolus versicolor* mushroom). The median time to develop metastasis or progression of metastasis was delayed in dogs receiving 100 mg/kg/day. Yunnan Baiyao is a neutraceutical/homeopathic Chinese powder that anecdotally has been shown to promote coagulation, and help prevent intraabdominal and myocardial hemorrhage. The definitive benefit of its use in dogs with hemangiosarcoma has yet to be determined.

Prognosis

Visceral and Myocardial Forms

The long-term prognosis is grave for dogs with the visceral form of hemangiosarcoma. The median survival time (MST) with surgery alone is approximately 72 days. With adjunctive chemotherapy, the median survival time is 6 months (one-year survival 6%). Stage has been shown to be prognostic. Dogs with a stage III presentation have an anticipated MST of three months in spite of standard therapy. Death is typically due to resistant metastatic disease or hemorrhage.

The prognosis for dogs with myocardial HSA is likewise grave. Although survival may be similar to those with the visceral form, a poorer outcome is more typical (MST 4 months) as many do not undergo cytoreductive surgery. In one study, the MST for dogs that had pericardectomy alone was one month.

Both renal and lingual forms are exceptions. With treatment, renal hemangiosarcoma has a MST of nine months, with an approximately 30% one-year survival. Dogs with lingual hemangiosarcoma (grade I and II) have an expected MST of 553 days. Local recurrence following therapy for the lingual form is common.

Integument

Dermal hemangiosarcoma is associated with the best prognosis. A MST of 2.5–3 years (one year 79%, two year 60% MST) can be anticipated. Prognostic factors include breed, tumor location, presence of solar actinic changes, and invasiveness. Predisposed breeds have a decreased risk for developing metastasis, and have a longer survival time (MST 1570 vs 593 days). Sun-exposed locations have a better prognosis and an increased overall survival rate (1085 days vs 539 days for tumors of other locations). Additionally, dogs with solar changes on histology such as solar elastosis, superficial dermal fibrosis, and epidermal dysplasia have an increased overall survival compared to those without solar changes (MST 1549 vs 545 days respectively). Of importance to note is that over 75% of dogs with dermal HSA will develop additional tumors in the same region of skin over time (usually predisposed breeds with the solar-induced form on their ventral abdomen).

The prognosis for dermal hemangiosarcoma is significantly more guarded if invasion into the subcutis or muscle has occurred. With surgery alone, MST is 172 days for stage II and 307 days for stage III disease. One study found the prognosis for dogs with stage II tumors was improved with the addition of chemotherapy (MST 1189 days) but the prognosis for stage III tumors remained similar (MST 273 days). Most dogs with stage III HSA (intramuscular) will die of metastatic disease prior to local recurrence.

Cat

In cats, similarl to dogs, location is a good predictor of survival. Subcutaneous tumors had a longer MST than visceral tumors, and dermal tumors had a longer MST than subcutaneous tumors. Higher mitotic indices (>3/10) were linked to shorter survival.

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153

Melanoma

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Etiology/Pathophysiology/Epidemiology

Melanoma is a relatively common tumor of dogs, especially in those with significant levels of skin pigmentation. Melanomas in cats are relatively rare. The most common location for canine melanoma is the haired skin, where they grossly appear to be small brown to black masses, but can also appear as large, flat, and/or wrinkled masses. Primary melanomas also can occur in the oral cavity, nailbed, footpad, eye, gastrointestinal tract, or mucocutaneous junction. Ocular melanomas of dogs and cats represent a distinct clinical syndrome and will be discussed elsewhere. Metastatic sites for canine malignant melanoma (CMM) can be varied, including local draining lymph nodes, the lungs, liver, meninges, adrenals, etc.

Melanoma arises from melanocytes, the cells which generate pigment through the melanosome by a number of melanosomal glycoproteins. In humans, cutaneous melanoma can arise due to mutations induced by repeated, intense exposure to ultraviolet light (for example, frequent tanning or working outdoors). Melanoma is currently the most rapidly increasing incident human cancer. Significant recent research into the etiology of human melanoma suggests multiple causes which are independent of the aforementioned UV-associated mutagenesis. Since most breeds of dogs have a hair coat, which affords them protection from sunlight, UV-associated melanoma is a less likely primary causative agent in the dog. However, pigment cells divide every time there is injury to the skin, or if there is constant trauma (for example, areas where dogs scratch or lick). Nevertheless, risk factors for canine melanoma are not well established.

Signalment

The most common oral malignancy in the dog is melanoma. Oral malignant melanoma is most commonly diagnosed in Scottish terriers, golden retrievers, poodles, and dachshunds. Oral melanoma is primarily a disease of older dogs without gender predilection, but may be seen in younger dogs. Additional oral tumor differentials include squamous cell carcinoma, fibrosarcoma, epulides/odontogenic tumors, osteosarcoma, and others. Melanomas in the oral cavities of dogs are found in the following locations in order of decreasing frequency: gingiva, lips, tongue, and hard palate. Feline melanoma is relatively rare, but appears to be malignant in most cases.

Diagnosis/Pathology/Molecular Biology

Melanomas can be difficult to diagnose pathologically in some situations, especially anaplastic amelanotic melanomas which can masquerade as soft tissue sarcomas. Numerous investigators have attempted to increase the precision of identification of melanomas predominantly through immunohistochemical (IHC) means. This may be accomplished through the use of multiple IHC assays on suspected melanoma tissue or through the use of an IHC cocktail of antibodies. The use of PNL2 and tyrosinase, beyond the typical use of Melan A and S100, appears to hold particular promise.

The molecular characterization of canine and feline melanomas is not as well defined as it is in humans. BRAF is a member of the MAPK signaling pathway, which is commonly mutated in human cutaneous melanoma, but infrequently mutated in oral mucosal

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melanoma. Interestingly, BRAF mutations are also uncommon in canine oral malignant melanoma, suggesting that certain canine and/or feline malignancies can have similar molecular signatures in addition to their already well-known clinical similarities in the context of resistance to chemotherapy and/or radiation, prognosis, and similar variable peculiar sites of metastatic propensity. A number of other investigators have reported a variety of molecular abnormalities and/or associations in canine and feline melanoma.

Staging

The staging of dogs with melanoma is relatively straightforward. A minimum database should include a thorough history and physical exam, complete blood count and platelet count, biochemical profile, urinalysis, three-view thoracic radiographs and local lymph node aspiration with cytology to determine whether lymphadenomegaly is present or not. Williams and Packer reported that local nodes from dogs with oral melanoma have ~70% metastasis when lymphadenomegaly was present, but more importantly, ~40% had metastasis when no lymphadenomegaly was present. Abdominal ultrasound should be considered in cases with moderate to high metastatic potential such as the oral cavity, feet or mucosal surface of the lips, as melanoma may metastasize to the abdominal lymph nodes, liver, adrenal glands, and other sites.

The use of sentinel lymph node mapping and lymphadenectomy is of diagnostic, prognostic and clinical benefit in human melanoma. Relatively few investigations have been reported to date for sentinel lymph node mapping and/or excision for dogs with malignancies and this author strongly encourages additional investigation in this area. Furthermore, the use of novel staging modalities such as gallium citrate scintigraphy is also encouraged.

Therapy

Surgery

Surgery is the most effective local treatment modality for melanoma. Incisional biopsy is an important part of the diagnostic work-up based on the clinical, therapeutic, and prognostic heterogeneity of tumors on the differential diagnosis list. In cases for which cytology results from draining lymph nodes are equivocal, lymph nodes should be surgically excised and submitted for pathologic examination as this outcome holds prognostic and therapeutic importance.

Cutaneous melanocytomas are often completely excised with 1 cm lateral skin and one fascial plane deep margins. In contrast, partial mandibulectomy and maxillectomy are typically required for complete removal of oral melanomas arising from the gingiva or from other oral mucosa in close proximity to bone. Imaging via computed tomography (CT) or magnetic resonance imaging (MRI) can be helpful for delineation of tumor extent/invasiveness and/or involvement of regional lymph nodes. Melanomas in mucosal areas not adjacent to bone such as tongue, lip or buccal mucosa may be amenable to excision of the soft tissues only. Local recurrence rates vary from ~20% to 50% following mandibulectomy and maxillectomy, respectively. Quality of life is typically very good to excellent and most dogs are eating in the first day or two following mandibulectomy or maxillectomy, with high owner satisfaction rates. The combination of surgery and radiation plus adjuvant therapy should be considered in those patients with tumors that are not amenable to clean margin resection.

Radiation Therapy

Radiation therapy can play an integral role in the treatment of a subset of canine and feline melanomas. Radiation therapy is unfortunately ineffective at controlling distant metastasis and therefore should be used for local tumor control when definitive local therapy via surgical removal is incomplete or not possible. Melanoma has historically been believed to be a relatively radioresistant tumor type. Therefore, most radiation protocols used in dogs and cats have utilized higher doses per fraction. Protocols with fewer treatments ("hypofractionated") have less cost, reduced emotional and time commitment for owners, and fewer anesthetic episodes with generally less severe acute side-effects when compared to full-length normally fractionated protocols. A 2–3 cm margin around the tumor is typical for most radiation plans with considerations for irradiation of the local draining lymph node.

The overall response rate to radiation for canine OMM is generally 80–90% with approximately 60% complete response and 25% partial responses. Progression-free median survival times with radiation are typically 5–8 months with high recurrence rates. Median survival times range from approximately five to 12 months. Dogs with less advanced, incompletely resected oral melanoma (majority were stage I with some stage II) that were treated with either carboplatin or cisplatin given once weekly before radiation therapy had a median survival time of approximately 12 months. The median survival time for five cats with oral malignant melanoma treated with radiation therapy and a variety of other adjuvant therapies was only 146 days.

Chemotherapy

Other modalities reported for local tumor control as case reports and/or case series have included intralesional cisplatin implants, intralesional bleomycin with electronic pulsing and many others, but widespread use has not been reported to date.

In dogs with melanoma in anatomic sites predicted to have a moderate to high metastatic rate, or dogs with cutaneous melanoma with a high tumor score and/or increased proliferation index through increased Ki-67 expression, the use of systemic therapies is warranted due to the high risk for metastasis. Rassnick and colleagues reported an overall response rate of 28% using carboplatin for dogs with malignant melanoma. Unfortunately, only one dog had a minimally durable complete response (~150 days), and the rest were nondurable partial responses. Similarly, Boria *et al*. reported an 18% response rate and median survival time of 119 days with cisplatin and piroxicam in canine oral melanoma. Other reports using single-agent dacarbazine, melphalan or doxorubicin suggest poor or absent activity. More recently, and importantly, three studies suggest that chemotherapy plays an insignificant role in the adjuvant treatment of canine melanoma, whereas one study suggests it may provide benefit.

While it can be argued that the studies performed to date to evaluate the activity of chemotherapy in an adjuvant setting for canine melanoma have been suboptimal for a variety of reasons, the extensive human literature suggests that melanoma is an extremely chemotherapy-resistant tumor. It is clear that new approaches to the systemic treatment of this disease are desperately needed.

One potential therapeutic avenue which has not been significantly reported to date in canine or feline melanoma is the use of COX-2 inhibitors. A number of authors have investigated the expression of COX-2 in canine melanoma and have found positive correlations of COX-2 expression to proliferation and survival. Further studies investigating the clinical responsiveness of canine melanoma to COX-2 inhibitors (and potential correlation to COX-2 expression) are encouraged.

Immunotherapy

Immunotherapy represents one potential logical systemic therapeutic strategy for melanoma. A variety of immunotherapeutic strategies for the treatment of human melanoma have been reported, with typically poor outcomes due to a lack of breaking innate or acquired immune tolerance to the tumor. Immunotherapy targets and strategies to date in canine melanoma have used autologous tumor cell vaccines (with or without transfection with immunostimulatory cytokines and/or melanosomal differentiation antigens), allogeneic tumor cell vaccines transfected with interleukin (IL)-2 or granulocyte macrophage-colony stimulating factor (GM-CSF), liposomal-encapsulated nonspecific immunostimulators (e.g., L-MTP-PE), topical imiquimod, intralesional Fas ligand DNA, siRNA (small interfering) against the survivin and/or Bcl-2 genes, bacterial superantigen approaches with GM-CSF or IL-2 as immune adjuvants, pegylated tumor necrosis factor (TNF)-alpha, suicide gene therapy, adenovector CD40 ligand and, lastly, canine dendritic cell vaccines loaded with melanosomal differentiation antigens.

Although these approaches have produced some clinical antitumor responses, the methodologies for the generation of these products can be expensive, time consuming, sometimes dependent on patient tumor samples being established into cell lines, and fraught with the difficulties of consistency, reproducibility, and other quality control issues. Furthermore, we are just beginning to more fully understand the native immune dysregulation potentially induced by the malignancy through increased T-regulatory (Treg) cells, which suppress antitumor responses.

The advent of DNA vaccination circumvents many of the previously encountered hurdles in vaccine development. DNA is relatively inexpensive and simple to purify in large quantities. The antigen of interest is cloned into a bacterial expression plasmid with a constitutively active promoter. The plasmid is introduced into the skin or muscle with an intradermal or intramuscular injection. Once in the skin or muscle, professional antigen-presenting cells, particularly dendritic cells, are able to present the transcribed and translated antigen in the proper context of major histocompatibility complex and co-stimulatory molecules. Although DNA vaccines have induced immune responses to viral proteins, vaccinating against tissue specific self-proteins on cancer cells is clearly a more difficult problem. One way to induce immunity against a tissue-specific differentiation antigen on cancer cells is to vaccinate with xenogeneic (different species) antigen or DNA that is homologous to the cancer antigen. As outlined in cartoon form in Figure 153.1, vaccination with DNA encoding cancer differentiation antigens is ineffective when self-DNA is used, but tumor immunity can be induced by DNA from another species.

Tyrosinase is a melanosomal glycoprotein, essential in melanin synthesis and routinely found to be overexpressed in a wide variety of melanomas across species. Immunization with xenogeneic human DNA encoding tyrosinase family proteins induced antibodies and cytotoxic T cells against syngeneic B16 melanoma cells in C57BL/6 mice, but immunization with mouse tyrosinase-related DNA did not induce detectable immunity. In particular, xenogeneic DNA vaccination induced tumor protection from syngeneic melanoma challenge and autoimmune hypopigmentation. Thus, xenogeneic DNA vaccination could break tolerance

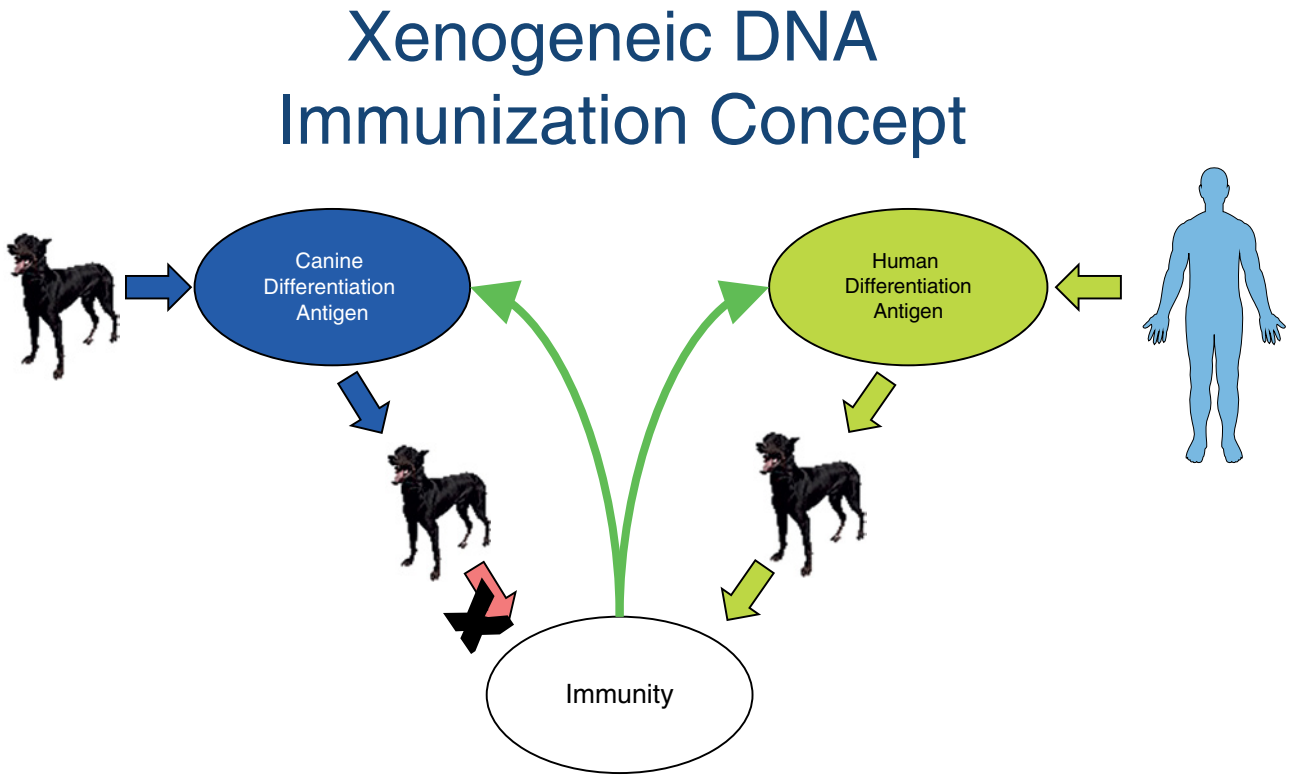


Figure 153.1 Xenogeneic DNA immunization concept.

against a self-tumor differentiation antigen, inducing antibody, T cell, and antitumor responses.

Dogs with stage I–III locoregionally controlled malignant melanoma receiving the xenogeneic melanoma vaccine have a Kaplan–Meier (KM) median survival time (MST) of >1075 days (median not yet reached) whereas those dogs with stage I–III CMM without local tumor control given the same vaccination have a KM MST of 553 days. Dogs which received the xenogeneic melanoma vaccine with stage I, II, III, and IV CMM had KM MSTs of >939 days (median not reached with 92.8% survival), >908 days (median not reached, 79% alive at one year, 63% alive at two years), >1646 days (median not reached, 77%, 65%, 57% alive at one, two, and three years), and 239 days (40.5% and 18.8% alive at one and two years), respectively.

The results of these trials demonstrate that xenogeneic DNA vaccination in CMM:

- is safe
- induces a specific antityrosinase immune response in some dogs
- potentially therapeutic in stage II–III locoregional controlled disease
- is an attractive candidate for further evaluation in an adjunct, minimal residual disease Phase II setting.

Based on these studies, a multiinstitutional safety and efficacy trial for USDA licensure in dogs with locally controlled stage II–III oral melanoma was initiated in 2006 with granting of conditional licensure in 2007, which represented the first US governmental regulatory agency approval of a vaccine to treat cancer across species. Results of this licensure trial documented a statistically significant improvement in survival for vaccinates versus controls and full licensure for the HuTyr-based canine melanoma vaccine from USDA-CVB was received in 2009 (Oncept™, Merial, Inc.).

We have also investigated the efficacy of local tumor control and use of xenogeneic DNA vaccination in dogs with digit malignant melanoma. These investigations led to the development of a canine digit melanoma staging scheme and found an improvement in survival compared to historical outcomes with digit amputation only. We also documented a decreased prognosis for dogs with advanced stage disease and/or increased time from digit amputation to the start of vaccination. Phillips and co-investigators have also recently reported the use of Oncept in horses and determined the safety and optimal use of the needle-free delivery device into the pectoral region in addition to documenting antigen-specific humoral responses after vaccination in all horses.

Human Melanoma Immunotherapy

A similar approach has been used in human patients with metastatic melanoma in the minimal residual disease setting. Although no clinical response data are available since these patients did not have measurable disease, several Phase I trials of xenogeneic DNA vaccines have been completed. Across studies of tyrosinase and gp100 DNA immunization, approximately 40% of patients develop quantifiable CD8+ T cell responses to the target antigen.

Two exciting new approaches which appear to confer a survival benefit in human metastatic melanoma are the use of the anti-CTLA-4 antibody ipilimumab (Yervoy^{TM}, Bristol-Myers Squibb) and the selective BRAF inhibitors vemurafenib (Zelboraf^{TM}, Genetech) and dabrafenib (GSK2118436, GlaxoSmithKline), in patients who are BRAF V600 mutation positive. As a small subset of dogs with malignant melanoma have exon 11 KIT gene mutations, the more routine use of KIT testing by polymerase chain reaction (PCR) of CMM and subsequent use of c-kit small molecule inhibitors (particularly in dogs with advanced stage disease and/or lack of response to Oncept) should be considered.

Canine malignant melanoma strongly appears to be a more clinically faithful therapeutic model for human melanoma when compared to more traditional mouse systems, as both human and canine diseases are chemoresistant, radioresistant, share similar peculiar metastatic phenotypes/site selectivity, and occur spontaneously in an outbred, immunocompetent scenario. It is hoped that in the future, this same vaccine may also play a role in the treatment of melanoma in other species (e.g., horses, cats, humans, etc.) due to its xenogeneic origins, and in melanoma prevention once the genetic determinants of melanoma risk in dogs are further defined.

Prognosis

Melanomas in dogs have extremely diverse biologic behaviors, depending on a large variety of factors. A thorough understanding of these factors helps the clinician to delineate in advance the appropriate staging, prognosis, and treatment options. The primary factors which determine the biologic behavior of an oral melanoma in a dog are site, size, stage, and histologic parameters. Unfortunately, even with a comprehensive understanding of all these factors, there are melanomas which have an unreliable biologic behavior; hence the need for additional research into this relatively common, heterogeneous, but frequently extremely malignant tumor. On divergent ends of the spectrum would be a 0.5 cm haired-skin melanocytoma, which is highly likely to be cured with simple surgical extirpation, in comparison to a 5 cm high-grade malignant oral melanoma with a poor to grave prognosis.

Similar to the development of a rational staging, prognostic and therapeutic plan for any tumor, two primary questions must be answered: what is the local invasiveness of the tumor and what is the metastatic propensity? The answers to these questions will ultimately determine the prognosis and appropriate therapies.

Anatomic Site

The anatomic site of melanoma is highly, though not completely, predictive of local invasiveness and metastatic propensity. Melanomas involving the haired skin which are not in proximity to mucosal margins often behave in a benign manner. Surgical extirpation through a lumpectomy is often curative, but histopathologic examination is imperative for delineation of margins as well as a description of cytologic features. The use of Ki67 IHC has been reported to more reliably predict potential malignant behavior compared to classic histology for cutaneous melanoma.

Oral and/or mucosal melanoma has been considered an extremely malignant tumor with a high degree of local invasiveness and high metastatic propensity. This biologic behavior is similar to the typically grave prognosis associated with human oral and/or mucosal melanoma. Two recent studies have called the veterinary portion of this dogma into question and suggest benign oral melanomas can occur more frequently than previously published. Caution is necessary when assessing histopathologic descriptions suggesting a benign course for oral melanoma as this author has seen approximately 25 dogs over the last 10 years presenting with florid systemic metastases with an original histopathologic report suggesting an expectation for a benign clinical course based on a high degree of differentiation. Similar to cutaneous melanoma, Ki67 appears to have prognostic import in canine oral melanoma.

Anatomic sites of intermediate prognostic significance between generally benign-acting haired-skin melanomas compared to often malignant and metastatic oral/mucosal melanomas in dogs include melanomas of the digit and footpad. Dogs with melanoma of the digits without lymph node or further metastasis treated with digit amputation are reported to have median survival times of ~12 months, with 42–57% alive at one year and 11-13% alive at two years. Unfortunately, metastasis from digit melanoma at presentation is reported to be ~30–40%, and the aforementioned outcomes with

surgery alone suggest that subsequent distant metastasis is common even when no metastasis is found at presentation or digit amputation. The prognosis for dogs with melanoma of the footpad has not been thoroughly established; this author has found this anatomic site to be anecdotally similar in metastatic propensity and prognosis to digit melanoma. Interestingly, human acral lentiginous melanoma (plantar surface of the foot, palms of the hand and digit) has an increased propensity for metastasis, suggesting further similarities between human and canine melanoma.

The most thorough review of prognostic factors in canine melanocytic neoplasms was published by Smedley *et al*. This review took a regimented, systematic approach to analyze published reports to date in order to identify those factors which appear to be repeatable and statistically defendable, while also identifying areas where additional work is necessary due to incomplete data.

Size and Stage

For dogs with oral melanoma, primary tumor size has been found to be extremely prognostic. The WHO staging scheme for dogs with oral melanoma is based on size and metastasis and is summarized in Box 153.1.

MacEwen and colleagues reported MST for dogs with oral melanoma treated with surgery to be approximately 17–18, 5–6, and three months with stage I, II, and III disease, respectively. More recent reports suggest that stage I oral melanoma treated with standardized therapies including surgery, radiation and/or chemotherapy has a MST of approximately 12–14 months, with most dogs dying of distant metastatic disease, not local recurrence. Other investigators have found dogs with stage I oral melanoma to have median progression-free survival times of 19 months, similar to the original MacEwen *et al*. report.

Box 153.1 TNM staging system

T = Primary tumor

T1 Tumor <2 cm in diameter
T2 Tumor 2–4 cm in diameter
T3 Tumor > 4 cm in diameter

N = Regional lymph nodes

N0 No evidence of regional node involvement
N1 Histologic/cytologic evidence of regional node involvement
N2 Fixed nodes

M = Metastasis

M0 No evidence of distant metastasis
M1 Evidence of distant metastasis
Stage I T1 N0 M0
Stage II T2 N0 M0
Stage III T2 N1 M0 or T3 N0 M0
Stage IV Any T, Any N and M1

Further Reading

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154

Nonmelanoma Skin Cancers

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Etiology/Pathophysiology

The skin is the largest organ in the body, and has a complex tissue structure made up of many cell types. Any of these cell types could give rise to a tumor. Some cells are more commonly affected by malignant transformation than others.

The skin is composed of layers, referred to as the epidermis and dermis. The epidermis contains stratified epithelium, while the dermis is largely composed of connective tissue, including collagen, extracellular matrix, fibrocytes, and fibroblasts. Within the dermis also reside adnexal structures such as sebaceous or eccrine glands, and the various cells that make up the hair follicles. Below the dermis, subcutaneous tissues largely contain adipocytes. Interspersed throughout the complex organ we call skin are cells of the immune system, which are present as either transient or permanent residents (lymphoid cells, macrophages, mast cells, Langerhans dendritic cells). Panniculus skeletal muscle, neurons and associated peripheral nerve sheath cells, vascular epithelium and hemangiopericytes, and the specialized neuroendocrine cells we know as melanocytes are all important to normal skin structure.

Thus, the number of potential histopathologic diagnoses for tumors of the skin is quite expansive. Skin tumors are generally classified as being of epithelial, mesenchymal, melanotic, or round cell type. Mesenchymal, melanotic, mast cell tumors, and cutaneous lymphoma will be discussed in other chapters.

The functions of this complex organ are also varied, and include prevention of water and electrolyte loss, thermoregulation, respiration, and sensory perception. A critical skin function is to provide a physical barrier to environmental insults, whether mechanical, chemical, osmotic, thermal, or microbiologic. As the front line of defense against environmental insults, the skin's most important defensive mechanism is its self-renewal and repair functions, which are dependent on the presence of both lineage-committed replicating cells and pluripotent stem cells. These replicating cells are subject to mutation as a consequence of repeated noxious environmental exposures, which may ultimately result in carcinogenesis.

Epidemiology

All cancers arise as a consequence of genetic predispositions and environmental exposures to carcinogens. The skin is at particular risk for environmental injury. As a tissue with cells that continuously replicate or that can be recruited to replicate, mutagenic induction followed by tumor cell promotion through repeated rounds of cell replication result in skin tumors of various kinds. Thus, cutaneous tumors are the most common type of neoplasia in both humans and dogs, although fortunately not all skin tumors are malignant.

Genetic contributions to skin carcinogenesis are evidenced by human familial hereditary syndromes, as well as by canine breed predispositions to specific tumor types. The skin is the most prevalent location for tumors in dogs, with an estimated 20–30% of these lesions being malignant. It is estimated that 25% of tumors of cats arise in the skin, and that 50–65% of these lesions are malignant. Excluding the common basal cell tumor of cats, which is generally benign, the incidence of malignancy in feline cutaneous tumors is estimated to be 70–80%. The estimated annual incidence of skin tumors in dogs and cats is 90.4 and 34.7 per 100 000 animals at risk, respectively, while for humans the annual incidence is reportedly 5.2/100 000 people at risk. Nonmelanoma cutaneous tumors are the most common malignant neoplasms affecting people in the United States, but fortunately are not the most fatal types of malignancy.

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In dogs and cats, basal cell tumors (also called trichoblastomas), epitheliomas, sebaceous adenomas, epidermal inclusion and other cysts, lipomas, and papillomas are the most prevalent benign tumors noted. Mast cell tumor is the most common malignant skin tumor in the dog, and is discussed in Chapter 155.

Trichoblastomas, which are more commonly still termed basal cell tumors, are the most common skin tumors of cats; approximately 15–26% of all skin tumors in cats are of this histology. Less than 10% of basal cell tumors in cats are malignant in behavior. When malignant, these lesions display a striking tendency toward lymphatic metastasis, which can result in a "chain of pearls" nodular progression up the draining lymphatics to the local lymph node. In dogs, poodles and setters are predisposed to basal cell lesions, which may be described by their histologic subtypes of ribbon, medusoid, trabecular, spindle, granular cell, and clear cell types. These lesions are now believed to arise from the germinal cells of the hair follicles, and are generally benign in behavior.

Dogs are commonly affected by benign tumors of glandular origin in the skin, although this is a rare occurrence in cats. Sebaceous hyperplasia, sebaceous adenoma, and sebaceous epitheliomas are very common in dogs. These lesions are most commonly benign and are rarely diagnosed as sebaceous gland carcinomas, which are generally locally aggressive and rarely metastatic. Benign lesions are often seen in female dogs (especially hyperplasia), with peak incidence in dogs 7–13 years of age. Miniature schnauzers, beagles, poodles, and cocker spaniels are breeds at increased risk, as are Nordic breeds, coonhounds, and terriers.

Apocrine gland adenomas and carcinomas arise from sweat glands in both dogs and cats. These lesions are rarely malignant but can be aggressive when transformed to carcinomas. Feline apocrine gland carcinoma lesions are seen primarily on the head, while benign lesions may be present on the head, limbs or abdomen of older cats. The front legs are the most common sites for canine apocrine gland carcinomas, with golden retrievers and coonhounds being predisposed breeds. Lesions are locally invasive with a predisposition to lymphatic spreading. Apocrine gland adenocarcinomas of the anal sac are discussed elsewhere.

Eccrine gland adenomas and carcinomas arise from specialized sweat glands of the footpads in dogs and cats and are exceedingly rare lesions.

Squamous cell carcinoma is common in both dogs and cats. This tumor of the skin is frequently caused by chronic ultraviolet light exposure in animals with white or fair skin and scant hair or fur covering. As sunlight is most damaging close to the equator and at high altitudes, these geographic regions of the globe have the highest incidence rates of cutaneous squamous cell carcinoma in both people and animals. Lifestyle and behavior contribute to sun exposure in all species of animals. Thus, white cats living largely outdoors are particularly vulnerable to cutaneous squamous cell carcinoma in sun-exposed areas of their head, including ear tips, nasal planum, lower eyelids, and the scantly furred preauricular area of the skin located between the ears and eyes on the lateral forehead. Siamese and other color-point breeds of cats are protected from cutaneous squamous cell formation by the pigment that is present in the exact facial areas that put white cats at risk. Similarly, dogs are most affected in areas of glabrous (nonhaired) skin that receive excessive sunlight exposure. This can occur when dogs "sunbathe" by lying on their back or sides in full sun. Outdoor dogs with no pigment in glabrous skin regions are most at risk. Thus, Dalmatians, pointers, pit bulls, bull terriers, and other dogs with white or pale skin on the ventral abdomen, prepuce, and medial thighs may suffer actinic dermal injury that can ultimately transition to squamous cell carcinoma. Dermal hemangioma and hemangiosarcoma lesions may similarly arise in areas of excessive ultraviolet light exposure.

In addition to physical carcinogenesis from ultraviolet light exposure, there is also a viral etiopathogenesis associated with causation of cutaneous squamous cell carcinoma. Papillomavirus infection in cats may cause the feline equivalent of a human syndrome called Bowen disease, which is a term used to identify multicentric cutaneous squamous cell carcinoma *in situ*. This form of squamous cell carcinoma occurs most frequently in haired skin and has no predilection to arise in nonpigmented areas of the body. These lesions can be seen as crusty, scabbed dermal lesions of the head, neck or trunk of affected cats. Papillomavirus is also associated with the development of feline fibropapillomas called feline sarcoids. Interestingly, cats have been found to be susceptible to human papillomaviruses 5, 21, and 38, which were discovered by polymerase chain reaction (PCR) analysis of papilloma lesions in several cats.

Dogs also harbor papillomaviruses, which may be involved in the causation of oral, footpad, and cutaneous papillomas, and potentially even in squamous cell carcinomas. These lesions are particularly observed in dogs that are immunocompromised.

Breed association is noted in dogs affected by tumors of adnexal skin structures. Infundibular keratinizing acanthomas are common benign tumors of dogs. Synonyms for these tumors include intracutaneous keratinizing epitheliomas, keratoacanthomas, and intracutaneous cornifying epitheliomas. Breeds at risk for these benign lesions include Norwegian elkhounds and other Nordic breeds, German and Belgian shepherd dogs, various terriers, and the Lhasa apso. These lesions are benign and generally cured by local excision, although they are frequently seen as multiple lesions.

Trichoepitheliomas are tumors that demonstrate differentiation into elements of the hair follicle, and are seen on the limbs, neck, and back of bassett hounds, coonhounds, setters, and English springer spaniels. These are rarely malignant, and are referred to as malignant trichoepitheliomas or metrical carcinomas in those rare cases.

Pilomatricomas are tumors of hair matrix cells, and are also benign in general. Kerry blue, soft-coated wheaten, and Airedale terriers are the most affected, as are standard poodles, bichon frise, old English sheepdogs, and bouviers des Flandres. These lesions may ulcerate and ossify. While these lesions are rarely malignant, they are reported to be highly metastatic when malignant transformation occurs.

Neuroendocrine tumors of the skin are referred to as Merkel cell tumors. They are thought to arise from mechanoreceptors in the skin, and are also rare in dogs and cats. While these tend to be highly malignant in humans, they are more benign in dogs.

Ear canal tumors can be classed with skin tumors as a continuous cutaneous organ. Most commonly seen are ceruminous gland adenomas and carcinomas. Ceruminous glands are modified apocrine glands localized to the ear canal. Other tumors of the ear canal include squamous cell carcinomas, basal cell carcinomas, mast cell tumors, histiocytomas, sebaceous gland tumors, plasma cell tumors, melanomas, and various sarcomas. Benign polyps arising in the ear canal are also noted, particularly in young cats.

Signalment

Most cutaneous tumors arise in aged animals, as it can take a lifetime of exposure to environmental carcinogens, coupled with geriatric waning of immune surveillance, to allow tumors to manifest. Occasionally skin tumors will arise in younger animals, particularly in cats affected by retroviruses or feline papillomavirus. There is generally no sex predisposition in the development of skin cancer. Many specific histologic types of skin cancer, particularly those arising in adnexal structures, are breed associated, as described in the section on epidemiology.

History and Clinical Signs

In most cases, the first sign of skin tumor development is the presence of a mass. Masses may be indolent in their growth pattern or may be rapidly progressive. Skin tumors are generally nonpainful, unless infection or inflammation occurs. Basal cell tumors tend to be slowly growing or static in growth pattern, and may be alopecic, ulcerated, and of blue-black or pink color. Cysts and sebaceous adenoma lesions may rupture or become infected, and thus may wax and wane in size. In many cases, owners assume that squamous cell carcinoma on the nose of a cat is a result of an infected fight wound. In these cases, there is a wound that fails to heal properly, and is intermittently scabbed or open and bleeding. Similarly, dermal hemangiosarcomas arise in areas of actinic injury, with a clinical appearance of small red spots or "blood blister" lesions that may bleed or become invasive.

Diagnosis

Diagnosis of skin tumors is by cytology or biopsy. Because these patients are often older, a minimum database (complete blood count, serum chemistry panel, and urinalysis) is helpful in anesthetic planning. However, skin tumors are not typically associated with paraneoplastic syndromes that could be detected on bloodwork. Interestingly, humans affected by squamous cell carcinoma may have hyperglobulinemia that is of polyclonal nature and directed against specific cytokeratins. Hyperglobulinemia may be noted in cats with sunlight-induced squamous cell carcinoma as well, although it is clinically insignificant.

The method of biopsy is determined by size and location of the lesion. Small superficial lesions may be best managed by excisional biopsy, which can be both diagnostic and therapeutic. Larger lesions may require incisional biopsy to allow for surgical or radiation treatment planning. Advanced local imaging with computed tomography (CT) or magnetic resonance imaging (MRI) may be helpful in determining the full extent of the lesion to be addressed.

Carcinomas of the skin may merit clinical staging with lymph node aspiration cytology or lymph node biopsy and thoracic radiographs. Abdominal staging may be considered in cases with malignant lesions on the caudal portion of the body, where lymphatic spread to intrapelvic or intraabdominal node sites may occur. Lymphadenomegaly should be investigated with cytology or biopsy. Pulmonary metastasis is rarely seen in dogs with skin cancer, although squamous cell carcinoma (SCC), malignant pilomatricomas, sebaceous gland carcinomas, apocrine gland carcinomas, and neuroendocrine carcinomas have the potential to metastasize.

Ear canal tumors often cause pain, malodorous discharge, difficulty opening the mouth and neurologic signs such as facial palsy and vestibular signs. These signs may lead to delayed diagnosis of tumor, as patients may undergo protracted periods of treatment of suspected otitis before biopsy diagnosis is obtained.

Ear canal tumors often require advanced imaging studies to determine operability and extent of surgery necessary, or to plan for radiotherapy adjunctively or as primary treatment of nonresectable, invasive lesions.

Therapy

Most skin tumors are best addressed by local surgical excision. Benign lesions of the skin can be excised with modest margins to affect a cure in most cases. Surgical excision allows for accurate diagnosis, histologic grading, and surgical margin assessment, which can guide further adjunctive therapy if necessary. However, surgery can be disfiguring, particularly when the lesion arises on the head and face. Squamous cell carcinoma of the ear tips can be managed by pinna amputation in cats. Nasal planum resection can also be curative in cats, although surgery of SCC of the nasal planum in dogs is often unsuccessful in controlling local disease. Surgery is always the best primary modality for treatment of any cancer, but owners may balk at the degree of disfigurement the dog or cat experiences with nasal planum resection.

Serial resection of squamous cell carcinoma or hemangiosarcoma, while still small, dermal and arising on glabrous skin, is recommended for dogs with field carcinogenesis from sunlight exposure. Highly invasive or large field lesions of the ventral abdomen, prepuce, and medial thighs of such dogs may be less amenable to surgical excision. In these cases, radiation therapy delivered to the local tumor site, or tumor site plus regional nodes, may be curative. Radiation therapy for skin tumors may involve traditional fractionated megavoltage irradiation with curative intent, or may be delivered as palliative fractionated therapy. Superficial radiation, such as delivered through topical plesiotherapy using a strontium-90 probe, is highly effective for small, noninvasive lesions. Photodynamic therapy utilizing laser light to activate photosensitizing agents is a common treatment for human skin cancer patients, although the technology is less readily available to veterinary medicine.

Ear canal tumors generally require surgical excision, which may entail vertical canal ablation in the case of superficial benign tumors, but more likely requires a more aggressive surgical approach with total ear canal ablation and lateral bulla osteotomy. Extensive surgery was associated with long median survivals in both dogs and cats (>36 months and 50.3 months, respectively). Mitotic rate was prognostic for a series of ear canal tumors, with a mitotic index of 2 or less being more favorable. Radiation therapy may be required for patients with incompletely resected tumors of the ear canal, regardless of histologic type of tumor.

Topical 5% fluorouracil cream may be applied to superficial squamous or basal cell lesions in dogs, as is the common practice in human dermatologic oncology. This agent is applied topically twice daily by gloved finger or cotton swab applicator for 3–6 weeks. Significant local irritation and inflammation are seen as part of the therapeutic response. Dogs should be prevented access to the treated site, as licking the topical cream can be harmful to oral mucosa and may be toxic systemically. Critically, fluorouracil should *never* be applied to cats, as even topical application can result in lethal neurotoxicity in this species.

Topical immunotherapy for superficial squamous cell carcinomas may be attempted. Imiquimod 5% cream is a nonspecific active immunotherapeutic agent that induces a strong macrophagic response when topically applied. This immunostimulant causes inflamed, crusted and scabbed lesions to arise in the treated area, which is the basis of the therapeutic effect. Imiquimod is applied topically to superficial lesions once daily, or in sensitive cases three times weekly, for 3–6 weeks.

Intralesional therapy with chemotherapy in sesame oil or purified bovine collagen matrix for depot delivery has also been described in the literature. Agents such as carboplatin, cisplatin, bleomycin, and fluorouracil have all been introduced intratumorally with sometimes striking results.

Systemic therapy with retinoic acid derivatives such as 13-cis-retinoic acid or isotretinoin has been attempted as a cellular differentiation or cytotoxic strategy in canine and feline skin tumors, particularly squamous cell and infundibular keratinizing acanthoma (keratoacanthoma). Retinoid therapy has been reported in the literature to have mixed success.

The use of COX-2 inhibitors has shown modest efficacy in treatment of squamous cell carcinomas of the oral cavity, and thus may be helpful in cutaneous SCC treatment as well. The COX-2 inhibitor nonsteroidal antiinflammatory drugs (NSAIDs) have both antiangiogenic and immunomodulatory effects, and are generally helpful in pain control for veterinary patients. Similarly, the newer class of agents called receptor tyrosine kinase inhibitors (toceranib, masitinib, imatinib) are inhibitors of cell signaling. These agents are promiscuous receptor signaling blockers and may modulate tumor regression through inhibition of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors, thus acting as antiangiogenic agents. The therapeutic concept referred to as metronomic chemotherapy employs smaller daily or alternate-day dosing of NSAIDs, low-dose cytotoxic agents such as cyclophosphamide, chlorambucil, or lomustine, often combined

with receptor tyrosine kinase inhibitors, to inhibit normal stromal cells that support neoplastic growth. Little information is currently available about the use of daily, low-dose combination metronomic chemotherapy in canine and feline skin or ear canal tumors.

Papilloma lesions may be addressed through the creation of an autologous vaccine. This approach is best used in dogs with multicentric papillomas, as is sometimes seen in dogs that have been heavily immunosuppressed in the transplant or autoimmune disease setting, or in dogs with immunosuppression from T-zone lymphoma. In this approach, 1–3 g of papilloma tissue are harvested from the dog and macerated in a tissue grinder or mortar and pestle along with 10 mL of sterile 0.9% saline. To this mixture is added 1 mL of neutral buffered formalin, which inactivates live virus as well as altering the structure of viral oncoproteins to facilitate immune recognition. The mixture is refrigerated for three days, and then sieved through sterile cheesecloth or a large-gauge filter to remove residual particulate material. The resultant autologous vaccine can be stored in the refrigerator in 1 mL sterile aliquots for future treatment. An immune adjuvant such as Immunocidin® (*Corynebacterium parvum* derivative), squalene, or BCG is added before injection into the residual papilloma lesions. This treatment can be repeated at weekly intervals until lesion regression is noted. There is no literature regarding use of commercial papillomavirus-preventive vaccines in the therapeutic setting.

Systemic chemotherapy or local electrochemotherapy has been attempted for aggressive or metastatic dermal carcinomas. Relatively few agents have been used in this setting, and results are generally anecdotal and not well documented. Cisplatin, carboplatin, bleomycin, actinomycin D, and mitoxantrone have all been used sporadically, with modest response rates noted in the literature. Local drug delivery enhanced by electrochemotherapy may increase the local efficacy of these cytotoxic agents.

Prognosis

The prognosis for patients with localized tumors of the skin, adnexal structures, or ear canals is generally highly favorable. Many lesions are benign and early detection is possible because of the superficial location of the tumors, and ear canal tumors are frequently localized to within the cartilaginous structures of the ear canal, which facilitates complete resection. Thus, most dogs and cats affected by skin or ear canal tumors are cured by surgical excision alone. Exceptions are noted in cases of malignant skin neoplasia, particularly when metastasis to nodes or distant sites is observed. Radiation therapy can be helpful for large or nodally involved lesions, as described earlier.

The most common aggressive skin tumors discussed here are squamous cell carcinomas, which have median survivals of 1–2 years with aggressive surgery and/or radiation therapy in both dogs and cats. The exception to this observed survival rate is in the case of nasal planum squamous cell carcinomas in dogs, which are both locally aggressive and metastatic to regional nodes, and have a poorer overall outcome despite aggressive therapy.

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155

Mast Cell Neoplasia

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Etiology/Pathophysiology

Mast cells are part of the normal canine, feline, and human immune system. They primarily exist throughout the skin, lungs, and intestinal tract but are rarely found within peripheral blood.

Mast cells arise from pluripotent hematopoietic stem cells of the bone marrow. Once mature, their cytoplasm contains a large amount of metachromatic granules. These granules contain a variety of substances including histamine, serotonin, platelet activating factor, eosinophilic chemotactic factor, and heparin, among others. In addition, mast cells produce a variety of cytokines that include interleukin (IL)-1, IL-3, IL-4, IL-5, IL-6, and tumor necrosis factor (TNF)-alpha.

The etiology for canine mast cell tumor development is unknown partially because there is no clear human model to provide key predictors.

Canine Mast Cell Neoplasia

Epidemiology

Canine mast cell tumor (MCT) is the most common skin tumor in dogs, representing upwards of 15–20% of all skin tumors. They are one of the most common tumors seen in practice.

Signalment

Mast cell tumor development has clear breed predispositions that include most brachycephalic breeds (boxer, Boston terrier, and pug), Labrador and golden retrievers, pit bull terriers, and shar-peis. There is no reported sex predilection and the mean age of diagnosis is 8.2 years. Clinically, all breeds are capable of developing MCT. While tumors are more often noted in middle-aged to older dogs, the author has seen numerous cases of MCT in juveniles less than 1 year of age.

History and Clinical Signs

Most dogs with a MCT present with a single dermal lesion. Twenty percent of all dogs, and specifically breeds that are predisposed, may present with multiple tumors. The history may include a nonpainful mass that increases and decreases in size. Physical manipulation of the tumor can result in a rapid increase in size due to traumatic local release of histamine (degranulation). Darier's sign is the dermatologic description of wheal formation, local erythema, and/or bruising secondary to manipulation of the tumor. Most MCTs are clinically quiescent and are discovered on routine physical exam by the veterinarian or owner.

Mast cell tumors occur predominantly in the dermis and are most commonly noted on the trunk and limbs. A less commonly noted form, at mucocutaneous sites (mouth, nasal planum, perirectal region), tends to have a more aggressive clinical behavior (Figure 155.1). Additionally, a lesser percentage of MCTs occur in the subcutaneous tissue and many have a clinical appearance consistent with a lipoma.

Primary visceral mastocytosis is a very rare condition in dogs. The disease has a predisposition for the intestinal tract in older (>8 years) miniature-breed dogs. Two independent studies have identified the Maltese breed as having a predisposition to the intestinal form. Clinical signs are typical of most primary gastrointestinal pathology.

Diagnosis

Cytology of the lesion is diagnostic for a MCT. Because of the clinical inefficiency and additional cost, premedication with an antihistamine prior to fine needle aspiration of a simple dermal mass less than 5 cm in

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Figure 155.1 A MCT at the mucocutaneous junction of the nasal planum. Tumors in this location often are biologically more aggressive with increased metastatic potential.

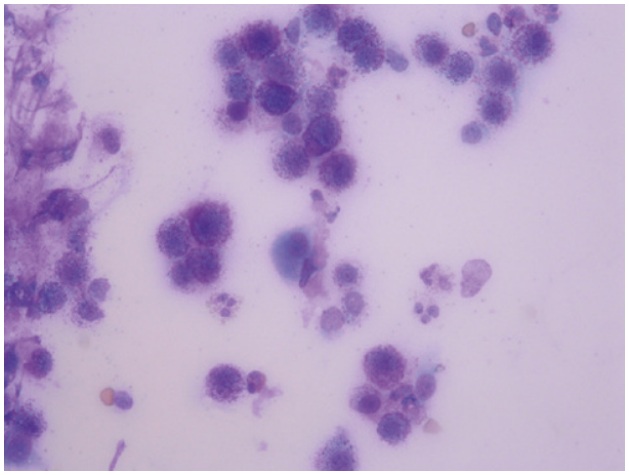


Figure 155.2 Mast cells seen at 40× with varying amounts of metachromatic granules throughout the cytoplasm.

diameter is not indicated. While Darier's sign may develop, significant systemic histamine effects are highly unlikely with simple dermal lesions. Cytology of larger masses, or more vascular organs like lymph node and spleen, does justify systemic protection with antihistamines.

Mast cells are mononuclear round cells with a significant amount of cytoplasm containing metachromatic granules. For comparison, mast cells range in size between a neutrophil and macrophage. Diff-Quik staining techniques are usually adequate in accentuating the diagnostic granules (Figure 155.2). When collecting samples, it is important to save an unstained slide for alternative staining techniques (i.e., Wright's) if mast cells are suspected but granules are not identified with Diff-Quik stain. Without appropriate staining, these poorly granulated

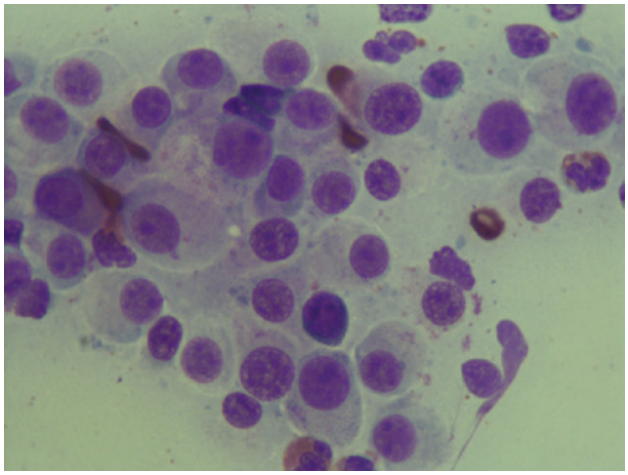


Figure 155.3 A population of Diff-Quik stained round cells at 40×. Notice the lack of consistent granules and cellular atypia (multiple nucleoli, varying N:C ratio, etc.). Alternative cytologic staining techniques (Wright's) are more adept at identifying the granules in high-grade MCT.

tumors may result in a cytologic diagnosis of "round cell tumor" (Figure 155.3). It is important to remember that cytology is ineffective in grading a MCT but the level of cellular pleomorphism may provide clues to the biologic behavior of a tumor.

Staging is important as both prognosis and treatment options are intimately dependent on it (Box 155.1). Initial staging of a MCT is dependent on physical exam findings. Close attention should be paid to the regional draining lymph nodes and organomegaly (hepatic and/or splenic).

Regional lymph nodes, regardless of size, should be cytologically evaluated for metastasis. The determination of lymph node metastasis via cytology is very sensitive but has a low specificity due to the inability to distinguish normal, responsive mast cells from malignant cells. Metastasis can be accurately confirmed if mast cells are the predominant cell type. Additionally, most pathologists will declare a node metastatic if the mast cells are noted in clumps or sheets and/or have marked cellular atypia. Biopsy or removal of the lymph node is recommended if there is an increase in the numbers of well-granulated mast cells but no other signs supportive of metastasis. Recent evidence supports that dogs with no metastasis to regional nodes had a 0% chance of distant metastasis.

Abdominal ultrasound is recommended for dogs with a high-grade MCT or proven lymph node metastasis. While a full abdominal ultrasound is encouraged, focus should rest on the liver, spleen, and lymph nodes (mesenteric, medial iliac, and sublumbar nodes). All abnormal lesions of the liver and spleen should be cytologically evaluated. Two independent studies confirmed that cytology of ultrasonographically normal

Box 155.1 Staging for mast cell tumors

WHO clinical staging system for canine mast cell tumors

Stage 0: Microscopic incomplete excision of any dermal MCT with no evidence of regional nodal or distant metastasis

Stage 1: A single MCT confined to the dermis with no evidence of regional nodal or distant metastasis

a) no clinical signs
b) clinical signs

Stage 2: A single MCT confined to the dermis with regional lymph node metastasis

a) no clinical signs
b) clinical signs

Stage 3: Multiple dermal MCT, any tumor invading local tissue with or without regional nodal metastasis

a) no clinical signs
b) clinical signs

Stage 4: Any MCT with confirmed distant metastasis

Modified WHO clinical staging criteria for canine mast cell tumors

Stage –1: Single MCT completely removed and no evidence of regional nodal metastasis
Stage 0: Microscopic incomplete excision of a single MCT with no evidence of regional nodal metastasis
Stage 1: A single MCT completely removed
Stage 2: Microscopic incomplete excision of a single MCT
Stage 3: A single MCT completely removed with positive regional node metastasis *in situ*
Stage 4: Microscopic incomplete excision of a single MCT with positive regional node metastasis *in situ*
Stage 5: MCT recurrence or positive distant metastasis

liver and spleen does not influence treatment or survival estimates.

While historically pursued, bone marrow aspiration for staging may no longer be indicated for a patient diagnosed with their first MCT or with no clinical evidence of lymph node metastasis. For these dogs, the incidence of bone marrow involvement is low (2.8%). This low yield, combined with cost, invasiveness of the procedure, and ability to prove distant metastasis on more routine testing (abdominal ultrasound), suggests that bone marrow aspiration may not be necessary for every patient. However, bone marrow metastasis/distant metastasis is a significant prognostic indicator and dogs with a recurrent MCT or which develop subsequent MCTs may have a higher incidence (18.7%).

Pulmonary metastasis is rare and sporadically reported for MCT. Consequently, thoracic radiography is not considered part of routine staging but may be helpful in assessing concomitant disease processes (cardiovascular, respiratory, etc.).

The most important prognostic indicator is the grading scheme. Tumor grade is determined by histopathologic features. Incisional biopsy is rarely recommended for a MCT due to the diagnostic capability of cytology and the increased potential for wound dehiscence secondary to both histamine and heparin release from the remaining tumor cells. If cytology is nondiagnostic, incisional biopsy should be minimal in size and in an area of minimal inflammation or necrosis. The incisional site should be easily excised in its entirety when the mass is removed. Overall, excisional biopsy is superior for both diagnostic and therapeutic purposes.

The Patnaik grading scheme is the most well known and used in pathology reports. Tumors are divided into three grades (I, II, and III). Grade I tumors have an indolent behavior with a metastatic potential of near 10%. Grade III MCTs are exceptionally aggressive with a metastatic rate of 80%. Grade II MCTs are by far the most common diagnosis. These tumors can behave similarly to both grade I and III and have a metastatic potential near 20%. Clinically, this grading scheme is very helpful for grade I and III lesions, but less predictive for grade II tumors.

As the vast majority of MCTs are in the grade II category, many clinicians struggle with interpretation and prognosis. Consequently, a recent collaboration of pathologists and oncologists proposed a new grading scheme. Kiupel *et al.* offered a two-tiered system composed of a low-grade and high-grade MCT. First, this study found an improved interpathologist agreement compared to the Patnaik scheme. Second, distinction between the two grades is based on a scoring system that evaluates mitotic index, karyomegaly, multinucleated cells, and bizarre nuclei. It is imperative to always request a microscopic description with mast cell histopathology as these characteristics are evaluated by that grading scheme. Low-grade MCTs (the majority of previously diagnosed grade I and IIs) have minimal metastatic potential and a median survival time of greater than two years. High-grade MCTs have a median survival time of less than four months due to the metastatic behavior of these tumors. To further aid clinical decisions, many diagnostic labs have started to report both grading systems in their histopathology reports.

Attempts have been made to link histologically determined cellular proliferation markers to MCT prognosis and clinical behavior. Proliferating cell nuclear antigen (PCNA), argyrophilic nucleolar organizing region-associated proteins (AgNORs), and the proliferation protein Ki-67 have all been evaluated with mixed results. Mitotic index has been repeatedly shown to have the most prognostic value and is required as part of the initial histopathology report. Tumors with a mitotic index of >5/10 hpf should be treated prognostically as high-grade MCTs.

Evaluation of c-kit mutation has prognostic utility but only when closely linked to histopathologic grade. More importantly, the presence of c-kit overexpression or mutation indicates a tumor that is more likely to be responsive to the new tyrosine kinase inhibitor class of drugs.

Therapy

The systemic toxicity of a MCT often requires treatment. Histamine is the compound found in mast cell granules that results in the most significant clinical changes. Activation of histamine receptors (H1 and H2) can lead to toxicity. Severe anaphylactic reactions are a result of systemic H1 receptor activation and can be treated with diphenhydramine and corticosteroids. In times of crisis, intravenous use of steroids is recommended. As a vasoactive molecule, histamine may also lead to marked hypotension which could require both colloidal and crystalloid support. H2 is more responsible for stimulation of gastric acid. Excessive H2 activation can lead to gastric ulceration and clinical side-effects that include anorexia, nausea, hematemesis, and melena. Routine H2 receptor antagonists such as famotidine and ranitidine can be effective but proton pump inhibitors (omeprazole) appear to be more potent at reducing gastric acid production and aiding healing of ulcers.

Currently, the author only recommends oral preventive diphenhydramine and famotidine (at routine dosing) for patients with documented MCT metastasis or tumor volumes greater than 5 cm in diameter.

Various components within mast cell granules are also responsible for delays in wound healing. This phenomenon is most commonly appreciated during incisional biopsy techniques. Wound failure is often noted within the first 3–5 days postoperatively.

Heparin is also released from mast cell granules. Coagulopathies are rare with MCTs as evidence suggests there is less heparin in malignant MCTs than in normal mast cells. Clinically, increased bleeding at the surgical site of a MCT is the most common coagulopathy noted.

Surgical removal of all MCTs is considered standard of care. Surgical removal of the lesion should include at least 2 cm of healthy tissue lateral to the lesion and one fascial plane deep to the tumor. Prior to pathology submission, it is recommended to mark margins with either suture or ink. Histopathology reports should comment on the surgical margins.

Many tumors are large or in too difficult of a location for a reasonable expectation of complete removal. A short trial (10–14 days) of antiinflammatory prednisone (1 mg/kg/day) can often result in significant tumor reduction. A recent study found that 70% of all MCTs treated with presurgical prednisone responded to therapy. The median reduction in tumor diameter was 45% with a median total tumor volume reduction of 80%. Tyrosine kinase inhibitors are also used to reduce tumor volume for surgery in situations where prednisone does not result in a significant response. When surgically amendable, these medications are not selected as the primary treatment due to their possible toxicities and cost (Figure 155.4).

For low-grade (both Kiupel grade I and the majority of Patnaik grade II) MCTs with no evidence of metastasis, complete surgical removal is considered curative and no adjuvant therapy is indicated.

Often, clinicians must determine treatment plans based on narrow tumor-free margins of 1–5 mm. Tissue specimens will constrict during processing. Adjuvant treatment is indicated if surgery is incomplete and tumor cells extend to the surgical margins. There are no clear guidelines for "narrow" surgical margins (1–5 mm) and each case should be evaluated uniquely. The author is usually more aggressive in adjuvant treatment recommendations for tumors with ≤1 mm clean margins as they have a higher potential to reoccur.

Numerous studies have suggested that there is a subset population (20–70%) of cutaneous MCTs that do not reoccur when tumor cells extend to the surgical margins. Theories include the lack of tumor volume resulting in a decrease in progrowth cancer signaling. The small tumor volume may also be amenable to self immune defense. Additionally, there is some belief that the peripheral mast cells in a tumor are normal mast cells that respond to chemotactic factors released by the tumor. When the tumor is removed and the signals are interrupted, the normal mast cells vacate the area.

Currently, there is no way to determine which low-grade MCT will reoccur. Thus, all incomplete excisions should be treated the same. An additional surgery is the ideal treatment and should be considered if there is adequate local skin for wound closure. For incompletely removed low-grade tumors that cannot be excised, radiation offers a 90% curative outcome. Radiation protocols usually entail a total of 45–55 Gy dispersed evenly over 18–22 total fractions or treatments. Although not evaluated in this adjuvant setting, hypofractionated radiation may also offer added benefit over monitoring alone.

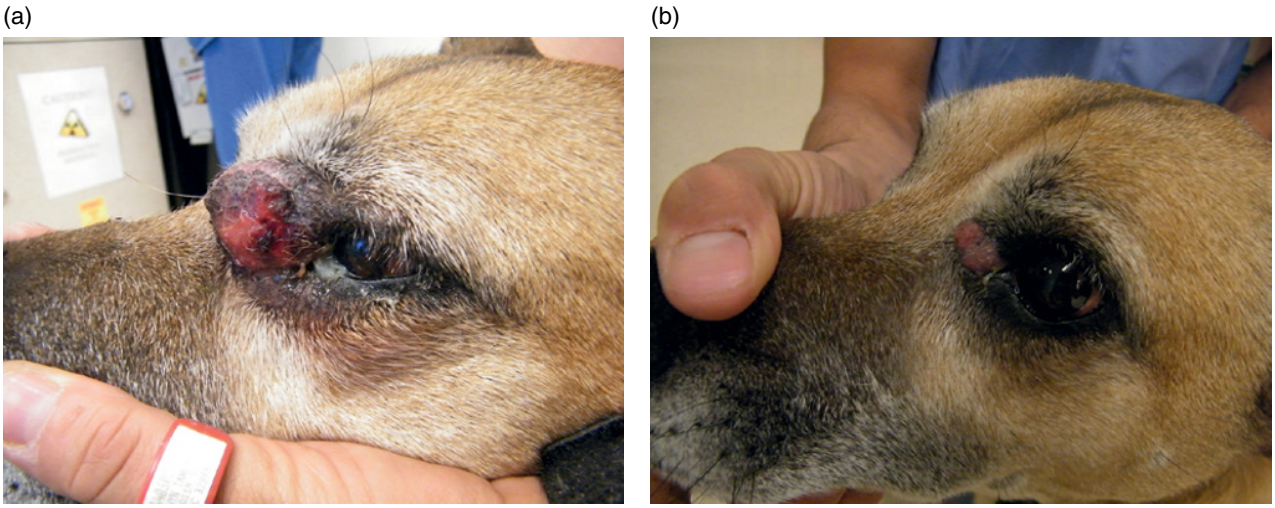


Figure 155.4 (a) A female mixed-breed dog at initial presentation with a MCT of the medial aspect of the upper eyelid. Enucleation of the eye was initially recommended. (b) The same patient after one month of tyrosine kinase therapy. Surgical margins were achieved with aggressive local excision without enucleation.

Either surgical removal or radiation of the draining lymph nodes should be considered for cases where regional node metastasis is confirmed (stage III).

There are a variety of chemotherapy treatment options for a MCT. The European consensus statement on MCTs indicates that chemotherapy is used to treat metastatic disease to either regional lymph nodes or distantly; when radiation or surgery are not available or possible; and as a neoadjuvant to reduce tumor burden prior to more traditional surgery or radiation. It is important to understand that chemotherapy does not offer the same curative results as radiation or surgery and should not be used as a convenient alternative to these modalities.

Prednisone has the longest history of use against MCTs. It is unclear if the effects of prednisone are truly cytotoxic or simply aid in reducing peritumoral edema and inflammation secondary to histamine release. A popular theory suggests that glucocorticoids block stem cell factor release from regional epithelial cells and fibroblasts. Stem cell factor is a known activating protein of the KIT pathway which is often mutated in MCTs. Antiinflammatory dosing of prednisone at 1 mg/kg/day is considered sufficient for MCTs. Immunosuppressive doses have not been found to be more effective and only increase the risk and severity of prednisone-induced side-effects.

Traditional chemotherapy options include the vinca alkaloids vinblastine and vinorelbine, the alkylating agent lomustine, and a taxane, paclitaxel. Both lomustine and vinblastine have an overall response rate of 40–50%. Recently, the drugs were combined with prednisone (Tables 155.1 and 155.2) and achieved an overall response

Table 155.1 CVP combination protocol as initially noted in Rassnick *et al*.

Week	Protocol
Week 1	Prednisone 2 mg/kg/day Lomustine 70 mg/m^2 PO
Week 3	Prednisone 1 mg/kg/day Vinblastine 3.5 mg/m^2 IV†
Week 5	Prednisone 1 mg/kg every other day until week 24 Lomustine 70 mg/m^2 PO
Week 7	Vinblastine 3.5 mg/m^2 IV
Week 9	Lomustine 70 mg/m^2 PO
Week 12	Vinblastine 3.5 mg/m^2 IV
Week 15	Lomustine 70 mg/m^2 PO
Week 18	Vinblastine 3.5 mg/m^2 IV
Week 21	Lomustine 70 mg/m^2 PO
Week 24	Vinblastine 3.5 mg/m^2 IV Taper off prednisone over 4 weeks

IV, intravenous; PO, by mouth (*per os*).

Table 155.2 Alternating lomustine and vinblastine protocol as initially noted in Cooper *et al*.

Week	Protocol
Week 1	Lomustine 60 mg/m^2 PO
Week 3	Vinblastine 2.0 mg/m^2 IV
Repeat for 4-6 cycles pending response	

IV, intravenous; PO, by mouth (*per os*).

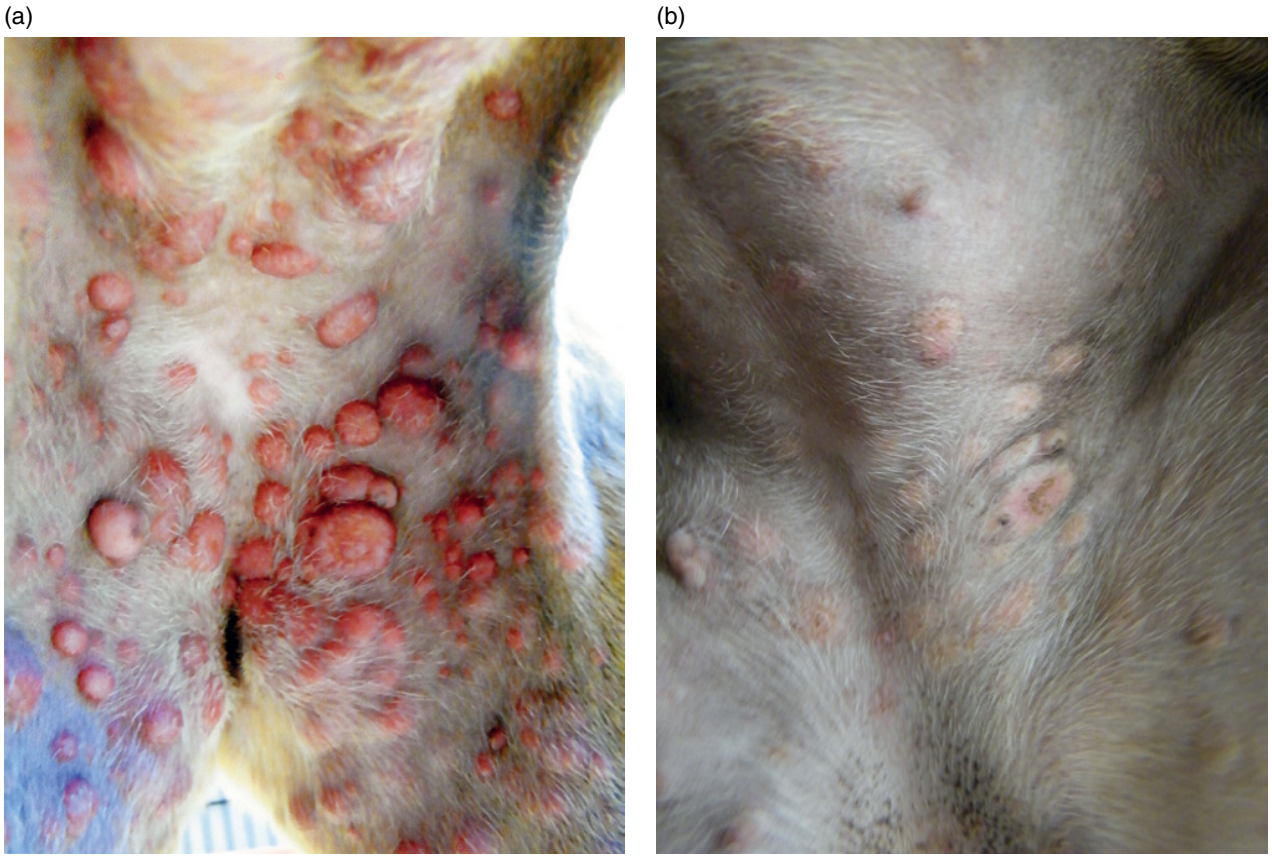


Figure 155.5 (a) A female boxer at presentation with over 300 dermal MCTs. (b) The same patient after two weeks of tyrosine kinase therapy.

of 65%. The micellar prepared paclitaxel has shown promise against MCTs but is not yet commercially available. The current formulation of paclitaxel (suspended in cremophor) has a marked increased risk of anaphylaxis during administration.

The tyrosine kinase receptor KIT is mutated and/or overexpressed in up to 40% of MCTs. These tandem duplication mutations at the juxtamembrane coding region result in the malignant behavior of cellular proliferation, adhesion, migration, and maturation. Consequently, KIT mutations have been found more commonly in higher grade MCTs.

Recent advancements in MCT treatments have led to the development of tyrosine kinase inhibitors. These drugs block the effects of mutated KIT receptors through competitive inhibition. Toceranib phosphate (Palladia™, Zoetis) is the first FDA-approved treatment for canine MCTs. It is labeled for the treatment of recurrent or nonsurgical high-grade mast cell tumors. Additionally, masitinib (Kinavet®, AB Science) achieved European regulatory approval under similar label guidelines but recently lost licensure by the FDA and is no longer available for use in the United States.

The reported efficacy of Palladia is near 40% (Figure 155.5). Palladia may be used for all grades of MCT but is more effective against MCTs with the known KIT mutation. The labeled dose of 3.25 mg/kg every other day results in significant gastrointestinal toxicity, myalgias, and neutropenia. Most clinical oncologists now prefer a lower dose of 2.5–2.75 mg/kg on a Monday-Wednesday-Friday treatment schedule. Oral famotidine and sucralfate may eliminate low-grade nausea or anorexia. Diarrhea is routinely treated with standard doses of loperamide. Protracted or severe clinical signs require a temporary discontinuation (drug holiday) of the medication until clinical improvement. Routine complete blood counts are recommended over the first six weeks of therapy. Therafter, a complete blood count chemistry panel and urinalysis are recommended approximately once every six weeks for patients that remain on tyrosine kinase inhibitors. Mild (grade I and II) neutropenias are commonly noted and do not require additional therapy or dosing alterations. However, patients should be monitored for progression. Idiosyncratic elevations in liver enzymes, hypertension and protein-losing nephropathies are also reported.

Adjuvant therapy with vinblastine/lomustine or Palladia for high-grade MCT is recommended even if the mass has been completely excised. Most adjuvant treatment protocols strive for 3–6 months of therapy, depending on tumor response and the patient's tolerance. In the adjuvant setting, chemotherapy results in median overall survival times of 11–16 months.

Prognosis

Multiple factors have prognostic value for canine MCTs. A subset of tumors have a more aggressive behavior based on their anatomic location. MCTs of the inguinal region (groin, perivulvar, scrotal, perianal) have historically been regarded as having greater metastatic potential. Newer information has revealed that survival is dependent on histologic grade. However, dogs with MCTs in these locations, specifically preputial and scrotal, have a decreased disease-free interval as both local recurrence and the development of subsequent MCTs are common. The biologic behavior of tumors in these areas is still debated so it is reasonable to use caution and proceed with routine MCT staging and more routine follow-up regardless of grade.

Mucocutaneous MCT (muzzle, vulva, sclera, etc.) and oral locations (tongue, palate) have a greater metastatic potential regardless of grade and should be aggressively staged at the time of cytologic diagnosis.

Mast cell tumors are the third most common tumor of the canine nailbed and have a more aggressive behavior compared to a traditional cutaneous MCT. Finally, primary visceral mastocytosis should be considered a highly aggressive neoplasm which is a terminal condition for most dogs.

As previously stated, histopathologic grading offers the most accurate prognosis. The majority of grade I (Patnaik) or low-grade (Kiupel) tumors are cured with complete excision. Less than 10% of grade I MCTs are reported to metastasize, with a median survival time of greater than two years. Alternatively, over 80% of grade III MCTs will metastasize and the median survival for high-grade MCT is less than four months.

Various proliferation markers may be used for additional prognostic information. Dogs with a Ki-67 index of <1.8 had a median survival time that was not reached within the time frame of the study and suggested a curative outcome. Those with a Ki-67 >1.8 had a median survival time of 9.7 months. While increases in both AgNORs and PCNA repeatedly support more aggressive tumors, they appear to only be prognostically valuable in conjunction with tumor grade. When evaluated independently of grade, both indices are ineffective in determining prognosis.

Feline Mast Cell Tumors

Epidemiology

Feline MCTs represent the second most common skin tumor in the cat. A genetic correlation has been linked to young Siamese cats. In addition, cats may develop both a visceral form of MCT that primarily originates in the spleen and a primary intestinal form.

Signalment

Cutaneous forms of feline MCTs are most commonly found in cats 10 years of age, with no reported gender predilection. Siamese less than 4 years of age are reported to be predisposed to the less common histiocytic form of cutaneous MCT. Visceral (both spleen and intestinal involvement) forms more commonly occur in older cats.

History and Clinical Signs

The majority of cutaneous lesions occur on the head and neck but can occur throughout the body. The most common presentation is a red, raised dermal lesion. As in the canine form, MCTs can appear with many other cutaneous manifestations including ulcerations, plaques, etc. (Figure 155.6).

Both abdominal forms of MCT result in a systemically ill patient. Vomiting, lethargy, and weight loss are most commonly noted. Splenomegaly can be severe on abdominal palpation while an intestinal mass is not always detected.

Diagnosis

Cytology is an appropriate diagnostic tool for both cutaneous and visceral lesions. Because of the incidence of



Figure 155.6 A clinically aggressive feline MCT. Note the change in coloration and ulceration throughout the lesion as well as the bruising at the base of the mass.

visceral mastocytosis associated with splenomegaly, the author strongly suggests the use of systemic antihistamines prior to cytology of an enlarged spleen. It is equally important to have corticosteroids readily available in case the cytology procedure results in an acute anaphylactic reaction. It is not necessary to premedicate all cats prior to cytology of an intestinal lesion. However, evidence of mast cells on the cytology sample justifies administration of antihistamines at that time.

An abdominal ultrasound is recommended for visceral mastocytosis. Additionally, mastocytemia is often noted on routine complete blood counts and can be isolated within the buffy coat.

Due to the low risk of metastasis, routine presurgical staging for skin tumors may not be indicated unless the patient has a clinical presentation (rapidly growing tumor) that supports a more aggressive phenotype. However, visceral and intestinal MCT should undergo complete staging with abdominal ultrasound, cytology of the liver and spleen, thoracic radiographs, minimum database bloodwork, buffy coat and potentially bone marrow aspiration.

Therapy

Cutaneous lesions that are <1 cm in diameter can be removed with routine excision. As their behavior is different from that of canine MCT, surgical margins of 2 cm are not indicated in cats. Routine "lumpectomy" or excisional biopsy margins are appropriate. If a minimal surgery is attempted, it is important to allow room for a second, wider surgery, should histopathology indicate a more aggressive lesion. For the clinically low-grade (dermal, <1 cm) tumors, local plesiotherapy with strontium-90 radiation probes offers the same curative outcome and can be used in areas where routine removal is unattainable.

Both intestinal and splenic (or true visceral) mastocytosis require abdominal exploratory surgery. Systemic therapy with antihistamines and corticosteroids is rarely effective at resolving clinical signs. Splenectomy is the treatment of choice for cats with the splenic form. Within reason, this procedure is still clinically applicable in the face of mild to moderate distant metastasis as splenectomy results in significant reduction in tumor burden and histamine release. However, splenectomy itself can be a life-threatening procedure due to the massive histamine release caused during splenic manipulation. It is recommended to premedicate all cats with appropriate dosing of diphenhydramine, famotidine, and dexamethasone preoperatively. Additionally, the spleen should be handled gently during vascular ligation and gently lifted out of the abdomen via a generous abdominal incision.

The visceral form is rarely cured with splenectomy so adjuvant treatment is recommended. Currently, there is no one accepted standard chemotherapy protocol for use in cats. Single-agent lomustine has been evaluated at a dose of 50–60 mg/m^2 (author's note: 10 mg/cat is considered an acceptable lomustine dose) with a reported overall response rate of 50%, with neutropenia and thrombocytopenia the most common and significant toxicities. Due to the variation in clinical picture, accurate survival times have not yet been determined.

Sixty-seven percent of feline MCTs are noted to have a c-kit mutation. At the time of publication, there are no published clinical data on the efficacy of tyrosine kinase inhibitors against feline MCTs. Masitinib has been evaluated in cats in a Phase I trial. The results indicate the drug is well tolerated at 12.5 mg/kg once a day with proteinuria noted as the most significant side-effect. Based on the tolerability of the medication and the proven c-kit mutation, use of tyrosine kinase inhibitor therapy in felines, in similar clinical situations as described in canines, appears reasonable.

If possible, intestinal resection with 5–10 cm margins should be considered for patients with the intestinal form. Unlike the splenic form, the presence of metastasis is much more clinically relevant as it will alter the prognosis significantly.

Prognosis

Neither the Patnaik nor Kiupel grading scheme is appropriate for feline cutaneous tumors. MCTs are labeled as either the more common mastocytic form or the histiocytic form. The latter type is often found in juvenile Siamese cats. The mastocytic form is then subtyped into either compact or diffuse. Compact mastocytic (more commonly referred to as well-differentiated) MCT represents 50–90% of all cutaneous MCTs in cats. The behavior of these lesions is benign and excisional biopsy may be all that is required for the majority of patients. The diffuse mastocytic form has a behavior similar to canine MCT. Thus, additional wide surgical margins and routine staging are indicated.

Splenectomy as a single treatment modality for the visceral form will result in a median survival time of 12–18 months. As previously stated, evidence of metastasis in other organs (lungs, liver, etc.) does not eliminate splenectomy as a surgical option due to the significant reduction in tumor burden and resulting improved clinical outcome. However, in the face of severe multifocal disease, splenectomy alone should not be considered.

The primary intestinal form historically caried the most guarded prognosis (4–6 weeks survival). However, more recent studies indicate that the prognosis may be far better (median survival time 531 days).

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156

Apheresis in Companion Animals

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Apheresis, which in Greek means "a taking away," is an extracorporeal therapy that has been an important part of physician-based medicine since the early 1970s. With the development of sophisticated cell separator machines and the commercial availability of human cytokines, centrifugal apheresis is an essential component in the treatment of a wide variety of human diseases, including cancer. Fortunately, with the availability of used, human cell separator machines to veterinarians employed at both academic institutions and high-end specialty practices, centrifugal apheresis is beginning to be recognized as a valuable tool in the treatment of a variety of canine diseases. This review will discuss how cell separators (also called apheresis machines) work, briefly discuss physician-based applications of apheresis, and review the current state of companion animal apheresis.

Cell Separator Machines

All cell separator machines, regardless of the manufacturer, are designed to separate specific blood components, most often based on cell density centrifugation. Therefore, an integral component of all machines is a large-scale centrifuge that is able to continuously separate blood into various fractions, including white blood cells (WBCs), platelets, and serum using continuous flow centrifugation (CFC). This means the blood can be collected into the machine, centrifuged, and returned to the patient simultaneously. The component of interest is typically pumped into a separate collection bag while the rest of the unused blood components are returned to the patient. Therefore, patients undergoing apheresis typically have a catheter placed in each leg or a dual-lumen catheter placed in one leg that allows blood to enter into the machine and pump the uncollected portions of the blood back into the patient. Because an anticoagulant, such as ACD-A, is added to the blood after it leaves the patient and before it enters the machine, apheresis patients actually experience very little loss of blood volume during the procedure.

The most popular cell collectors for physician-based medicine are the COBE® Spectra and Spectra Optia® apheresis systems manufactured by TerumoBCT (formerly CaridianBCT) and CS-3000 Plus and Amicus™ apheresis systems manufactured by Fresenius Kabi (formerly Fenwal, Inc). Other popular machines, due to their small size and portability, are the Haemonetics® MCS®+8150 Multicomponent Collection System (red blood cells and plasma only) and the MCS®+9000 Mobile Platelet Collection System.

Physician-Based Applications of Apheresis

The most widely used application of cell separator machines in physician-based medicine is the collection of platelets (plateletpheresis) for use in cancer patients receiving chemotherapy, radiation treatments, or bone marrow transplants, as well as patients with aplastic anemia and blood coagulation disorders. It takes approximately five whole units of blood to harvest the amount of platelets that can obtained from one 90-minute plateletpheresis. Therefore, one unit of platelets harvested using plateletpheresis can be used to treat 2–3 patients (www.redcrossblood.org/donating-blood/types-donations/platelet-donation). Plateletpheresis is considered absolutely safe with the most common side-effect being a tingling sensation in the lips due to transient hypocalcemia that is treated with calcium-containing antacid tablets.

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Therapeutic plasma exchange (TPE), a form of plasmapheresis, is a procedure where the cell separator machine separates and removes the patient's plasma which is then replaced with either donated plasma or a protein solution such as 5% human albumin. TPE is typically used to remove disease-causing antibodies that cause a variety of immune-mediated diseases, including Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), and myasthenia gravis. It can also be used to treat thrombotic thrombocytopenia purpura (TTP) patients in an effort to reduce the thickness of the blood. TPE can also be used to remove large amounts of medication if the need arises.

Low-density lipoprotein (LDL) apheresis removes LDL cholesterol from the blood of patients with hypercholesterolemia using two specific types of apheresis machines approved by the US Food and Drug Administration (FDA). The Liposorber uses a filter covered with dextran that binds LDL cholesterol and removes it from the circulation. Another machine, called HELP, uses heparin to bind and remove LDL cholesterol. Since hypercholesterolemia is usually caused by the combination of mutations in a variety of genes (especially LDLRAP1) and lifestyle choices, treatment using LDL apheresis is usually life-long.

Photopheresis is a very specialized type of apheresis where the harvested white blood cells are exposed to a photoactive drug called methoxsalen which renders them sensitive to ultraviolet (UV) light. The cells are then exposed to UV light inside the machine and returned to the patient. This procedure can improve the symptoms of certain conditions such as graft versus host disease (GVHD), cutaneous T cell lymphoma, or organ transplant rejection, although it is currently not known exactly how photophoresis works. The length and number of procedures needed to provide benefit are highly variable.

Leukapheresis is used to remove extra white blood cells from the blood in patients with diseases that can cause very high white blood cell counts, including acute lymphoblastic and acute myeloblastic leukemias. Leukapheresis in these patients can significantly decrease blood viscosity and also decrease the chance of acute tumor lysis syndrome in patients starting induction chemotherapy.

Peripheral blood stem cell collections are used to harvest monocytes from patients after some type of blood cell mobilization, such as G-CSF (Neupogen) administration. A small percentage of the harvested monocytes (~1–4%) are CD34+ progenitor cells that can lead to complete hematologic reconstitution after some type of myeloablative therapy (such as total body irradiation or high-dose chemotherapy). This procedure is used to collect CD34+ progenitor cells for their use in both autologous and allogeneic bone marrow transplants when treating patients with lymphoma, leukemia, and multiple myeloma. The cells can also be used to treat other conditions including myelodysplastic syndromes and childhood neuroblastoma.

Companion Animal Apheresis

Plasmapheresis (the separation of plasma from blood to be used in primary and supportive disease management) is the most commonly reported apheresis procedure in the veterinary literature. In horses, plasmapheresis has been explored using continuous-flow cell separator machines based on data showing that plasma harvested from equine blood using fast erythrocyte sedimentation contains a high number of erythrocytes that could cause recipient sensitization and evidence that bacterial contamination can occur using an open collection system. In two studies, Feige *et al*. found that automated plasmapheresis using a Blutz separator AS 104 (Fresenius, Stans, Switzerland) was the method of choice when compared to whole-blood collection followed by either centrifugation or gravity sedimentation and that the plasmapheresis procedure itself was very well tolerated by the donor horses. To this author's knowledge, the use of TPE to treat equine patients with immune-mediated diseases has not been reported.

Canine plasmapheresis has also been reported using both membrane filtration and continuous-flow centrifugation. Bartges *et al*. used discontinuous membrane filtration plasmapheresis (Therapore, Therapeutic Apheresis Systems, Sarns/3M, Ann Arbor, MI) twice, in conjunction with corticosteroids, to treat a dog with acquired myasthenia gravis, which dropped the AchR antibody titer by ~70%. Crump and Seshadri used continuous membrane filtration (Prisma CRRT and TPE Control Unit, Gambro Inc., Lakewood, CO) to treat a dog with immune-mediated hemolytic anemia. In both reports, plasmapheresis was performed safely with minimal side-effects and the dogs responded clinically.

Canine TPE has also been reported, although the majority of studies were performed in the 1980s. Matus *et al*. used a cell separator (IBM 2997 cell separator, IBM Corp., Princetown, NJ) to treat three dogs with an IgA monoclonal gammopathy and secondary hyperviscosity. In all three dogs, one total plasma volume was removed and replaced with lactated Ringer's solution (LRS) and all three dogs responded clinically within 24 hourrs of treatment. This same group also treated one dog with systemic lupus erythematosus using a

combination of plasmapheresis and immunoabsorption. Plasmapheresis was performed eight times over a period of 45 days using the same cell separator and the harvested product was then passed over a column loaded with *Staphylococcus* purified protein A/SSPA, which binds canine IgG classes of antibodies. This dog also responded well clinically. Based on this case report, Matus *et al*. then treated five dogs with systemic lupus and two dogs with immune-mediated hemolytic anemia using plasmapheresis alone, using the same IBM cell separator. One total plasma volume was removed and replaced with LRS and all dogs responded clinically within 24 hourrs of the procedure.

Dogs have been undergoing leukapheresis in a research setting since 1967, although the collection of large amounts of cells needed for routine clinical use using CFC was not possible until the cloning and large-scale production of recombinant hematopoietic cytokines in the 1990s and the development of highly automated computer-controlled cell separators soon thereafter. Although there is a large body of research literature utilizing dogs as a preclinical model to develop leukapheresis techniques to collect a sufficient number of peripheral blood CD34+ cells to allow complete hematologic reconstitution following myeloablative therapy, the use of leukapheresis in the veterinary clinical setting is still in its infancy.

In 2006, Lupu *et al*. reported the use of a COBE Spectra cell separator to harvest enough peripheral blood CD34+ progenitor cells (>5 × 10^6/kg) for use in an allogeneic bone marrow transplant setting. Their choice of cell separator was based on the experience of the group at the Fred Hutchinson Cancer Research Center which showed that automated apheresis using a COBE Spectra machine developed for humans could also be used in dogs. Our group at North Carolina State University also found that an adequate number of peripheral blood progenitor cells could be safely harvested from dogs using a Fresenius Kabi CS-3000 Plus cell separator. We also showed that the CD34+ component of the harvest product was adequate to achieve complete hematopoietic reconstitution following lethal total body irradiation.

Finally, since all cell separator machines are designed for adult humans and their use in small children and dogs can be challenging, our group showed, similar to human pediatric data, that apheresis using a COBE Spectra cell separator can be safely performed in dogs weighing <14 kg if appropriate machine priming techniques are utilized. The smallest dog on which our group has performed apheresis on weighed 4.6 kg (unpublished data). This combination of older and more recent data clearly shows that canine leukapheresis is safe in a clinical setting and the procedure can harvest an adequate amount of hematopoietic progenitor cells for use in the canine bone marrow transplant setting.

Leukapheresis Followed by Bone Marrow Transplantation

Early research, performed mainly at the Fred Hutchinson Research Center, proved that canine peripheral blood CD34+ progenitor cells harvested using human cell separators could lead to complete hematologic reconstitution following lethal myeloablative therapy. Further work showed that dogs with lymphoma could be successfully treated in both an autologous and allogeneic bone marrow transplant setting with long-term survivals longer than chemotherapy alone.

More recently, our group at North Carolina State University used a combination of total body irradiation and autologous peripheral blood CD34+ progenitor cells, harvested using either a CS-3000 Plus or COBE Spectra cell separator, to treat dogs with high-grade B and T cell lymphoma. Five of 15 (33%) dogs with B cell lymphoma transplanted while in remission for their disease remained alive >2 years (median overall survival 524 days), while two of 13 (15%) dogs with T cell lymphoma transplanted while in remission for their disease remained alive >2 years (median overall survival 240 days). Importantly, when we transplanted dogs with B cell lymphoma who were not in clinical remission, their median disease-free intervals were significantly shorter than those who were in remission (52 days vs 456 days). In dogs with T cell lymphoma, although a smaller percentage of dogs were alive >2 years compared with the B cell lymphoma dogs, the median overall survival from the time of diagnosis to death was 602 days (range 246–928 days), which is significantly longer than when dogs are treated with chemotherapy alone.

Our group has also performed two allogeneic bone marrow transplants using DLA-matched donor peripheral blood CD34+ cells to treat one dog with B cell and one dog with T cell lymphoma (unpublished data). Both dogs underwent complete hematologic reconstitution and achieved full donor engraftment within six weeks of transplant. The dog with B cell lymphoma died of unexplained causes ~6 months post transplant, while the dog with T cell lymphoma remains alive ~22 months post transplant. We also treated a dog with acute large granular lymphocytic leukemia using DLA-matched donor peripheral blood CD34+ cells and this dog remains disease free at ~30 months post transplant. Both autologous and allogeneic bone marrow transplantation as treatments of canine lymphoproliferative disorders are currently offered at North Carolina State University and three private practices in the United States (CA, WA, and OH).

Plateletpheresis

Although, as stated previously, one of the primary uses of cell separator machines in physician-based medicine is plateletpheresis, canine plateletpheresis has been rarely reported and remains an underutilized resource in the clinical veterinary setting. Callan *et al*. used a Terumo COBE Spectra machine to assess the safety and feasibility of plateletpheresis using 14 normal adult dogs. In all cases, a high-quality, leukoreduced ($<1 \times 10^6$ WBCs) platelet concentrate (mean total yield of 3.3×10^{11} platelets) was collected in a mean procedure time of only 105 min. Since citrate-induced hypocalcemia was noted in some dogs, prophylactic IV Ca supplementation was recommended. Appleman *et al*. then extended this work by examining the effects of platelet *in vitro* function and *in vivo* survival using two different methods of cryopreservation (6% DMSO or Thrombosol). Although cryopreserved platelets using either method were not able to mimic fresh platelets in terms of *in vivo* platelet recovery, the authors concluded that both cryopreserved products could be considered for dogs with acute, life-threatening bleeding when fresh platelet products are not available.

Conclusion

Although cell separator machines are used daily in physician-based medicine to treat a wide variety of diseases, their use in veterinary-based medicine remains largely unexplored. Recent studies show that dogs can tolerate apheresis using human cell separator machines and that specific blood components can be harvested in a clinical veterinary setting. Moreover, it is clear that animals with a variety of diseases, including cancer, can achieve positive clinical outcomes when treated with cell separator harvest products. As such, apheresis in veterinary medicine remains a largely untapped resource that should expand in the future as more veterinarians become aware of the technology and more machines become available to our profession.

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Section 12

Skin and Ear Diseases

157

Approach to the Patient with Dermatologic Disease

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Skin and ear diseases are among the most common reasons why clients seek veterinary consultation. Not only are diseases such as hypersensitivity disorders and skin and otic infections very common, the skin is the most accessible organ of the body, making it readily visible to owners. Thus, owners can easily detect abnormalities in the appearance, odor, and feel of the skin and haircoat, as well as appreciate how the disease is impacting their pet's quality of life along with their own. Because dermatologic problems are usually multifactorial, chronic, recurrent and noncurable, and often involve several dermatoses occurring simultaneously, owners and veterinarians alike can easily become overwhelmed.

It is the goal of this chapter to make the diagnosis and management of dermatologic disease more rewarding by guiding veterinarians toward a more methodical and efficient approach to the dermatologic patient. This will be accomplished by emphasizing the recognition of crucial lesions and their distribution, and assimilating these findings and other physical exam abnormalities with the history such that a comprehensive list of systematized differential diagnoses will be formulated and the most appropriate diagnostic tests selected. Finally, the chapter will end with a discussion of the common diagnostic tests utilized in the dermatologic patient, including indications, techniques, and interpretation.

History

Despite its complexity, the skin has limited means by which it "reacts" to indicate the presence of an underlying disease process, and because numerous skin diseases will manifest clinically in a similar way, the patient history is vital. Not uncommonly, obtaining a thorough and complete history will take longer than the examination itself. This process can be expedited by having a history form or questionnaire made available to the client to be completed either in the reception area or, ideally, emailed or mailed to the client prior to the consultation. There are several examples of dermatologic history forms available from multiple textbooks (included in the Further Reading section at the end of this chapter), online through the Veterinary Information Network (www.vin.com), and through various veterinary pharmaceutical companies. These forms can be adapted and modified to the clinician's own preferences.

The previously completed dermatology history form can be quickly reviewed with the client before or during the consultation, which decreases the time needed to extract a good history, and should begin with the client's primary complaint. Neglecting this can quickly result in a dissatisfied, "unheard" client, especially when the veterinarian's concerns do not immediately reflect the primary concerns of the client. Addressing the chief complaint will often result in an immediate list of differential diagnoses aimed at identifying the etiology of the underlying disease process. During review of the dermatologic history form, additional questions can be asked or posed in different ways to help extract pertinent information that pertains to specific problems. This is an art and takes practice!

The patient's signalment can further assist with formulating and ranking differential diagnoses, as there are some skin diseases that are more likely to occur in specific age ranges, sexes (including neuter status), and in certain breeds. The age of onset of the dermatologic disease can be particularly helpful in the very young and very old patient. For instance, younger animals are more commonly afflicted with diseases such as demodicosis, otodectes, and dermatophytosis, as well as congenital and hereditary diseases, whereas middle-aged to older animals are more commonly diagnosed with autoimmune dermatoses, neoplastic conditions,

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and endocrinopathies. However, most diseases manifest between approximately 1 year and 6–8 years of age where no clear relationship between age and disease exists. The breed of the patient may help with the development of an initial differential diagnosis list. There are some breeds, including those with a specific coat color, that seem to be predisposed to specific dermatologic conditions. In addition, certain diseases are congenital or have an identified heritable basis while others simply occur more frequently in some breeds than in others (Table 157.1).

Occasionally, sex predilections for various diseases exist and can help in formulating and ranking the differentials. For instance, females are anecdotally reported to be more prone to systemic lupus erythematosus. Neuter status should also be taken into consideration. Estrus has been known to exacerbate pruritus in females, and intact males are at increased risk for male feminization syndrome.

The disease history can be further clarified by addressing some key questions including the date of onset (in addition to the age of onset, discussed above), location and appearance of the initial lesions, duration and progression of the disease. The approximate date of onset may help to track seasonality or possibly create a timeline for assessment of a drug- or vaccine-induced cutaneous reaction. Depending on geographic location, disorders such as insect bite hypersensitivities and flea allergy dermatitis tend to occur in the summer. In temperate climates, atopic dermatitis often begins as a seasonal disease, typically worsening in the spring, summer, and/or fall. However, some patients with house dust mite hypersensitivity may worsen in the winter in addition to having year-round pruritus. Canine flank alopecia, also known as seasonal or cyclical flank alopecia, tends to result in cyclical episodes of noninflammatory, nonpruritic alopecia in the winter where a shorter photoperiod induces follicular arrest with resolution occurring in the spring.

Specifying the initial lesion location and pattern of distribution can be extremely helpful in developing a differential diagnosis list, as many diseases have distinct areas of involvement. For instance, pemphigus foliaceus affects the pinnae, dorsal aspect of the muzzle, and the pawpads. Sarcoptic mange tends to affect the pinnal margins, elbows, and tibiotarsal areas. The importance of lesional distribution will be further discussed in the physical exam (PE) section. Questions pertaining to disease duration and progression should include if and how location, appearance, and distribution have changed, whether the onset was acute or slow and insidious, and if the disease is continuous or intermittent (seasonal or nonseasonal). An acute onset of severe pruritus often occurs with sarcoptic mange, and diseases such as pemphigus foliaceus and contact dermatitis tend to erupt rapidly. Cutaneous adverse food reaction may also have a rapid onset, whereas endocrinopathies tend to have a slow onset. A patient with seasonal pruritus would not require a food elimination trial, as adverse food reactions cause year-round signs.

One of the most important historical questions to address is whether or not the disease was precipitated by or associated with pruritus, as this information can rapidly help to generate and shorten the list of differentials. If pruritus preceded the lesions, then allergic or parasitic diseases are most likely. If lesions, such as alopecia, precede the pruritus, endocrinopathies, follicular dysplasias and follicular demodicosis must be explored. If papules, pustules, epidermal collarettes or crusts precede the pruritus, the so-called "rash that itches," pursue bacterial, any nonpruritic dermatoses prone to developing secondary bacterial infection such as endocrinopathies, and sterile pustular diseases (e.g., pemphigus foliaceus). Diseases that are typically or always pruritic include atopic dermatitis, cutaneous adverse food reaction, flea bite allergy, contact hypersensitivity, sarcoptic and notoedric mange, and demodicosis caused by *Demodex gatoi* in cats and *Demodex cornei* in dogs. Variably pruritic conditions include cheyletiellosis, demodicosis caused by *Demodex injai*, *Malassezia* dermatitis, superficial pyoderma, feline dermatophytosis, autoimmune diseases such as pemphigus foliaceus, and epitheliotropic lymphoma. Diseases that are nonpruritic include endocrinopathies, follicular dysplasias, canine dermatophytosis, and demodicosis caused by *Demodex canis* and *Demodex cati*. However, these conditions can be pruritic if accompanied by secondary infection.

Identifying patterns of pruritus is also important for identifying underlying disease triggers. A patient whose pruritus always improves with a change in environment likely has atopic or contact dermatitis. In a patient with nonseasonal pruritus that also has seasonal "flares," adverse food reaction should be explored in addition to atopic dermatitis. A patient that suddenly becomes pruritic after residing at a boarding kennel should be evaluated for sarcoptic mange.

Owners often do not recognize the various manifestations of pruritus, such as licking, biting, chewing, rubbing, rolling, and scooting, and the clinician needs to ask about these variable signs. Therefore, evaluation of pruritus should not stop at asking if the patient "itches." Also, determining the level of pruritus is important in the development of an adequate treatment plan and evaluating the patient's response to treatment. Commonly, owners are asked to rank their pet's level of pruritus on a scale of 0 to 10, with 0 representing no itch at all and 10 being so itchy that the pet cannot sleep at night (and neither can the poor owner!).

Table 157.1 Common skin diseases in various breeds

Breed	Disease
Abyssinian cat	Follicular dysplasia Psychogenic alopecia
Afghan hound	Hypothyroidism
Airedale terrier	Atopic dermatitis Canine flank alopecia Hypothyroidism
Akita	Postclipping alopecia Pemphigus foliaceus Sebaceous adenitis Uveodermatologic syndrome
Alaskan malamute	Alopecia of plush-coated breeds (alopecia X, follicular dysplasia, follicular arrest syndrome) Postclipping alopecia Zinc-responsive dermatosis
American bulldog	Atopic dermatitis Ichthyosis Solar dermatitis
American Staffordshire terrier	Atopic dermatitis Canine flank alopecia Demodicosis Solar dermatitis
American water spaniel	Pattern alopecia
Basset hound	Atopic dermatitis Intertrigo *Malassezia* dermatitis
Beagle	Atopic dermatitis Alopecia areata Demodicosis Hypothyroidism Immunoglobulin (Ig)A deficiency Sebaceous adenitis
Bearded collie	Black hair follicular dysplasia Pemphigus foliaceus Symmetric lupoid onychitis
Beauceron	Epidermolysis bullosa Dermatomyositis
Belgian shepherd dog, Belgian tervuren	Dermatomyositis Sebaceous adenitis Vitiligo
Bengal cat	Ulcerative nasal dermatitis
Bernese mountain dog	Color dilution alopecia Histiocytic sarcoma Systemic histiocytosis
Border collie	ABCB1 genetic mutation Black hair follicular dysplasia
Borzoi	Hypothyroidism
Boston terrier	Atopic dermatitis Demodicosis Pattern alopecia Hyperadrenocorticism Tail and facial fold intertrigo
Bouvier des Flandres	Canine flank alopecia
Boxer	Atopic dermatitis Canine acne Canine flank alopecia Demodicosis Dermoid cyst Food hypersensitivity Hyperadrenocorticism Hypothyroidism Histiocytoma Mast cell tumor Solar dermatitis (white boxers) Sterile granuloma pyogranuloma syndrome Superficial bacterial folliculitis Urticaria
Brittany spaniel	Complement deficiency Discoid lupus erythematosus Hypothyroidism Lip fold intertrigo
Bullmastiff and mastiff	Bacterial folliculitis and furunculosis Vitiligo
Bull terrier	Atopic dermatitis Lethal acrodermatitis Nasal folliculitis and furunculosis Pedal folliculitis and furunculosis Solar dermatitis Zinc-responsive dermatitis
Cairn terrier	Atopic dermatitis Ichthyosis
Cavalier King Charles spaniel	Black hair follicular dysplasia Caudal occipital malformation syndrome Eosinophilic granuloma (oral) Ichthyosis Primary secretory otitis media
Chesapeake Bay retriever	Atopic dermatitis Follicular dysplasia Superficial bacterial folliculitis
Chihuahua	Color dilution alopecia Pattern alopecia Pinnal thrombovascular necrosis
Chow chow	Alopecia of plush-coated dogs (alopecia X, follicular dysplasia, follicular arrest syndrome) Atopic dermatitis Color dilution alopecia Demodicosis Hypothyroidism Pemphigus foliaceus Postclipping alopecia Tyrosinase deficiency Uveodermatologic syndrome

(*Continued*)

Table 157.1 (Continued)

Breed	Disease
Cocker spaniel	Atopic dermatitis Hypothyroidism Lip fold intertrigo Otitis externa (proliferative) Pemphigus foliaceus Sebaceous nodular hyperplasia and/or adenomas Seborrhea, primary Vitamin A-responsive dermatosis
Collie	ABCB1 gene mutation Cyclic neutropenia (gray collie syndrome) Cutaneous histiocytosis Dermatomyositis Discoid lupus erythematosus Nasal furunculosis, bacterial Pemphigus erythematosus Sertoli cell tumor (male feminization syndrome) Sterile granuloma pyogranuloma syndrome Vesicular cutaneous lupus erythematosus
Curly-coated retriever	Canine flank alopecia Follicular dysplasia Hypothyroidism Pattern alopecia
Dachshund	Acanthosis nigricans Alopecia areata Color dilution alopecia Ear margin dermatosis Hyperadrenocorticism Hypothyroidism Idiopathic onychodystrophy Juvenile cellulitis Nodular panniculitis (sterile) Pattern alopecia Pemphigus foliaceus Pinnal vasculitis Sterile granuloma pyogranuloma syndrome Sternal callus Vasculitis
Dalmatian	Atopic dermatitis Solar dermatitis Superficial bacterial folliculitis Waardenburg–Klein syndrome
Devon rex cat	Familial hypotrichosis
Doberman pinscher	Acral lick dermatitis Canine acne Color dilution alopecia Drug reaction (especially sulfonamides) Flank sucking Follicular dysplasia Hypothyroidism Pedal folliculitis and furunculosis Sterile granuloma pyogranuloma syndrome Superficial bacterial folliculitis Vitiligo
Dogue de Bordeaux	Hereditary footpad hyperkeratosis Sterile granuloma pyogranuloma syndrome
English bulldog	Atopic dermatitis Canine acne Canine flank alopecia Demodicosis Facial and tail fold intertrigo Hypothyroidism Pattern alopecia Pedal folliculitis and furunculosis Sterile granuloma pyogranuloma syndrome Superficial bacterial folliculitis
English springer spaniel	Acral mutilation syndrome Cutaneous asthenia Food hypersensitivity Hypothyroidism Ichthyosis Lip fold intertrigo Otitis externa Psoriasiform-lichenoid dermatitis Sebaceous adenitis Seborrhea, primary
Flat-coated retriever	Histiocytic sarcoma
German shepherd dog	Atopic dermatitis Calcinosis circumscripta Collagen disorder of footpads Discoid lupus erythematosus Erythema multiforme Familial vasculopathy Flea bite hypersensitivity Fly bite dermatitis Food hypersensitivity German shepherd dog pyoderma Insect- or arachnid-related eosinophilic furunculosis (face) Metatarsal fistulae Mucocutaneous pyoderma Mucous membrane pemphigoid Nasal folliculitis and furunculosis Nodular dermatofibrosis with renal cystadenocarcinoma Otitis externa Pemphigus foliaceus Perianal fistulae Pituitary dwarfism Pythiosis Symmetric lupoid onychitis Systemic lupus erythematosus Vitiligo
German shorthaired pointer	Acral mutilation syndrome Epidermolysis bullosa Exfoliative cutaneous lupus erythematosus

Table 157.1 (Continued)

Breed	Disease
Golden retriever	Acral lick dermatitis Acute moist dermatitis Atopic dermatitis Cutaneous lymphosarcoma Footpad hyperkeratosis Histiocytic sarcoma Hypothyroidism Ichthyosis Juvenile cellulitis Nasal hypopigmentation ("Dudley nose") Pyotraumatic folliculitis and furunculosis Sterile granuloma pyogranuloma syndrome Superficial bacterial folliculitis Systemic histiocytosis
Gordon setter	Atopic dermatitis Black hair follicular dysplasia Hypothyroidism Juvenile cellulitis Symmetric lupoid onychitis Vitamin A-responsive dermatosis
Great Dane	Acral lick dermatitis Calcinosis circumscripta Canine acne Color dilution alopecia Demodicosis Dermoid cyst Epidermolysis bullosa acquisita Hygromas Hypothyroidism Pedal folliculitis and furunculosis Solar dermatosis Sterile granuloma pyogranuloma syndrome Superficial bacterial folliculitis
Great Pyrenees	Acute moist dermatitis
Greyhound	Footpad keratosis (corns) Cutaneous and renal glomerular vasculopathy Drug reactions Pattern alopecia
Himalayan	See Persian cat
Irish setter	Acral lick dermatitis Atopic dermatitis Color dilution alopecia Granulocytopathy Hereditary footpad hyperkeratosis Hypothyroidism Seborrhea, primary Superficial bacterial folliculitis
Irish water spaniel	Follicular dysplasia
Irish wolfhound	Hygromas Hypothyroidism Systemic histiocytosis
Keeshond	Alopecia of plush-coated breeds (alopecia X, follicular dysplasia, follicular arrest syndrome) Hypothyroidism Infundibular keratinizing acanthoma Melanoma Postclipping alopecia
Kerry blue terrier	Dermoid cyst Footpad keratosis (corns) Hair follicle tumors Otitis externa Spiculosis
Labrador retriever	Acral lick dermatitis Acute moist dermatitis Atopic dermatitis Color dilution alopecia Familial nasal hyperkeratosis Food hypersensitivity *Malassezia* dermatitis Mast cell tumor Superficial bacterial folliculitis Symmetric lupoid onychitis Systemic histiocytosis Vitamin A-responsive dermatosis Vitiligo Wells syndrome (eosinophilic dermatitis and edema)
Lhasa apso	Atopic dermatitis Vaccine-induced alopecia (rabies)
Malamute	Demodicosis Follicular dysplasia Hypothyroidism Zinc-responsive dermatosis
Maltese terrier	Traction alopecia Vaccine-induced alopecia (rabies)
Manchester terrier	Follicular dysplasia Pattern alopecia
Miniature pinscher	Pattern alopecia Vitiligo
Newfoundland	Acute moist dermatitis Atopic dermatitis Hypothyroidism Pemphigus foliaceus Superficial bacterial folliculitis
Norfolk terrier	Ichthyosis
Norwegian elkhound	Alopecia of plush-coated breeds (alopecia X, follicular dysplasia, follicular arrest syndrome) Infundibular keratinizing acanthoma Keratinization disorders Postclipping alopecia
Norwich terrier	Atopic dermatitis Keratinization disorders

(*Continued*)

Table 157.1 (Continued)

Breed	Disease
Old English sheepdog	ABCB1 gene mutation Atopic dermatitis Drug reactions Pedal folliculitis and furunculosis Vitiligo
Papillon	Black hair follicular dysplasia
Parson Russell terrier (Jack Russell terrier)	Atopic dermatitis Black hair follicular dysplasia Dermatophytosis Familial vasculitis Ichthyosis
Pekinese	Facial fold intertrigo Vaccine-induced alopecia (rabies)
Persian cat	Dermatophytosis Facial fold intertrigo Idiopathic facial dermatitis Seborrhea, primary
Pointer	Acral mutilation syndrome Black hair follicular dysplasia Calcinosis circumscripta Canine flank alopecia Epidermolysis bullosa Exfoliative cutaneous lupus erythematosus Nasal folliculitis and furunculosis
Pomeranians	Alopecia of plush-coated breeds (alopecia X, follicular dysplasia, follicular arrest syndrome) Vaccine-induced alopecia (rabies)
Poodle	Atopic dermatitis Congenital hypotrichosis Ectodermal defect Epidermolysis bullosa Follicular dysplasia (miniature poodle) Hyperadrenocorticism (miniature poodle) Hypothyroidism (standard poodle) Otitis externa Pattern alopecia Sebaceous adenitis (standard poodle) Vaccine-induced alopecia (rabies)
Portuguese water dog	Dermatomyositis Follicular dysplasia Pattern alopecia
Pug	Atopic dermatitis Demodicosis Facial fold and tail fold intertrigo Hypothyroidism Mast cell tumor Pigmented viral plaque
Rex cat	Hypotrichosis *Malassezia* dermatitis
Rhodesian ridgeback	Dermoid cyst Dermoid sinus Hypothyroidism Pattern alopecia
Rottweiler	Follicular lipidosis Follicular parakeratosis Histiocytic sarcoma Superficial bacterial folliculitis Symmetric lupoid onychitis Systemic histiocytosis Vasculitis Vitiligo
Saint Bernard	Acral lick dermatitis Acute moist dermatitis Hygroma, elbow Lip fold intertrigo Nasal arteritis Superficial bacterial folliculitis Uveodermatologic syndrome
Samoyed	Alopecia of plush-coated breeds (alopecia X, follicular dysplasia, follicular arrest syndrome) Sebaceous adenitis Uveodermatologic syndrome
Schipperke	Hypothyroidism Pemphigus foliaceus
Schnauzer	Atopic dermatitis Aurotrichia Canine flank alopecia Drug reactions Hyperadrenocorticism Hypothyroidism Schnauzer comedo syndrome Symmetric lupoid onychitis Subcorneal pustular dermatosis Sterile pustular erythroderma of miniature schnauzers Vitamin A-responsive dermatosis (giant schnauzer)
Scottish terrier	Atopic dermatitis Canine flank alopecia Familial nasal pyogranuloma and vasculitis Hyperadrenocorticism Melanoma Superficial bacterial folliculitis
Shar-pei	Atopic dermatitis Demodicosis Food hypersensitivity Intertrigo Hypothyroidism Idiopathic cutaneous mucinosis IgA deficiency Superficial bacterial folliculitis
Shetland sheepdog	ABCB1 gene mutation Cutaneous histiocytosis Dermatomyositis Discoid lupus erythematosus Drug reactions Hypothyroidism Superficial spreading pyoderma Systemic lupus erythematosus Vesicular cutaneous lupus erythematosus

Table 157.1 (Continued)

Breed	Disease
Shih tzu	Atopic dermatitis Demodicosis Traction alopecia
Siamese cat	Epidermolysis bullosa Food hypersensitivity Hypotrichosis Periocular leukotrichia Psychogenic alopecia Vitiligo
Siberian husky	Atopic dermatitis Discoid lupus erythematosus Eosinophilic furunculosis Eosinophilic granuloma Follicular dysplasia Idiopathic onychodystrophy Postclipping alopecia Uveodermatologic syndrome Zinc-responsive dermatosis
Silky terrier	Color dilution alopecia Follicular dysplasia Vaccine-induced vasculitis
Sphynx cat	Urticaria pigmentosa
Staffordshire bull terrier	Atopic dermatitis Canine flank alopecia Demodicosis Pedal folliculitis and furunculosis Pattern alopecia
Vizsla	Sebaceous adenitis
Weimaraner	Canine acne Color dilution alopecia Immunodeficiency (commonly IgG) Mast cell tumor Melanoma Pattern alopecia Sterile granuloma pyogranuloma syndrome
West Highland white terrier	Atopic dermatitis Demodicosis Epidermal dysplasia Food hypersensitivity Ichthyosis *Malassezia* dermatitis Seborrhea, primary
Wheaten terrier	Atopic dermatitis Cutaneous asthenia Ichthyosis
Whippet	ABCB1 gene mutation Color dilution alopecia Pattern alopecia Solar dermatitis
Yorkshire terrier	Color dilution alopecia Demodicosis Dermatophytosis Follicular dysplasia Melanoderma and alopecia Pinnal alopecia Traction alopecia Vaccine-induced alopecia (rabies)

The presence of systemic signs and the pet's general health should be addressed, such as water intake, appetite, vomiting, diarrhea, frequency/number of bowel movements, changes in urination, respiratory changes, lethargy, and body condition changes. General information about the patient's environment and geographic location needs to be considered. Certain diseases are endemic in various regions such as blastomycosis in the Mississippi, Missouri and Ohio river valleys or coccidioidomycosis in the southwestern portion of the United States. For the same reason, travel history should also be obtained. It is pertinent to ask if other animals in the home or the owners themselves are affected. If so, contagious and zoonotic diseases need to be considered.

Other medical problems, vaccine history, lists of previous and current treatments and medications, including topical therapy, flea control products and frequency of administration, need to be addressed, including the responses to these therapies. Reviewing previous medical records can be particularly helpful regarding medication history, as often owners find it difficult to remember all the previous medications, including the ones the patient may be currently taking. Asking owners to bring these medications to the initial consultation can also be helpful in this regard. Any previous medical records should be reviewed to help track episodes of recurrence (is there a seasonality?) and progression of the skin disease, verify client observations, and identify past and current medications, including dose and duration. The response to various treatments can also be extremely helpful in the identification of underlying disease processes. For example, a patient that presents on high doses of glucocorticoids for suspected allergic dermatitis that is still markedly pruritic needs to be evaluated for sarcoptic mange and/or undergo a treatment trial for this disease if the mites cannot be found, as allergic patients tend to be glucocorticoid responsive. When presented with a patient that is on an appropriate dose and duration of antibiotic therapy for superficial pyoderma and is not responding, a skin culture needs to be performed.

Finally, a complete dietary history including vitamins, herbs, and other supplements should be taken. This will be useful if a food elimination trial needs to be performed as well as to assess if the diet is complete and balanced. Poor diets can lead to keratinization disorders, poor haircoat quality, and zinc-responsive dermatosis.

Physical Examination

The patient's weight, rectal temperature, and pulse should be obtained by the veterinary technician or assistant before or during review of the patient history. Every patient examination should be approached in a systematic fashion to ensure a thorough PE. Avoid focusing

solely on the area(s) that the owner mentions or you may miss hidden, subtle lesions that can offer important diagnostic clues pertaining to the underlying disease process. A well-lit room is essential and a hand-held magnifying lens may be useful for close examination of lesions. In some instances, the hair may need to be clipped to allow for proper visualization. Painful or "uncooperative" patients may require sedation.

Many dermatologists prefer to start with the nose and head region and work caudally, including all accompanying mucosal and mucocutaneous surfaces. The interdigital spaces, claws, ungual folds, and pawpads must always be evaluated with the patient either standing or in lateral recumbency. Part the hair or roll the skin into individual folds to separate the hair and allow for easier evaluation of the cutaneous surface and follicular ostia while also noting the haircoat quality, color, and luster. Throughout the evaluation, look for evidence of pruritus, such as excoriations and salivary staining, the latter of which commonly manifests as a brownish-red discoloration of the haircoat. An otoscopic examination should be performed in all patients. Examination findings can be documented using topography maps available at www.vin.com or in the texts listed in the Further Reading section. These maps allow for quick illustration of lesion distribution and character during the initial consultation and subsequent rechecks which assist the clinician in making comparisons regarding disease progression between appointments. The patient should be auscultated, and the lymph nodes and abdomen palpated. These aspects of a general examination are important as they can reveal an underlying systemic disease which may be giving rise to the dermatologic changes. Also, findings on a general PE may dictate or change the choice of drug therapy. For instance, the discovery of a cardiac murmur in a feline patient may prompt the clinician to be more cautious with the administration of injectable glucocorticoids, given that cats are at increased risk of developing congestive heart failure when receiving them, especially methylprednisolone acetate.

During the course of the PE, the clinician must learn to identify the major features of the skin lesions. This will allow the disease to be placed in diagnostic categories that facilitate diagnosis. Most important are the type of lesions (primary or secondary) and lesion distribution (body sites involved). Proper identification of lesions is crucial, as they can be correlated with specific diseases.

Morphology of Lesions

Lesion morphology refers to the categorization of cutaneous lesions as primary, secondary, or either primary or secondary. The ability to accurately identify these lesions as well as having an understanding of their development is critical in refining the list of differentials. Also, knowing how primary lesions typically evolve into secondary lesions gives the clinician a better understanding of disease progression. A primary lesion develops spontaneously and is a reflection of the underlying disease process; thus these lesions are the most important to identify. Secondary lesions evolve from primary lesions or are created by the patient scratching or external forces such as trauma, medications, and infection of primary lesions. Some lesions can be considered primary or secondary. Table 157.2 provides a list and description of basic cutaneous lesion morphology. An accompanying figure is provided for most of these lesions which elaborates on their significance/pathomechanism and provides examples of differentials (Figures 157.1–157.18).

Table 157.2 Terminology used to describe lesion morphology

Lesion	Definition
Primary lesions	
Macule/patch (see Figure 157.1)	Circumscribed, flat, nonpalpable change in skin color <1 cm. If larger, termed a patch
Papule/plaque (see Figure 157.2)	Solid elevation of skin ≤1 cm in diameter. Plaque formed by confluence of papules >1 cm in diameter. Can be follicular or nonfollicular
Vesicle/bulla (see Figure 157.3)	Circumscribed, elevated skin lesion containing fluid ≤1 cm in diameter. If greater than 1 cm, termed a bulla. Can be intraepidermal or subepidermal
Pustule (see Figure 157.4)	A vesicle containing purulent exudate. Can be follicular or nonfollicular
Wheals (see Figure 157.5)	Flat-topped sharply circumscribed elevation of the skin caused by edema. If regionalized or generalized, referred to as angioedema
Nodule/tumor (see Figure 157.6)	Solid or cystic elevation of skin >1 cm in diameter. Tumor if >2 cm in diameter
Secondary lesions	
Epidermal collarette (see Figure 157.7)	Circular lesion with a rim of loosely adhered scale or peeling keratin. Often described as the "footprint" of a pustule or vesicle
Excoriation (see Figure 157.8)	Superficial excavations of the epidermis that may be linear or punctate
Erosion/ulceration (see Figure 157.9)	Superficial epidermal defect that heals without scarring due to trauma or inflammation. If deep enough to affect the dermis, an ulcer occurs and heals with scarring
Scar	Formation of fibrous tissue in place of damaged dermis or subcutaneous tissue

Table 157.2 (Continued)

Lesion	Definition
Fissure (see Figure 157.10)	Linear cleavage in the skin
Lichenification (see Figure 157.11)	Thickening and hardening of the skin characterized by an exaggeration of the superficial skin markings. Commonly hyperpigmented
Callus	Alopecic, thickened, rough, often lichenified plaque
Primary or secondary lesions	
Alopecia (see Figure 157.12)	Partial to complete loss of hair
Scale (see Figure 157.13)	Accumulation of loose fragments of stratum corneum
Crust (see Figure 157.14)	Dried exudates of purulent material, serum or blood on surface of skin
Follicular casts (see Figure 157.15)	Accumulation of follicular and keratinaceous debris that adheres to multiple hair shafts at the level of the follicular ostia
Comedones (see Figure 157.16)	Dilated hair follicles filled with cornified epithelium and debris
Pigmentary abnormalities (see Figures 157.17 and 157.18)	Changes in skin coloration caused by a variety of pigments (typically increased or decreased melanin) including black, blue, gray, tan, brown, as well as red/purple (hemorrhage within skin) and yellow-green (bile pigment)

Distribution of Lesions

In addition to recognizing lesion morphology, the location and distribution must be identified. Lesion distribution refers to whether the lesions are localized, multifocal, regionalized or generalized, bilaterally symmetric versus asymmetric, and identifying the general regions of the patient that are involved. Bilaterally symmetric lesions tend to occur in endocrinopathies, immune-mediated and autoimmune diseases, and can also occur in allergic skin diseases. Asymmetric lesions are often the result of infectious and parasitic disease processes. Certain diseases have predilection sites for various areas of the body and familiarity with these regional characteristics is advantageous in honing the list of differential diagnoses (Table 157.3).

Dermatologic Diagnostic Tests and Techniques

After a list of differential diagnoses has been generated based on a thorough history and PE, diagnostic tests can be employed to further narrow the list of differentials



Figure 157.1 *Macule* – pigment changes occur due to increased or decreased melanin (inflammatory and noninflammatory causes), erythema or local hemorrhage. Other types of macules include purpura, petechiae, and ecchymoses. Differential diagnoses (DDx) – hyperpigmentation (noninflammatory): lentigo, pigmented nevi, endocrinopathies, hormonal diseases, color dilution alopecia and other follicular dysplastic diseases, such as canine flank alopecia. Hyperpigmentation (inflammatory): bacterial or yeast infections, dermatophytosis, parasitic disease, and any disease resulting in pruritus. Depigmentation: vitiligo, uveodermatologic syndrome, mucocutaneous pyoderma, discoid lupus erythematosus. Erythema: inflammation secondary to a variety of underlying causes such as bacterial or yeast infections, dermatophytosis, demodicosis, *Sarcoptes*, vasculitis, erythema multiforme, toxic epidermal necrolysis, pemphigus, cutaneous T cell lymphoma, superficial necrolytic dermatitis (SND), hypersensitivity disorders and solar dermatitis or hemorrhage due to trauma, vasculopathies or coagulopathies. Photograph illustrates lentigo.



Figure 157.2 *Papule* – these palpably solid elevations are usually pink to red in coloration and are caused by a localized inflammatory cellular infiltrate within the dermis, epidermal hyperplasia, and early tissue infiltration of neoplastic cells. DDx – superficial bacterial folliculitis, dermatophytosis, demodicosis, *Sarcoptes*, *Cheyletiella*, insect/arachnid hypersensitivity, contact hypersensitivity, flea allergy dermatitis, atopic dermatitis, immune-mediated disease, and drug reactions. Photograph illustrates papules associated with sarcoptic mange.



Figure 157.3 *Vesicle* – lesions are fragile, transient, and difficult to find given that they develop secondary to inflammation and loss of cutaneous cellular and structural cohesion. DDx – viral infections, irritants, drug reactions, and autoimmune diseases including pemphigus vulgaris, lupus, and subepidermal blistering diseases such as mucous membrane pemphigoid, and epidermolysis bullosa acquisita. Photograph illustrates vesicles on the lower lip margin in a dog with epidermolysis bullosa acquisita. *Source*: Courtesy of Sandra Koch.



Figure 157.4 *Pustule* – lesions arise due to neutrophilic inflammation, occasionally eosinophilic. DDx – superficial bacterial folliculitis, impetigo, dermatophytosis, demodicosis, pemphigus foliaceus, lupus, and subcorneal pustular dermatosis. If eosinophils predominate, consider sterile eosinophilic pustulosis, insect or contact hypersensitivity and ectoparasites. Photograph illustrates pustules associated with superficial bacterial folliculitis.

and/or confirm a specific diagnosis. There are four basic screening tests that every clinician should be adept at and perform often, as they are easy, rapid, and inexpensive to conduct and yield immediate results. This minimum database generally includes cytology, including various techniques of cutaneous cytology and otic cytology, as well as trichography, skin scrapes, and cultures. Other diagnostic tests of importance to the dermatologic patient that will be discussed include

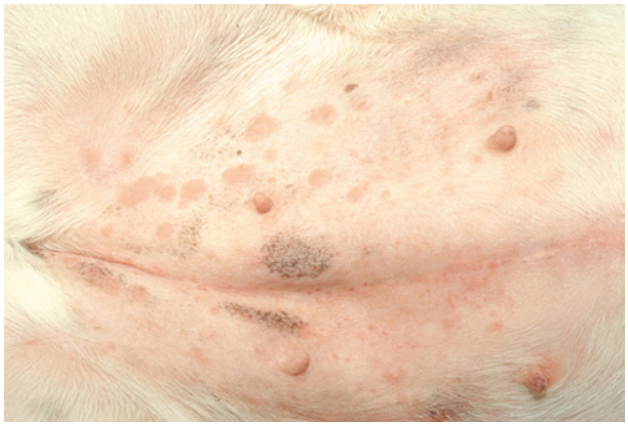


Figure 157.5 *Wheal (hive)* – these edematous lesions typically disappear within minutes to hours. When larger regional areas are involved such as the muzzle or eyelids, this is called angioedema. DDx – vaccine, drug and insect bite reactions, and hypersensitivity disorders. Photograph illustrates urticaria on the abdomen of a dog.



Figure 157.6 *Nodule* – these lesions develop due to an inflammatory or neoplastic cellular infiltrate, or from deposition of metabolic products such as fibrin and crystalline material extending to the dermis and subcutis. There are numerous neoplastic and nonneoplastic causes. Nonneoplastic causes include infectious and noninfectious etiologies. DDx – infectious causes: bacterial infections such as actinomycosis, nocardiosis, feline leprosy, canine leproid granuloma, atypical mycobacteriosis, and bacterial furunculosis. Fungal causes include blastomycosis, cryptococcosis, coccidioidomycosis, sporotrichosis, histoplasmosis, dermatophytic kerion, aspergillosis, phaeohyphomycosis, hyalohyphomycosis, pythiosis, and lagenidiosis. Algal causes include protothecosis. Parasitic and protozoal causes include leishmaniasis, dracunculiasis, *Cuterebra*, and *Neospora*. Noninfectious causes: calcinosis cutis, xanthomas, sterile nodular panniculitis, sterile granulomatous pyogranulomatous syndrome, cutaneous reactive histiocytosis, juvenile cellulitis, foreign body reaction, and eosinophilic granuloma. Photograph illustrates multiple nodules on the muzzle of a dog with sterile granulomatous pyogranulomatous syndrome.

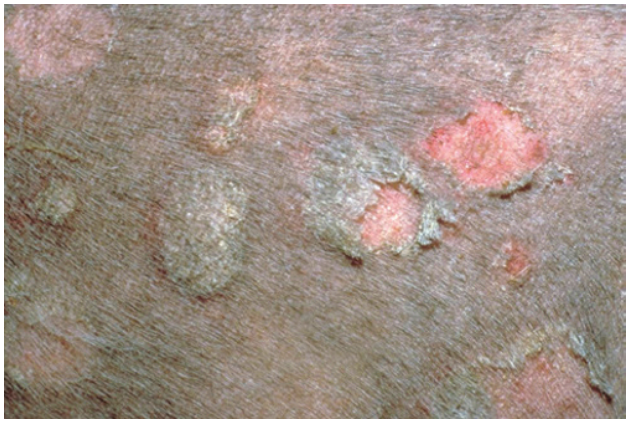


Figure 157.7 *Epidermal collarette* – these are formed from the remnants of a pustule or vesicle after the roof has been lost, or caused by a point source of inflammation, as seen with papules. DDx – superficial bacterial folliculitis most commonly. Fungal infection, immune-mediated dermatoses, contact hypersensitivity, and insect bite reaction are less common causes. Photograph illustrates an epidermal collarette associated with superficial bacterial folliculitis.



Figure 157.8 *Excoriation* – these lesions are self-induced and occur secondary to scratching, biting, and/or rubbing. Usually result from pruritus. Photograph illustrates excoriations and erosions due to scratching and licking on the lateral aspect of the thorax of a cat with adverse food reaction.

therapeutic trials, biopsy and histopathology, and tests of noncutaneous organs.

Screening Tests

Cytology

Cytology is a powerful tool, allowing one to quickly determine whether a lesion is sterile or if infectious organisms and inflammation are present. It allows the clinician to presumptively diagnose a patient with autoimmune diseases, such as pemphigus, when acantholytic cells are observed. Neoplastic processes may also be identified, such as



Figure 157.9 *Erosion/ulceration* – develop due to rapid death and/or loss of keratinocytes as a consequence of self-inflicted trauma or inflammation. An ulcer denotes a deep pathologic process. DDx – autoimmune dermatoses, erythema multiforme, toxic epidermal necrolysis, drug reaction, SND, feline indolent ulcer, deep pyoderma, deep mycoses, vasculitis, neoplasia, chemical/thermal burn. Photograph illustrates an ulcer on the lateral aspect of the thorax of a dog with a cutaneous adverse drug reaction secondary to itraconazole therapy.



Figure 157.10 *Fissure* – lesions may be caused by underlying disease or injury when the skin is thick and then subjected to sudden swelling. DDx – SND, canine distemper, zinc-responsive dermatosis, chronic skin diseases, and keratinization disorders. Photograph illustrates fissures on the metacarpal pawpad of a dog with SND.

cutaneous lymphoma and mast cell tumors. Cytology can be performed in a number of ways depending on the area and the condition of the skin being sampled.



Figure 157.11 *Lichenification* – results from chronic trauma, often due to friction. Lichenification is often accompanied by superficial bacterial folliculitis and/or *Malassezia* dermatitis. DDx – chronic and pruritic dermatopathies, intertrigo, and keratinization disorders. Photograph illustrates the abdomen and inguinal area of a dog with chronic atopic dermatitis.



Figure 157.12 *Alopecia* – may arise from several causes that lead to damage to hairs and/or hair follicles, or result from abnormal hair growth. DDx – primary: endocrinopathies, follicular dysplasia, telogen effluvium, and anagen defluxion. Secondary: pruritus, superficial bacterial folliculitis, dermatophytosis, and demodicosis. Photograph illustrates multiple annular to coalescing areas of alopecia in a beagle with alopecia areata.



Figure 157.13 *Scale* – results from increased production of keratinocytes, such as occurs with abnormalities of keratinization, inflammatory disorders or from increased retention of corneocytes. DDx – primary: ichthyosis, primary idiopathic seborrhea, various follicular dysplasias. Secondary: chronic inflammation or any direct insult to the epidermis such as epidermal infiltration of neoplastic lymphocytes in cutaneous T cell lymphoma. Photograph illustrates large, whitish-gray sheets of scale in a golden retriever with ichthyosis.

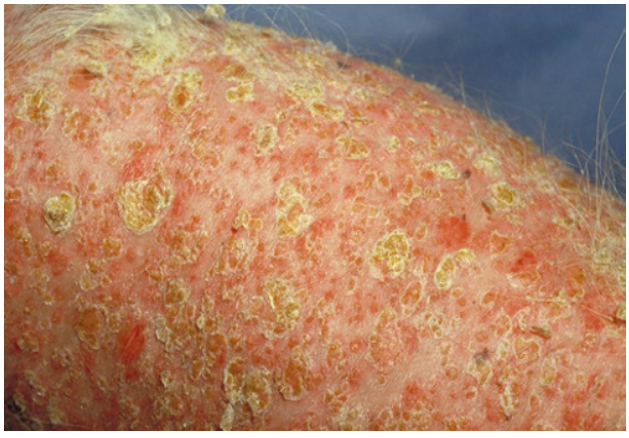


Figure 157.14 *Crust* – forms when purulent exudate, serum, blood, other dried exudates, or cells and/or scales adhere to the skin surface. DDx – primary: SND, vitamin A-responsive dermatitis, zinc-responsive dermatosis, primary idiopathic seborrhea. Secondary: pyoderma, dermatophytosis, pemphigus, and lupus. The coloration, thickness, and adherence of crusts can provide insight as to the underlying disease process. Pyoderma can result in brown-dark red (indicating hemorrhage) or yellow-green crusts. Dark crusts indicate deeper tissue damage or hemorrhage as occurs with traumatic wounds, furunculosis, and vasculitis. Honey-colored crusts usually indicate an infection but also occur with some autoimmune diseases, particularly pemphigus foliaceus. Thick, dry yellowish crusts are more common with scabies and zinc-responsive dermatosis. Tightly adhered crusts are more common in zinc-responsive dermatosis, SND, pemphigus, and some cases of seborrhea. Photograph illustrates the typical honey-colored crusts associated with pemphigus foliaceus.



Figure 157.15 *Follicular casts* – these lesions are composed of a combination of keratin and follicular material that adheres to the hair shaft(s), extending above the surface of the follicular ostia. DDx – primary: sebaceous adenitis, vitamin A-responsive dermatosis, idiopathic seborrhea. Secondary: dermatophytosis and demodicosis. Photograph illustrates clumps of keratosebaceous material adhered to the base of multiple hairs from a dog with sebaceous adenitis.



Figure 157.16 *Comedones* – in general, these lesions may form as a result of primary keratinization disorders or hyperkeratosis due to endocrine abnormalities or inflammation. DDx – primary: endocrinopathies, feline acne, some primary idiopathic seborrheas, congenital hypotrichosis (e.g., Chinese crested dogs), schnauzer comedo syndrome, and vitamin A-responsive dermatosis. Secondary: seborrheic skin disease, application of occlusive greasy medications and administration of systemic or topical corticosteroids, demodicosis and, less commonly, dermatophytosis. Photograph illustrates comedones on the caudolateral aspect of the dorsum of a dog.



Figure 157.17 *Pigmentary abnormalities* – hypopigmentation-hypomelanosis occurs due to a loss of epidermal melanin. DDx – primary: vitiligo. Secondary: common postinflammatory change. Photograph illustrates depigmentation of the nasal planum, rostral muzzle, and lips of a dog with vitiligo.

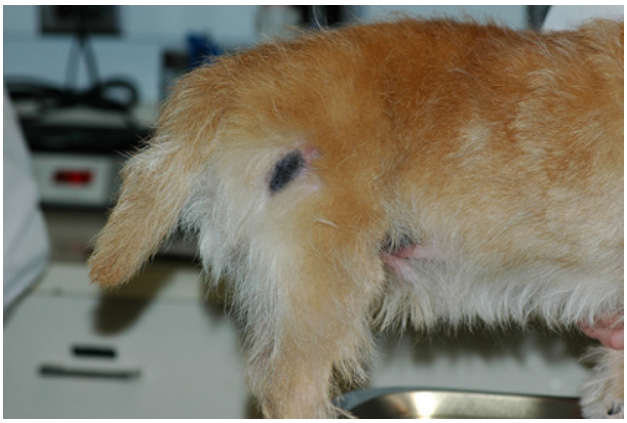


Figure 157.18 *Pigmentary abnormalities* – hyperpigmentation-hypermelanosis occurs with increased epidermal and/or dermal melanin. DDx – primary: endocrinopathies. Secondary: commonly seen in chronic inflammation and as a postinflammatory change associated with a variety of dermatopathies. Photograph illustrates postinflammatory hyperpigmentation in a dog with rabies vaccine-induced alopecia.

Impression Smear

A routine impression smear is one of the most commonly employed dermatologic tests, and an excellent technique to use when pustules, crusts, epidermal collarettes, and draining nodules are present and for moist or greasy areas of the skin. When a pustule is present, gently "open" the pustule by using a 25 gauge needle and pass it in a parallel fashion through the tip of the pustule. Avoid directly "poking" or "sticking" the pustule, as this will artefactually contaminate the specimen with blood and blood-associated leukocytes. When crusts are present, gently remove the crust and sample the contents underneath by pressing the slide gently onto the affected skin. This helps to avoid surface contaminants. When epidermal collarettes are present, rather than

Table 157.3 Regional predilections of skin diseases

Region	Common diseases	Less common diseases
Head	Demodicosis Dermatophytosis Facial fold intertrigo Folliculitis, bacterial Food hypersensitivity, feline Herpes dermatitis Mosquito bite hypersensitivity, feline *Notoedres*	Blastomycosis Cryptococcosis Dermatomyositis Feline leprosy Furunculosis, eosinophilic Idiopathic facial dermatitis of Persian and Himalayan cats Juvenile cellulitis Leishmaniasis Pemphigus erythematosus Pemphigus foliaceus Sporotrichosis Sterile granuloma pyogranuloma syndrome Systemic lupus erythematosus Vasculitis Zinc-responsive dermatosis
Ear	Atopic dermatitis Demodicosis Dermatomyositis Dermatophytosis Ear margin dermatosis Fly bite dermatitis Food hypersensitivity Otitis externa Otodectic mange *Notoedres* *Sarcoptes*	Auricular chondritis Bullous pemphigoid Canine leproid granuloma syndrome Canine proliferative eosinophilic otitis externa Ceruminous cystomatosis Cold agglutinin disease Drug reaction Feline proliferative and necrotizing otitis externa Frostbite Juvenile cellulitis Melanoderma and alopecia of Yorkshire terriers Pattern alopecia Pemphigus erythematosus Pemphigus foliaceus Pinnal thrombovascular necrosis Solar dermatitis, feline Sterile eosinophilic pinnal folliculitis Sterile granuloma pyogranuloma syndrome Trombiculosis Vasculitis
Eyelid	Allergic blepharitis Bacterial blepharitis Chalazion Demodicosis Dermatophytosis Distichiasis Entropion Herpetic blepharitis Meibomitis	Dermatomyositis Discoid lupus erythematosus Epitheliotropic lymphoma Immune-mediated blepharitis Juvenile cellulitis Uveodermatologic syndrome Vitiligo
Nasal planum	Discoid lupus erythematosus Drug eruption Erythema multiforme Nasodigital hyperkeratosis Pemphigus erythematosus Pemphigus foliaceus	Aspergillosis Blastomycosis Canine distemper Contact dermatitis Cutaneous histiocytosis Dermatophytosis (*Microsporum persicolor*) Epitheliotropic lymphoma Familial nasal pyogranuloma and vasculitis (Scottish terriers) Hereditary nasal parakeratosis of Labrador retrievers Leishmaniasis Mucous membrane pemphigoid Nasal arteritis Protothecosis Sterile granuloma pyogranuloma syndrome Uveodermatologic syndrome Vitiligo

Table 157.3 (Continued)

Region	Common diseases	Less common diseases
Lip	Demodicosis Discoid lupus erythematosus Indolent ulcer Lentigo Lip fold intertrigo Mucocutaneous pyoderma Muzzle folliculitis and furunculosis Oral papillomatosis, canine Vitiligo	Candidiasis Contact dermatitis Epitheliotropic lymphoma Juvenile cellulitis Uveodermatologic syndrome Vasculitis
Oral cavity (mucosal lesions)	Eosinophilic granuloma, canine and feline Eosinophilic plaque, feline Erosions, chemical Erosions, viral, feline Erythema multiforme Gingival hyperplasia Plasma cell stomatitis Vegetative glossitis (foreign body)	Bullous pemphigoid Candidiasis Chronic ulcerative paradental stomatitis Epidermolysis bullosa acquisita Epitheliotropic lymphoma Mucous membrane pemphigoid Pemphigus vulgaris Systemic lupus erythematosus Vasculitis
Mucocutaneous junctions	Epitheliotropic lymphoma Erythema multiforme Mucocutaneous pyoderma Systemic lupus erythematosus Vitiligo	Bullous pemphigoid Candidiasis Epidermolysis bullosa acquisita Mucous membrane pemphigoid Pemphigus vulgaris Superficial necrolytic dermatitis Toxic epidermal necrolysis Vesicular cutaneous lupus erythematosus (collie and Shetland sheepdog)
Chin	Canine acne Demodicosis Eosinophilic granuloma, feline Feline chin acne Folliculitis and furunculosis, bacterial Juvenile cellulitis	Dermatophytosis *Malassezia* dermatitis
Neck	Atopic dermatitis, feline Dermoid sinus Flea bite hypersensitivity, feline Food hypersensitivity, feline Injection reactions *Malassezia* dermatitis	Contact dermatitis (collars) Ulcerative dermatitis with linear subepidermal fibrosis, feline
Axilla	Acanthosis nigricans Atopic dermatitis Food hypersensitivity *Malassezia* dermatitis Superficial bacterial folliculitis	Bullous pemphigoid Contact dermatitis Erythema multiforme Pemphigus vulgaris Vesicular cutaneous lupus erythematosus (collie and Shetland sheepdog)
Dorsum	Atopic dermatitis Flea bite hypersensitivity Psychogenic alopecia, feline Seborrhea Schnauzer comedo syndrome Superficial bacterial folliculitis	Calcinosis cutis Cheyletiellosis Pediculosis
Trunk	Demodicosis, generalized Hyperadrenocorticism Hypothyroidism Sebaceous adenitis Superficial bacterial folliculitis	Cutaneous histiocytosis Hyperestrogenism, female Hyposomatotropism Nodular panniculitis, sterile Sterile eosinophilic pustulosis Subcorneal pustular dermatosis Vitamin A-responsive dermatosis

(*Continued*)

Table 157.3 (Continued)

Region	Common diseases	Less common diseases
Abdomen	Atopic dermatitis Eosinophilic plaque, feline Feline symmetric alopecia Food hypersensitivity Hyperadrenocorticism Impetigo Linear preputial erythema Nodular panniculitis, sterile Psychogenic alopecia, feline Solar dermatitis, dog Superficial bacterial folliculitis Trombiculosis	Bullous pemphigoid Calcinosis cutis Contact dermatitis Epidermolysis bullosa acquisita Erythema multiforme Hookworm dermatitis Mycobacteriosis, atypical, feline Pelodera dermatitis Vesicular cutaneous lupus erythematosus (collie and Shetland sheepdog)
Tail	Feline symmetric alopecia Flea bite hypersensitivity Hyperplasia of tail gland Hypothyroidism Mechanical irritation (tail biting) Psychogenic alopecia, feline Pyotraumatic dermatitis Trauma (tip of tail)	Cold agglutinin disease Dermatomyositis Frostbite Tail dock neuroma Vasculitis
Anus	Anal sac disease Atopic dermatitis Food hypersensitivity Perianal fistulae Perianal staphylococcal and/or *Malassezia* dermatitis	Bullous pemphigoid Superficial necrolytic dermatitis Pemphigus vulgaris Perianal gland hyperplasia
Legs	Acral lick dermatitis Contact dermatitis Demodicosis Dermatophytosis Elbow callus pyoderma Eosinophilic granuloma, feline Hygroma Metatarsal fistulae Scabies	Arteriovenous fistula Decubital ulcers Feline leprosy Lymphangitis, bacterial, fungal Lymphedema Pelodera dermatitis
Paws	Atopic dermatitis Demodicosis Dermatophytosis Digital pad hyperkeratosis Food hypersensitivity Interdigital foreign bodies *Malassezia* dermatitis Pedal folliculitis and furunculosis Pemphigus foliaceus Plasma cell pododermatitis Sterile granuloma pyogranuloma syndrome Trauma Trombiculosis	Acral mutilation syndrome Arteriovenous fistula Contact dermatitis Epidermolysis bullosa acquisita Epitheliotropic lymphoma Hookworm dermatitis Leishmaniasis Mosquito bite hypersensitivity, feline Mycetoma Pelodera dermatitis Pemphigus vulgaris Phaeohyphomycosis Protothecosis Superficial necrolytic dermatitis Systemic mycoses Vasculitis (footpads) Vesicular cutaneous lupus erythematosus (collie and Shetland sheepdog) Vitiligo (footpads) Zinc-responsive dermatosis

Table 157.3 (Continued)

Region	Common diseases	Less common diseases
Claws	Hyperthyroidism, feline Paronychia secondary to: bacteria,fungi feline leukemia virus trauma Pemphigus foliaceus Physical trauma Symmetric lupoid onychitis	Bullous pemphigoid Leishmaniasis Onychomycosis Pemphigus vulgaris Systemic lupus erythematosus Vasculitis Vitiligo

sampling the center of the lesion, a more diagnostic sample can be obtained by lifting the scales and crusts from the perimeter and sampling the edge of the lesion as described for crusts.

Once the lesion is prepared for an impression, a glass slide should be gently pressed against the site, heat fixed (either by using a lighter passed under the slide until a light smoky black residue is observed or by using a slide warmer for 20 seconds) or allowed to air-dry, and stained with a modified Wright's stain (e.g., Diff-Quik). Gram stain or new methylene blue can also be used. When using Diff-Quik (which the author prefers), allow the slide to sit in each reagent for approximately 20 seconds. Rinse the slide gently with water after the third solution. The slide should then be air- or blow-dried.

The sample should first be evaluated under the microscope using low-power magnification (×10) to peruse for an infectious versus inflammatory versus neoplastic process. The author finds it easiest to look for acantholytic cells and certain fungal organisms, such as blastomycosis, under the low-power objective, whereas immediate use of the oil immersion objective (×100) may result in the missing of rare organisms or cells. The oil immersion objective is then used (after a drop or two of immersion oil is placed on the slide) to look for organisms and for closer observation and confirmation of inflammatory , neoplastic , and/or acantholytic cells. Draining nodules can also be evaluated by directly pressing the slide to the draining contents and staining as previously described.

Acetate Tape Preparation

This technique is helpful for sampling intertriginous areas, nailfolds, interdigital areas, and dry, scaly, hyperplastic or lichenified skin surfaces. This is the author's preferred technique when *Malassezia* overcolonization or infection is suspected. This test is performed by pressing an approximately 2 cm piece of clear tape sticky side down firmly against the skin several times. The tape is then held at either end and immersed in the No. 3 Diff-Quik stain for 15–20 seconds and then gently rinsed with water to remove excess stain. The tape is allowed to completely air-dry or is blow-dried. A strip of immersion oil is placed on the slide and the tape is placed sticky side down on the strip of oil. Another drop of immersion oil is placed on top of the tape and microscopic evaluation is performed at ×10 and ×100 magnification. A cover slip is not needed.

Surface Skin Scrape

This technique is very useful when evaluating the skin for bacteria and yeast and for sampling areas where an impression smear may be difficult to obtain. However, it is best reserved for sampling affected areas that are greasy, otherwise the sample will not adhere well to the scalpel blade. A No. 10 scalpel blade is used to gently scrape just the surface of the affected area in the direction of the hair growth. It is not necessary to obtain capillary bleeding. Mineral oil is not utilized. The collected material is smeared onto a glass slide and heat fixed, stained, and microscopically evaluated according to the guidelines indicated above for impression smears.

Cotton-Tipped Applicator Smears

Cotton-tipped applicators or swabs are useful for sampling moist lesions and intertriginous areas. The swab is gently rubbed on the surface of the skin and the sample is then rolled onto a glass slide. This technique can also be utilized for hard-to-reach areas where the skin is dry, except that the cotton swab is moistened with saline prior to sampling in order to minimize cell damage during sample collection and preparation. Once the sample is applied to the slide, it is heat fixed, stained, and evaluated as described above for impression smears.

Otic Cytology Otic cytology is also performed using cotton-tipped applicators. Samples are obtained from each external ear canal using a separate cotton swab. A standard system should be used for making slides (i.e., the left ear sample is prepped next to the frosted side of the glass slide and the right ear sample on the other half of the slide). The slide is heat fixed and stained as described above for impression smears. Begin

microscopic evaluation at ×10 and then ×100 magnification. The evaluation of otic cytology is discussed in more detail in Chapter 167.

Fine Needle Aspirate

Fine needle aspirates are best utilized for evaluation of nodular to tumorous lesions. A 20–25 gauge needle attached to a 6–12 cc syringe is used to aspirate the lesion. It is important to release the pressure on the syringe before the needle is withdrawn from the lesion. Once the needle and syringe are removed from the lesion, the needle is detached and the plunger of the syringe is pulled back to draw air into the barrel. The syringe is then reattached to the needle and the contents are expressed onto a slide, gently smeared using a separate clean slide and allowed to air-dry. Alternatively, the fine needle capillary technique can be used. A 22–25 gauge needle is introduced into the lesion by holding onto the hub. Several quick, back-and-forth movements are then made in multiple directions within the lesion, without completely withdrawing the needle, to ensure a representative sample is obtained. The needle is then withdrawn and attached to a syringe (6–12 cc) into which air was already drawn. The plunger is then depressed to expel the material within the needle onto a clean glass slide, spread, and allowed to air-dry.

Following the use of either technique, the slide is then stained with Diff-Quik. Other staining options include gram stain or new methylene blue. Evaluation for microorganisms, such as bacteria, yeast and deep fungal species, and for the overall cell type (i.e., inflammatory or neoplastic) is performed by first evaluating the specimen using the ×10 objective and finally with the high-power objective (×40). The oil immersion objective can also be utilized to evaluate the sample in greater detail.

Trichography (Hair Examination)

Trichography is used for a number of indications. It can be used to detect the presence of parasitic or infectious organisms, such as *Demodex* and dermatophyte arthrospores. Traumatic hair loss due to pruritic behaviors can be confirmed by the presence of hair shafts with blunted tips. When hairs are predominantly found to be in telogen (i.e., resting phase), this may be an indication that an underlying endocrinopathy or follicular arrest may be present. Finally, a presumptive diagnosis of various follicular dysplasias can be made when, for example, marked melanin clumping is present within the hair shafts. The author prefers to gently pluck the hairs using the fingertips so as not to create iatrogenic trauma. The hairs are then placed onto a slide with a drop of mineral oil in an orderly array. A cover slip is placed atop the sample and evaluation is initially performed using ×10 magnification. When aberrant hairs are identified, they can be examined more closely with ×40 magnification.

Skin Scrapes

In general, surface-dwelling mites such as *Sarcoptes*, *Notoedres*, *Cheyletiella*, *D. cornei*, and *D. gatoi* are best procured via superficial skin scrapes, whereas follicular mites, including *D. canis*, *D. cati*, and *D. injai*, require deep skin scrapes for diagnosis.

The superficial skin scrape is performed by applying several drops of mineral oil onto the area to be scraped or onto the chosen skin scraping tool. If necessary, the overlying hair can be shortened with a No. 40 clipper blade to facilitate the scraping procedure, but the clipper blade should not touch the skin surface or any lesions, if present. A No. 10 scalpel blade is used to scrape a large, broad area approximately 10–15 times. Alternatively, a skin scraping spatula (Jorgensen Laboratories, Loveland, CO) can be used. Obtaining capillary bleeding is not necessary, as it is more important to scrape broad, large areas to increase the chances of procuring these difficult-to-find surface-dwelling mites. For scabies, preferred sampling sites include the margins of the pinnae, elbows, and tibiotarsal areas, as these are the most commonly afflicted sites, even if one only identifies mild, subtle lesions. Papules, if present, should also be scraped. The material is then transferred to a glass slide and a cover slip is applied. The sample is then evaluated microscopically with either ×4 (scanning objective) or ×10 magnification in a systematic fashion. The condenser should be lowered to increase contrast and facilitate the finding of mites. Look for all parasitic life stages. The observation of just one egg is considered a positive finding; however, a negative skin scrape does not rule out surface mites. In these cases, when the aforementioned mites are suspected but cannot be confirmed with superficial skin scrapings, a treatment trial may be needed to verify the presence (or absence) of these mites (see Diagnostic Treatment Trials below and see also Chapter 165).

Deep skin scrapes differ from the superficial version in that the sample will be procured from a focal, localized area, squeezing the skin prior to the scrape (and during the scrape if possible) to facilitate extrusion of the mites from the follicles. Several drops of mineral oil are applied either directly to the sample area or to the No. 10 scalpel blade or skin scraping spatula and the skin is scraped in the direction of hair growth until capillary bleeding is evident. Lesions that should be scraped include areas where comedones, erythema, scaling, papules, and pustules are evident. The author finds that comedones are especially important lesions to scrape when follicular demodicosis is suspected. The collected material is then transferred to a glass slide and a cover slip applied and evaluated as described above. If properly performed with

an appropriate number of deep skin scrapes along with the sampling of appropriate lesions, a negative skin scrape can rule out *D. canis* and *D. cati*. However, the diagnosis of pododemodicosis may require biopsy and certain breeds require biopsy to confirm a diagnosis, particularly shar-peis. The identification and treatment of parasitic diseases will be discussed in Chapter 165.

Culture

Bacterial Culture

In this age of methicillin and multidrug resistance, bacterial culture and sensitivity has become a more routinely implemented test in patients with superficial bacterial folliculitis. While performing an aerobic bacterial culture is never contraindicated, there are some instances which make it a necessary test. These include the following:

- poor response and the emergence of new lesions in spite of appropriate antibiotic therapy
- patients with chronic recurrent pyoderma, especially those with a history of multiple courses of antimicrobial therapy
- when rods or unusual organisms are present on cytology
- in cases of deep pyoderma

In cases of superficial bacterial folliculitis, pustules are the ideal lesion to sample; however, epidermal collarettes and crusts can also be sampled. The skin is not cleaned prior to sampling. The pustule is gently lanced with a sterile 25 gauge needle and a mini-tip culturette is touched to the purulent material, taking care to avoid contact with the surrounding nonlesional skin. If crusts are present, the culture should be obtained from underneath the crust. When epidermal collarettes are present, the sample should be obtained from the leading edge where the epithelium is lifted to avoid surface contaminants. The culturette is then placed back into the transport media device and refrigerated until sent overnight to the laboratory. Mini-tip culturettes are commercially available through most microbiology laboratories.

Bacterial cultures of deep infection can vary somewhat depending on the type of lesion being sampled. Fine needle aspiration can be performed to obtain specimens from bullae and dermal or subcutaneous lesions with pockets of fluid. Tissue cultures using sterile technique are best when a nodule, tumor or cellulitis is present. It is also ideal to obtain a tissue culture in the presence of deep infection characterized by exudative draining tracts, rather than merely swabbing any drainage, which will often be contaminated with superficial organisms while deeper organisms may be missed.

The surface should be aseptically prepared by gently swabbing the area with 70% alcohol and can be followed by a rinse with nonpreserved saline. Specimens are obtained via punch biopsy from nonulcerated areas (punch biopsy technique is described in detail below). Local anesthesia is accomplished by infusing 1–2 mL of 2% lidocaine subcutaneously using a 25 gauge needle. Care must be taken not to inject the lidocaine too superficially as it can inhibit microbial growth within the specimen. When in doubt, a ring block may be more appropriate, especially if subcutaneous tissue is also going to be submitted. Sterile instruments should be used as well as gloves. The epidermis is then aseptically removed with a No. 10 surgical scalpel and the remaining deep dermal tissue is used for culture. Removal of the epidermis prevents overgrowth of the tissue culture by surface bacteria that are not relevant to the deep infection. The dermal tissue is placed in a sterile red-top tube with just enough nonbacteriostatic sterile saline to keep the sample moist, and refrigerated and shipped overnight to the laboratory. The tissue sample can be submitted for aerobic, anaerobic, and mycobacteria culture purposes. The laboratory should be notified of the differential diagnoses, as culture media adjustments will be made to facilitate the growth, isolation, and identification of the suspected organisms.

Fungal Culture

Fungal Culture for Deep Mycoses When deep fungal infection is suspected, samples are obtained using the same principles as described above for bacterial cultures of deep infection. Laboratories should be contacted in advance of the differential diagnoses so that modification of culture techniques can be implemented in advance, not only for diagnostic purposes but also because of the human health risks associated with various fungal diseases. Laboratories should also be consulted regarding special requirements for tissue submission. Depending on the suspected organism, additional tests beyond culture may be required, such as polymerase chain reaction (PCR) testing.

Dermatophyte Culture In cases of suspected dermatophytosis, cultures (considered the gold standard for diagnosis) can be performed in hospital using dermatophyte test medium (DTM) or, alternatively, samples may be submitted to a diagnostic laboratory. The clinician should check with their laboratory regarding the preferred means of sample submission. Dermatophyte test medium is most useful because the red color indicator is a helpful diagnostic aid and it also contains inhibitors of bacterial and saprophytic contaminants (e.g., Sab-Duets, Hardy Diagnostics, Santa Maria, CA, USA). Sab-Duets are also popular in that they are double plated: one side contains DTM and the other side contains plain Sabouraud dextrose agar. Dermatophyte test medium may decrease development of conidia, and therefore it is best to perform microscopic identification using the sample plated onto

Sabouraud dextrose agar. The most common dermatophytic agents include *Microsporum canis*, *Microsporum gypseum*, and *Trichophytan mentagrophytes*.

When procuring samples for DTM, hairs should be plucked from within the lesion close to the periphery. A medical-grade plug-in long wave Wood's lamp with magnification can be helpful for identifying fluorescing hairs that can be selected for culture in approximately 50% or more of cases caused by *M. canis* and rarely with *M. gypseum*. The Burton Ultraviolet (Wood's) Exam Light (Philips Burton, Franklin Park, IL, USA) is an excellent model as it provides magnification, and replacement bulbs can be purchased. Medical-grade Wood's lamps do not require a period to warm up, but the room should be darkened and the evaluator allowed to let their eyes adjust for 2–3 minutes. The lamp should be held close to the skin (i.e., 4–10 cm). Infected hair shafts will fluoresce a bright apple green. These are often hiding under crusts, and thus it is important to lift crusts and examine the hairs beneath. Fluorescing hairs are then plucked for culture and can also be evaluated by direct examination to confirm an infection (ectothrix arthroconidia may be observed). Besides directly plucking hairs for culture purposes, the MacKenzie toothbrush technique can be used. Individually packaged toothbrushes can be purchased readily online. This method is especially helpful for sampling poorly circumscribed lesions and nonlesional patients when looking for asymptomatic carriers. A newly unwrapped toothbrush is used to brush the lesions (or the entire patient in asymptomatic animals), and the scales and loose hairs caught in the bristles are gently embedded onto the agar. A sterile needle or hemostat can also be used to remove trapped hair and scale from the toothbrush for placement onto the culture medium.

After inoculation, the culture plate should be placed in a sealable plastic baggie to prevent contamination and dehydration, and put in an incubator. The incubation temperature should be maintained at 75–80 °F and the humidity should be approximately 30%. A digital aquarium thermometer can be used to monitor the temperature, and placing a pan of water in the incubator should be enough to sustain adequate humidity. The plates should be kept away from sunlight or fluorescent light. Cultures should be examined daily and color change (which occurs due to a change in the pH of the media) and colony growth findings must be recorded. Pale, buff-colored to white colonies that simultaneously develop a red ring of color around them as they grow are indicative of dermatophytes. The colonies are typically cottony or velvety and growth will often occur in 4–7 days. A contaminant is likely when there is colony growth and no associated color change of the media or the color change appears more than 10 days after colony growth. Contaminants are also likely when there is a color change but the colony is pigmented. Cultures should be incubated for three weeks before declaring them negative to ensure that there is no late growth of a pathogen.

Cultures grossly suspicious for dermatophyte growth should be evaluated microscopically. The sticky side of clear acetate tape is gently brushed against the colony growing on Sabouraud dextrose agar and placed over several drops of lactophenol cotton blue stain on a glass slide. The sample should sit for 5–10 minutes before examination. This allows for proper absorption of the stain by the spores and thus better visualization. The sample is then ready to be evaluated with the ×10 and ×40 objectives. The macroconidia of *M. canis* are spindle-shaped and have thick, spiny walls that have six or more divisions with a knob at the terminal end. *M. canis* does not produce as many macroconidia as *M. gypseum*, which are thin-walled and ellipsoid with rounded ends having less than six divisions. Microscopic evaluation of *T. mentagrophytes* will typically reveal large numbers of spherical microconidia, rare cigar-shaped macroconidia, and spiral hyphae. The website https://drfungus.org/ contains helpful information regarding the macro- and microscopic evaluation of dermatophytes.

Diagnostic Treatment Trials

Treatment trials are performed often in veterinary dermatology and are used to confirm a suspected diagnosis where the response to therapy is either the only or the best way to diagnose the possible underlying disease. Examples of this include the improvement or elimination of clinical signs with insecticidal therapy in presumptive cases of flea bite hypersensitivity, sarcoptic mange, and *D. gatoi* infestation in cats. In other cases, confirmation of the underlying disease is made when a relapse is observed after discontinuing the trial with subsequent resolution on restarting the trial, as is the case when food elimination trials are performed for diagnosing adverse food reactions. Another example of this concept is the use of glucocorticoids to support a diagnosis of allergic dermatitis when other infectious and parasitic diseases have been ruled out. Further discussion of specific treatment trials can be found in the relevant chapters of this section.

Biopsy and Histopathology

There are several indications for performing skin biopsy early on in the clinical work-up. These include the presence of unusual lesions or lesions that evolve dramatically and/or severely, as in the case of a possible cutaneous adverse drug reaction. Erosive to ulcerative draining dermatoses, especially those that are nodular, also should be biopsied early on. At any point when there is concern of

a life-threatening dermatosis, autoimmune or metabolic disease, or the suspicion of neoplasia, biopsy should be immediately undertaken. Finally, skin biopsies are particularly indicated when a specific condition is suspected and the histopathology is recognized to be diagnostic of that disease. Other less critical reasons for pursuing biopsy include when other tests have not resulted in identification of the condition and when treatment has not resolved the problem. It is important to remember that performing a skin biopsy is never useless. In the best case scenario, it provides a definitive diagnosis, and in the worst case it can rule out other dermatoses and narrow down the category of diseases to be considered. Inform the owner that a precise diagnosis may not be reached but in any case the information obtained will be useful.

In order to maximize results, biopsies must be taken that are representative of the entire disease process. This entails the procurement of spontaneous, primary lesions which generally occur earlier in the course of the disease, along with secondary, more chronic lesions. Therefore, in almost all cases, multiple biopsies should be taken in order to capture the clinical spectrum and evolution of the disease. It is prudent to select lesions that have not been altered by scratching or infection. For depigmenting diseases (e.g., discoid lupus erythematosus), newly depigmented areas are ideal sites for biopsy (e.g., the slate gray areas of the nasal planum rather than the more chronic white/pink or ulcerated areas). When ulcerated areas need to be sampled, biopsy the advancing edge to include some of the epidermis rather than the center of the ulcer. For diseases characterized by alopecia, biopsies should be obtained from the most chronic area of complete alopecia as well as from the junctional and normal areas.

If possible, glucocorticoid therapy should be discontinued 2–3 weeks prior to biopsy. If a long-acting injectable corticosteroid was administered to the patient, it is best to postpone the biopsy for 6–8 weeks, when feasible. Generally, 3–5 biopsies are an acceptable average. When possible, a 6 or 8 mm punch biopsy tool is used. A 3 or 4 mm instrument is used only for difficult-to-biopsy areas (e.g., periocular region, pinnae, nasal planum or footpad). In many cases, punch biopsies can be performed using local anesthesia with 2% lidocaine, with or without sedation. However, when biopsying challenging areas, general anesthesia may be best.

It is helpful to create a small dermatology surgery pack so that all necessary instruments and materials are readily available. Include a No. 10 scalpel blade and handle, straight and curved iris scissors, gauze, Mayo and Metzenbaum scissors, needle and suture, an atraumatic forceps such as a Debakey tissue forceps, and a needle holder. Disposable biopsy punches and 10% formalin-filled vials are readily available in a number of sizes and volumes, respectively.

The biopsy sites must remain perfectly intact and be handled carefully. A scissors or clippers can be used if necessary to gently shorten the overlying hair and improve visualization of the area to be biopsied, taking extreme care not to touch the skin surface or disturb the lesion itself, including crusts. Preliminary scrubbing should never be performed, except in the case of dermal or subcutaneous nodules, where a light prep with 70% alcohol should suffice. An indelible marker is used to circle the lesion and a local anesthetic, such as 2% lidocaine, is injected subcutaneously using a 25 gauge needle and fanning it under the area of the circle. The needle is inserted at the periphery of the site to be biopsied so as not to disturb the lesion itself. Typically 0.5–2.0 mL of anesthetic per site should suffice. The maximum dose of lidocaine that may be administered is 5 mg/kg in dogs and 2.5 mg/kg in cats to avoid adverse effects, such as cardiac arrhythmias. Wait at least five minutes prior to biopsy to allow for optimal analgesic effect.

Center the lesion within the punch biopsy tool and choose a size that minimizes the amount of normal skin margin. However, for vesicles, bullae and pustules, which are fragile and can easily rupture with biopsy, use the largest punch possible or perform an excisional or wedge biopsy. If the procurement of subcutaneous fat is essential to establishing an underlying diagnosis, it may also be pertinent to use an excisional or wedge biopsy technique, and anesthetize the area using a ring block to minimize distortion of the subcutaneous tissue due to local lidocaine infiltration. Rotate the punch biopsy tool in one direction to minimize damaging shearing forces and apply even, continuous pressure until an adequate depth has been obtained to free the tissue down to the subcutaneous fat layer, which should be included in the specimen as it may be important for the accurate assessment and diagnosis of many inflammatory processes. An edge of the subcutaneous fat is gently grasped using an atraumatic tissue forceps to elevate the specimen. The epidermis or dermis should not be grasped, as this could result in a crushing artifact and lead to a nondiagnostic sample. The subcutaneous attachment is then cut. The author prefers a straight or curved iris scissors in most cases. The biopsy sample is then gently blotted to remove excess artefactual blood from the surface.

The sample should be immediately placed in 10% formalin, with a minimum of 10 parts formalin to 1 part tissue required for adequate fixation. Thin samples should be placed, panniculus down, on a small piece of tongue depressor before placement into the fixative to prevent rolling of the specimen, which can make histopathologic evaluation more challenging. Affixed samples must be placed face down into the formalin jar. The

incision is then closed utilizing 1–2 simple interrupted or cruciate sutures.

Provide a thorough history on your biopsy submission form, as well as a description of the physical exam. Preliminary diagnostic tests and their results should also be included if applicable, along with a list of differential diagnoses. Current and past therapy, including response, may also be beneficial. Submission of digital photographs can be very helpful and ideally a dermatohistopathologist should be utilized.

Tests of Noncutaneous Organs

When a dermatopathy is suspected to co-exist with an underlying systemic disease or endocrinopathy, a complete blood count, small animal chemistry profile, and urinalysis may be indicated. These basic tests are also advised to obtain baseline information prior to initiating various treatments. Specific endocrine tests are available for the evaluation of hypothyroidism, hypercortisolism, and sex hormone abnormalities. Various imaging modalities may also be indicated such as radiography and ultrasound. Advanced imaging modalities, including magnetic resonance imaging (MRI) and computed tomography (CT) scans, may also be needed in some cases. The indications and use of these various tests will be elaborated upon in the relevant chapters of this section.

Therapeutic Plan and Client Education

After thorough evaluation, the therapeutic plan most beneficial to the patient can be formulated. Client education is one of the most important aspects of treating the dermatologic patient adequately. Because many skin diseases are controllable but not curable, close communication is essential for a satisfactory long-term result.

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158

Principles of Therapy of Dermatologic Diseases

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This chapter gives a broad overview of a variety of dermatologic therapies and presents the most important general principles that guide their use, including supporting concepts and most common indications. The reader is referred to other chapters in this textbook or reference therapeutic books for details regarding the treatment of various dermatologic diseases using the therapy modalities discussed here.

Topical Therapy

Topical therapy is a useful and versatile treatment modality widely used for skin and otic disorders. Advantages of topical therapy include direct delivery to the target tissue resulting in high drug concentration at the treated site, replacement or reduction of the usage of systemic therapy, avoidance of drug metabolism or gastrointestinal disturbances, lower cost compared to most systemic medications and less probability of causing microbial resistance as seen with systemic antibiotics. On the other hand, topical therapy requires client education for proper use, and can be time-consuming and unpleasant to clients because of staining or greasy preparations.

There are many factors that need to be considered when prescribing topical therapy such as the condition of the skin and ears, the type of lesions present, the need for residual activity, the presence of hair in the area, and the body region and surface area to be treated. Other factors to consider include the active and inactive ingredients (i.e., vehicle) of the medication and administration of adequate drug volume. The vehicle influences treatment effectiveness and may have therapeutic effects; however, it may cause adverse effects such as irritant dermatitis. The ability of the owners to follow instructions and frequency of use should also be considered.

Lastly, there are different formulations or delivery systems available that should be tailored to each patient's needs. These formulations include shampoos, rinses, lotions, powders, creams, ointments, emulsions, sprays, gels, mousses, spot-on solutions, wipes, and ear cleaner solutions. They may have similar active ingredients but their vehicle, efficacy, irritant or cosmetic aspects, ease of administration, and cost will be different according to each formulation and method of application.

Common Formulations of Topical Agents

Shampoos

Medicated shampoos may be effective for cleansing and hydrating the skin, soothing and reducing pruritus, and preventing or treating skin infections. Shampoos may be used for localized or generalized skin disease and may vary in their lathering effect. The type of shampoo and frequency of use are decided on an individual basis according to the skin disorder and ability of the client to bathe their pet. In most shampoo formulations, the active ingredients have limited residual effect; therefore it is generally recommended to keep the shampoo in contact with the skin for 5–10 minutes prior to rinsing. Shampoos are also frequently used as maintenance therapy, such as in allergic animals and those predisposed to skin infections. Different shampoos may be used on an alternating basis or on different parts of the body.

Medicated shampoos are typically classified based on their function, as emollient and moisturizing or hypoallergenic, antipruritic and/or anti–inflammatory, antiseborrheic (keratolytic and/or keratoplastic, and/or degreasing), antibacterial and/or antifungal, and antiparasitic.

Rinses

Rinses are commonly used after shampoos and are available in different forms including those that need to be rinsed off, leave-on formulations that dry on the skin and

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allow more prolonged effect, and newer formulations such as microemulsion sprays which can work well on large body surfaces without the need for baths. The active ingredients in rinses may vary but they often include moisturizers, antiseborrheic agents, and antimicrobials.

Lotions

Lotions are often used for their cooling, antipruritic, antimicrobial, and drying effects, depending on their inactive agents such as water, alcohol and propylene glycol, and their anti–inflammatory, antipruritic, and antimicrobial active ingredients. They are usually recommended for a determined period of time but may also be used for maintenance.

Creams and Ointments

Creams and ointments lubricate the skin, facilitate hydration of the stratum corneum, help prevent water loss, and form a protective covering increasing the penetration of active ingredients. However, these formulations are contraindicated in exudative areas. They may contain water-washable bases such as polyethylene glycol or hydrophobic oils such as mineral oil. The main disadvantages of these products include their somewhat difficult application to hairy skin, their occlusive properties which can potentially lead to folliculitis, and they can be greasy and messy (ointments). Also, their use is limited to localized and small areas such as the paws, elbows, and nose. They are also often used in ears. Most commonly, these formulations contain antimicrobials, anti–inflammatory, antipruritic, keratolytic, and ultraviolet (UV) radiation-blocking agents. Creams are white and nongreasy and contain preservatives to protect against growth of bacteria and fungi. Ointments are oil based or emulsions of oil and water droplets that do not dissipate well when applied to the skin. They are greasy and clear and do not require preservatives. Ointments are selected when increased absorption, hydration, and occlusion are required.

Gels

Gels do not have a sticky residue and are not messy, compared to creams and ointments. Most commonly, they contain anti–inflammatory, antimicrobial, and keratolytic agents in combination with other inactive agents such as propylene glycol and carboxypolymethylene. They are mostly used for localized treatment or small skin areas.

Sprays

Sprays can be very useful and convenient for the treatment of large body areas when frequent baths are not possible and can also complement the use of medicated shampoos. They may also facilitate treatment of difficult areas such as perianal areas and the interdigital aspects of paws. Sprays may contain emollients, moisturizers, antiseborrheic agents, astringents, anti–inflammatory, antimicrobial, and antiparasitic ingredients. Some animals may not allow their application. Alcohol-containing sprays, which are meant to quickly dry, may be irritating, particularly in acute inflamed skin disorders.

Mousses

Mousses are a new form of topical therapy in veterinary medicine and provide an easy and pleasant way for pet owners to deliver active ingredients to haired and non-haired skin. The product must be applied directly to the skin in order to be effective. Mousses may contain antipruritic, antimicrobial, and antiseborrheic agents.

Spot-On Solutions

Spot-on formulations include flea and tick preventatives, fatty acids, ceramides and keratolytic or antiseborrheic agents. These formulations are usually lipophilic with large molecular weights which slow dermal absorption, lower systemic bioavailability, and provide a large area of distribution.

Wipes

Medicated wipes are very useful for treatment of intertriginous areas such as the interdigital, perianal, perivulvar, facial, and tail skinfolds. They contain antimicrobials or antiseptics and can be used for prevention and treatment of bacterial and yeast skin infections. Alcohol-containing wipes may be irritating, particularly in acute inflamed skin disorders.

Ear Cleaner Solutions

Ear cleaners can be used for the treatment of ear infections, on a maintenance regimen to help prevent infections, and after bathing or swimming to keep the ear canals dry. Ear cleaners are often used in conjunction with topical antibiotics, antifungals, and/or glucocorticoids. The frequency of cleaning varies from once daily to once weekly according to the needs of each patient. It is important to demonstrate the cleaning technique to pet owners to improve compliance and efficacy.

The choice of cleaner depends on the condition of the ears. Ceruminolytic agents help remove dry waxy material by dissolving cerumen and include propylene glycol, mineral and vegetable oils, essential oils, glycerine, and xylene. Astringents work as drying agents, reducing humidity and helping prevent maceration. They are indicated for moist ears and include isopropanol, boric acid, benzoic acid, salicylic acid, acetic acid, and aluminum acetate. Drying agents are typically used after debris or exudate has been removed from the ear canals with a ceruminolytic agent. Surfactants emulsify debris and are good for removing tightly adhered debris and include docusate, calcium sulphosuccinate, and sodium lauryl

sulfate. Antimicrobial agents help remove purulent discharge and treat bacterial and fungal infections; they include chlorhexidine, ethylenediaminetetraacetic acid-tromethamine (Tris-EDTA), monosaccharides, para-chlorometaxylenol (PCMX), and organic acids.

The appropriate use and indications for the various ear cleansing agents will be discussed in more detail in Chapter 167.

Systemic Therapy

Systemic therapy is commonly implemented to treat various dermatoses; however, it requires much knowledge of the patient's medical history, drug pharmacokinetics and pharmacodynamics, potential side-effects, toxicity monitoring guidelines, and potential drug interactions. The veterinarian needs to be familiar with the disease being treated and be aware of all treatment options and decide on the most appropriate therapeutic intervention in order to achieve the best clinical efficacy with the least possible toxicity.

Categories and Indications of Topical and Systemic Therapy

Some of the major categories used in veterinary dermatology include anti–inflammatory, antipruritic, immunosuppressive, antibacterial and antifungal agents, antiparasitics and medications to treat hormonal disorders.

Anti–inflammatory Agents

Topical anti–inflammatory agents include glucocorticoids and essential fatty acids. Topical glucocorticoids may be a useful adjunct to systemic therapy in the treatment of both allergic and autoimmune skin disease. They are often used in pruritic and/or inflammatory skin and otic conditions. Common topical glucocorticoids include betamethasone, hydrocortisone, isoflupredone acetate, fluocinolone, mometasone furoate monohydrate, and triamcinolone acetonide. These products are available in the form of ointments, creams, lotions, gels, wipes, shampoos, rinses, and sprays. Many of the available products are otic preparations containing antimicrobials that are also used extra-label on the skin. Topical essential fatty acids may be used as adjunctive therapy to treat inflammatory dermatoses including atopic dermatitis and sebaceous adenitis, as well as keratinization disorders. They are available in formulations such as spot-on, sprays, shampoos, rinses, and mousses.

Systemic products with anti–inflammatory and/or antipruritic and immunosuppressive effects include glucocorticoids, cyclosporine, oclacitinib maleate, essential fatty acids, pentoxifylline, and a combination of a tetracycline and niacinamide. Systemic glucocorticoid therapy is somewhat arbitrarily divided into anti-inflammatory and immunosuppressive, depending on the dosage used to treat the disease.

There are many indications for the anti–inflammatory effects of glucocorticoids including treatment of pruritic dermatoses such as allergic skin diseases and otitis. Indications for the immunosuppressive effects of glucocorticoids include many autoimmune skin disorders such as the pemphigus complex and various sterile inflammatory dermatoses. Commonly used systemic glucocorticoids include methylprednisolone, prednisone or prednisolone, dexamethasone, and triamcinolone acetonide. The glucocorticoid potency must be chosen based on the disease being treated, its severity, and the patient's overall health. It has been shown that only 21% of orally administered prednisone was present in the blood of cats when compared to prednisolone, suggesting poor prednisone absorption or inadequate conversion into prednisolone in the liver. Therefore, prednisolone should be used in cats instead of prednisone due to potential lack of response to prednisone. Injectable glucocorticoids should be avoided for treatment of chronic skin and ear diseases because this route of administration does not offer any therapeutic benefits over oral administration and is associated with more severe hypothalamic-pituitary-adrenal axis side-effects.

Cyclosporine is a calcineurin inhibitor that is used as an anti–inflammatory or immunosuppressive medication according to the condition being treated and the dose used. It is labeled for the treatment of atopic dermatitis in dogs and cats. Other indications include perianal fistulae in dogs, sebaceous adenitis, autoimmune diseases such as the pemphigus complex (particularly in cats), and various sterile and inflammatory skin disorders. For most treated conditions, cyclosporine may take 4–6 weeks to be effective.

Oclacitinib maleate, a novel immunomodulatory drug, is a selective Janus kinase (JAK) inhibitor, preferentially JAK-1, labeled for the control of pruritus and inflammation associated with canine allergic skin diseases, including atopic dermatitis, in dogs at least 12 months of age. It has a rapid mode of action in most patients, reducing pruritus within 24 hours.

Essential fatty acids are nutritional supplements with anti–inflammatory properties. They may be used concurrently with other medications to treat pruritic and/or inflammatory dermatoses such as atopic dermatitis, sebaceous adenitis, and symmetric onychodystrophy, as well as keratinization disorders. They may also help improve the skin barrier and hair coat quality and ameliorate dry and scaly skin. Omega-3 formulations

(containing eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) are usually recommended for inflammatory conditions such as allergic skin diseases, while omega-6 or omega-3/omega-6 combination products are typically recommended for keratinization disorders or to improve the skin barrier. There is no current evidence of the ideal formulation, combination, dosage or ratio of essential fatty acids and many different formulations are available. It may take 8–12 weeks for full clinical benefit to be seen.

Pentoxifylline is a methylxanthine derivative with important anti–inflammatory and rheologic properties which results in increased red blood cell pliability, an especially important feature for the treatment of ischemic dermatopathies such as vasculitis. It may be used as an adjunctive or single agent for the treatment of various dermatoses including vaccine-induced dermatopathies, canine familial dermatomyositis, symmetric onychodystrophy, cutaneous vasculitis, and various sterile inflammatory skin diseases. It may take 4–6 weeks for clinical improvement to be seen.

Combinations of a tetracycline and niacinamide have been used to treat a number of immune-mediated diseases such as discoid lupus erythematosus, pemphigus foliaceus, symmetric onychodystrophy, and sterile granulomatous diseases with variable response and a lag period for efficacy of 4–6 weeks.

Antipruritic Agents

Topical antipruritic substances can provide temporary relief and soothing effect for itching and also pain (e.g., lidocaine), and may be used for adjunctive treatment of localized skin conditions including minor skin irritations, allergic or pruritic reactions, acute moist dermatitis, intertrigo, and acral lick dermatitis. These agents include colloidal oatmeal, diphenhydramine hydrochloride (HCl), lidocaine, neutralized zinc and pramoxine HCl, and glucocorticoids (previously discussed). Depending on the product, they are available as powders, solutions, shampoos, lotions, conditioners, rinses, sprays, gels, ointments, and creams.

Systemic antipruritic medications commonly used include antihistamines and glucocorticoids (previously discussed). Antihistamines are usually indicated for the management of histamine-mediated pruritic and allergic skin diseases including urticaria and insect bite hypersensitivity. Despite the frequent use of antihistamines to treat atopic dermatitis, currently there is no conclusive evidence of the efficacy of type 1 antihistamines for treatment of chronic and acute flares of canine atopic dermatitis. The response to any selected antihistamine is generally individualized and unpredictable. Commonly used antihistamines include amitriptyline HCl, diphenhydramine, hydroxyzine HCl or pamoate, chlorpheniramine maleate, and doxepin HCl. Their sedative effect can be beneficial when treating pruritic skin disorders. Although the newer generation antihistamines such as fexofenadine HCl and cetirizine HCl present a more convenient once-daily dosage, there is no current evidence that these antihistamines have superior efficacy compared to the older generation antihistamines. However, their less sedative effect may be a disadvantage for the treatment of pruritic skin disorders. A novel anti-IL31 monoclonal antibody therapy, labeled for the treatment of canine atopic dermatitis, is available for subcutaneous administration, under veterinarian supervision, with 4–8 weeks of efficacy duration.

Immunosuppressive Agents

Topical immunosuppressive agents include tacrolimus and glucocorticoids (previously discussed). Tacrolimus is a calcineurin inhibitor similar to ciclosporin; however, it is available as an ointment and is 100% more potent. It may be beneficial as adjunct therapy for allergic skin diseases, discoid lupus erythematosus, pemphigus erythematosus, localized cutaneous vasculopathies, and perianal fistula.

Systemic immunosuppressive agents are commonly used for the management of immune-mediated skin diseases including autoimmune diseases, such as the pemphigus complex, cutaneous bullous diseases, and various forms of cutaneous lupus erythematosus. These medications include azathioprine, chlorambucil and cyclophosphamide, in addition to glucocorticoids and cyclosporine (previously discussed).

Azathioprine is a derivative of 6-mercaptopurine and is commonly used in conjunction with a glucocorticoid for the first weeks or months as there is a lag period of up to six weeks before its effect can be noted. The use of azathioprine in cats is not recommended because cats are very susceptible to bone marrow suppression when treated with azathioprine.

Chlorambucil and cyclophosphamide are alkylating agents that are more commonly used individually or in conjunction with other drugs such as glucocorticoids. Their lag period for efficacy is usually up to eight weeks.

Antibacterial Agents

Topical antibacterial agents are often used to treat localized bacterial skin infections such as those associated with wounds, acne, perianal dermatitis, pododermatitis, allergic skin diseases, acral lick dermatitis, and otitis externa. They can also be a good adjunct to systemic therapy in severe or generalized cases of bacterial skin infection. These agents include acetic acid, boric acid, bacitracin, benzoyl peroxide, clindamycin, gentamicin,

neomycin, mupirocin, nitrofurazone, silver sulfadiazine, nisin, and enzyme systems. Often, topical antibacterial agents contain glucocorticoids and antifungals which enhance their effect against other organisms and help reduce inflammation and pruritus. Benzoyl peroxide and clindamycin are often efficacious products for acne cases. Mupirocin is particularly effective against *Staphylococcus* infections, including methicillin-resistant bacteria. These products are usually available as creams, ointments, gels, sprays, or wipes and some may also be available in the form of shampoos, such as benzoyl peroxide, and ear solutions, such as acetic and boric acid.

Systemic antibiotics are usually indicated to treat severe and generalized bacterial skin infections including superficial and deep pyodermas and wounds. The use of systemic antibiotics in cases of otitis media remains controversial; however, high doses of antibiotics may be used in combination with topical therapy in selective cases. The most common systemic antibiotics used include amoxicillin-clavulanic acid, cefovecin sodium, cefpodoxime proxetil, cephalexin, clindamycin HCl, potentiated sulfonamides, doxycycline HCl, chloramphenicol, enrofloxacin, and marbofloxacin. Ideally, for recurrent or chronic infections, systemic antibiotic selection should be based on bacterial culture and sensitivity. Broad-spectrum antibiotics such as fluoroquinolones should be avoided empirically and as first-choice agents as they may select for bacterial resistance. Ciprofloxacin has poor and variable oral bioavailability in dogs and cats and should be avoided in these species.

Antifungal Agents

Topical antifungals are usually prescribed for localized fungal infections, otitis externa associated with *Malassezia* infections, or as concurrent therapy with systemic medications for more generalized or severe cases. The most commonly used topical antifungal agents include clotrimazole, miconazole nitrate, nystatin, ketoconazole, posaconazole, terbinafine, and lime sulfur. Some of these products may contain a combination of glucocorticoids and antibiotics which might be beneficial when concurrent bacterial infection and inflammation and/or pruritus are present. These agents are usually available as creams, ointments, gels, solutions, shampoos, rinses, and wipes.

Systemic antifungals are usually indicated for extensive or severe superficial, subcutaneous and systemic or deep fungal infections including dermatophytosis, *Malassezia* dermatitis, onychomycosis, candidiasis, sporotrichosis, blastomycosis, cryptococcosis, histoplasmosis, and aspergillosis. Systemic antifungals may also be used in severe otitis externa cases in conjunction with topical therapy. The most commonly used systemic antifungal agents include ketoconazole, itraconazole, fluconazole, terbinafine, and amphotericin B.

Ketoconazole is most commonly used in cases of *Malassezia* dermatitis and dermatophytosis in dogs. It should not be used solely as a first choice for systemic mycosis and should be avoided in cats due to its hepatotoxic effects.

Itraconazole is better tolerated in cats compared to ketoconazole. Itraconazole is also commonly used in systemic infections and *Malassezia* dermatitis, but may be cost-prohibitive in large-breed dogs.

Fluconazole can be used for *Malassezia* dermatitis, but it is mostly useful in systemic infections when brain or ocular penetration is needed.

Terbinafine has been reported to be effective in *Malassezia* dermatitis and can also be used for dermatophytosis and systemic or deep mycoses.

Amphotericin B is mostly indicated for cases of systemic mycosis but potential nephrotoxicity is a limiting factor to its use. Lipid-based formulations are available and are much less nephrotoxic than the traditional (deoxycholate) form.

Antiparasitics

Antiparasitic products are used for prevention of fleas, ticks and lice, and treatment of parasitic diseases such as ear mites, demodicosis, sarcoptic mange, and cheyletiellosis. Most commonly used antiparasitic formulations include collars, sprays, shampoos, dips, spot-on solutions, otic solutions, and ointments.

Amitraz solution diluted and applied as a dip is labeled for the treatment of canine demodicosis. Amitraz should be avoided or used carefully in cats. Rotenone ointment may also be used in localized forms of canine demodicosis. Flea and tick preventatives are available in a variety of combinations and include deltamethrin, imidacloprid, flumethrin, fipronil, (S)-methoprene, dinotefuran, pyriproxyfen, permethrin, spinetoram, moxidectin, and indoxacarb. An imidacloprid and moxidectin combination has also been used successfully for the treatment of sarcoptic mange, cheyletiellosis, and mild cases of demodicosis. Products containing permethrin should not be used in cats due to their sensitivity to this compound. Other pyrethroids should be used carefully and according to label instructions, particularly in small kittens. Lime sulfur dip is effective against canine and feline scabies (*Notoedres*), feline surface demodicosis (*Demodex gatoi*), cheyletiellosis and lice, but it is ineffective against fleas. There are several effective products available for the treatment of ear mites including products containing pyrethrin, ivermectin, milbemycin, selamectin, and thiabendazole.

Systemic antiparasitic agents include ivermectin, doramectin, moxidectin, milbemycin oxime, selamectin,

nitenpyram, lufenuron (+/- milbemycin oxime), spinosad (+/- milbemycin oxime), and the newest class of parasiticides called isoxazolines, which include fluralaner, afoxolaner, sarolaner and lotilaner.

Ivermectin, doramectin, moxidectin, and milbemycin oxime are macrocyclic lactones that have been used successfully to treat diseases caused by *Otodectes*, *Sarcoptes*, *Notoedres*, *Demodex*, and *Cheyletiella* in dogs and cats under numerous extra-label dosage and administration regimens.

Selamectin is also a macrocyclic lactone and is labeled for use in dogs and cats for the prevention and treatment of fleas, ticks and biting lice, and treatment of sarcoptic mange in dogs and otoacariasis in dogs and cats. It has also been used for the treatment of cheyletiellosis with good results.

Nitenpyram is a neonicotinoid labeled for the control and treatment of flea infestation in dogs and cats. Since it is an adulticide, it should be combined with an insect growth regulator.

Lufenuron is a benzoylurea compound that is used as an insect growth regulator for flea control in dogs and cats.

Spinosad stimulates the nicotinic acetylcholine receptor in insects with efficacy against adult fleas in dogs and cats.

Isoxazolines work by selective inhibition of GABA- and glutamate-gated chloride channels, leading to hyperexcitation and death of the flea or tick. They are indicated for the treatment and prevention of adult fleas and tick infestations. Additionally, they have been used successfully extra-label for the treatment of parasitic diseases such as demodicosis, sarcoptic mange, cheyletiellosis, and otodectes in dogs and cats.

Systemic Medications for the Treatment of Hormonal Disorders

Systemic medications commonly used for the treatment of hormonal disorders include mitotane, trilostane, melatonin, and levothyroxine sodium.

Mitotane is an adrenolytic agent that selectively destroys the zonas fasciculata and reticularis of the adrenal cortex, while generally sparing the zona glomerulosa. Mitotane is indicated for the treatment of pituitary-dependent hyperadrenocorticism in dogs and may also be used in cases of adrenal-dependent hyperadrenocorticism; however, the induction dose may be higher and the duration longer compared to pituitary-dependent cases.

Trilostane is an adrenal suppressant that reversibly blocks 3-beta-hydroxysteroid dehydrogenase, an enzyme necessary for steroid synthesis in the adrenal cortex. Trilostane is approved for the treatment of hyperadrenocorticism of pituitary or adrenal origin in dogs and may also be beneficial for the treatment of hyperadrenocorticism in cats and alopecia X or hair cycle arrest in dogs.

Melatonin is a hormone synthesized in the pineal gland used in dogs to treat alopecia X with anecdotal success in 50% of cases. It may take 3–4 months for beneficial effects to be noticed.

Levothyroxine sodium is indicated for the treatment of hypothyroidism in dogs and cats.

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159

Atopic Dermatitis

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Etiology/Pathophysiology

In the dog, atopic dermatitis is defined as "a genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features associated with IgE antibodies most commonly directed against environmental allergens." Although the exact pathogenesis of disease development is incompletely understood, current theory supports a multifactorial involvement of genetic predisposition, immunologic dysregulation, and epidermal barrier dysfunction.

During sensitization, it is suspected that epidermal barrier defects allow enhanced contact of allergens with Langerhans cells in the epidermis. These cells capture the allergens and migrate to regional lymph nodes, acting as antigen-presenting cells. In the lymph nodes, Langerhans cells interact with T lymphocytes, creating a skewed distribution and formation of type 2 T helper (Th2) cells. Upon repeated exposure to the allergen, the sensitized Th2 cells produce a variety of inflammatory cytokines which promote production of IgE and infiltration of inflammatory cells into the skin.

Increased levels of interleukin (IL)-4, IL-5, and IL-13 are noted in dogs with atopic dermatitis, along with elevated levels of interferon (INF)-gamma. Recent studies have also documented elevated levels of IL-31 in dogs with atopic dermatitis. This novel cytokine is also produced by Th2 cells and appears to be responsible for much of the pruritus associated with clinical allergic skin disease. In more chronic lesions, the response favors Th1 cytokine production which will contribute to perpetuation of the inflammatory process.

Historically, atopic dermatitis in dogs was believed to be due primarily to immunologic dysregulation and genetic predisposition (as evidenced by the current definition of the disease). However, more recent evidence supports abnormalities in the epidermal barrier which may also influence disease development. Abnormal structure and composition of the stratum corneum intercellular lipid lamellae, altered ceramide content, and abnormal expression of filaggrin (the epidermal filament-associated protein responsible for binding keratin molecules) have been documented in many dogs with atopic dermatitis. Subsequent to these structural abnormalities, increased transepidermal water loss is also noted. The combination of these changes can increase inflammation and severity of disease. Whether these changes are seen in all dogs with atopic dermatitis or only a percentage of patients is currently unknown. There is a similar disease in dogs, termed "atopic-like dermatitis," which manifests with identical history and clinical signs (see below), but in which documentation of IgE involvement cannot be confirmed. Epidermal barrier dysfunction may be a more important contributing factor for disease development in these patients.

In the cat, the etiology and pathogenesis are even less well defined. Although many of the immunologic mechanisms appear to be similar to those seen in the dog, there is a question of the true implication of IgE involvement with disease development. Additionally, epidermal barrier function has not been evaluated in the cat as a contributing factor. For these and other reasons, many prefer to use the term "nonflea nonfood hypersensitivity dermatitis" when discussing atopic dermatitis in cats.

Epidemiology

Atopic dermatitis can present in dogs and cats worldwide, though geographic differences may play a role in the development of disease (e.g., clinical signs may manifest earlier in life in animals in warm weather climates where the level of allergen exposure is rather high), as well as prevalence in that region. A few older studies have

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reported variable prevalence of the disease, ranging from less than 5% to greater than 25% of the canine population; true prevalence of disease is uncertain. For the past few years, atopic dermatitis (or "skin allergies") has been consistently listed in the top 10 reasons for dogs and cats to be presented to veterinarians in the United States.

Signalment

Depending on literature cited, age of onset may range from 4 months to 7 years, though the majority of dogs and cats with atopic dermatitis will typically start to manifest clinical disease between 6 months and 3 years of age. There does not appear to be consensus on whether the disease is more prevalent in females or males, or whether sex predilection affects disease development. Although any breed of dog may be diagnosed with atopic dermatitis, breed predisposition has been reported due to the genetic component of disease pathogenesis. More commonly affected breeds include but are not limited to Boston terrier, boxer, Chinese shar-pei, Dalmatian, English bulldog, German shepherd, golden retriever, Labrador retriever, pug, and West Highland white terrier dogs. Although genetic involvement has also been noted in cats, no specific breed predispositions have been identified.

History and Clinical Signs

The hallmark of atopic dermatitis in both dogs and cats is pruritus, which will often be reported as mild at first but progresses to become more moderate to severe as the disease advances. Depending on which specific allergens are involved and/or flare factors in the animal's particular environment, pruritus may be present seasonally or nonseasonally. This may also be affected by geographic location; in dogs and cats with historically mild disease, the severity might increase if they move to a warmer climate where allergen load is higher or different from what they were exposed to historically. If concurrent allergic conjunctivitis or rhinitis is present, serous ocular or nasal discharge, sneezing, or congestion, respectively, may also be present with pruritic skin. In cats, feline asthma may also be a concurrent finding.

In early stages of disease, pruritus may present *sine materia*, or without concurrent lesions. More often, though, dogs without secondary bacterial skin infection or yeast overgrowth will present with fairly symmetric, variably erythematous macules and patches (Figure 159.1) or small papular lesions (Figure 159.2). Additionally, signs of self-trauma may be noted in the form of excoriations (often linear), hemorrhagic crusts, self-induced alopecia/barbered hair, hyperpigmentation, and lichenification (Figure 159.3).



Figure 159.1 Moderately erythematous, coalescing macules in the inguinal region of a dog with atopic dermatitis.



Figure 159.2 Pinpoint, faint papules on the sternum of a dog with mild atopic dermatitis.

Uncommonly, urticarial lesions (hives) may be seen in dogs with atopic dermatitis. Salivary staining of the hair is commonly noted, particularly in light-colored dogs, which also supports the presence of pruritus (Figure 159.4).

On close physical examination, the clinician will often find broken pieces of barbered hair stuck between the gingival tissue and dental arcade, another "clue" that pruritus is present. When additional lesions are noted, such as pustules, crusts, or epidermal collarettes, alternative disease entities including parasites (*Demodex*) and



Figure 159.3 Marked lichenification and hyperpigmentation of the periocular skin in a dog with severe atopic dermatitis. Additionally, hemorrhagic crusts and additional hyperpigmentation with associated alopecia can be seen along the dorsal aspect of the muzzle. Facial pruritus was marked in this patient.



Figure 159.4 Salivary staining on the paws of a patient with atopic dermatitis. Moderate erythema can also be appreciated within the interdigital webs of the right front paw.

infections (particularly superficial bacterial pyoderma and dermatophytosis) need to be investigated.

The distribution pattern of lesions and pruritus is most helpful when considering atopic dermatitis. Clinical disease in dogs most commonly affects ventral sparsely haired areas including the abdomen, thorax, inguinal, and axillary folds. Facial distribution including periocular skin and muzzle is also common. The dorsal and ventral interdigital webbing of the paws along with the lower portion of the limbs is often concurrently pruritic; flexural surfaces of the elbows are included in this body region. Otitis externa and perianal pruritus are often reported by owners, and may manifest as head shaking



Figure 159.5 Cat with moderate-to-severe periocular erythema, swelling, and self-induced excoriation from scratching.

or scooting, respectively. In most cases, the dorsal aspect of the dog is spared, unless concurrent flea allergy dermatitis is noted (caudal hind end distribution including rump and tail head). In some dogs, a more widespread distribution of lesions and pruritus is noted. This may be seen more commonly in different breeds including German shepherd, Chinese shar-pei, and West Highland white terrier dogs, which have shown phenotypic diversity compared to other dog breeds with more standard distribution of lesions reflecting atopic dermatitis.

In cats, the distribution pattern and clinical lesions tend to be less consistent. Cats will, however, generally present with one or more cutaneous reaction patterns: cervicofacial dermatitis (head, neck, pinnal pruritus) (Figure 159.5), self-induced noninflammatory alopecia (Figure 159.6), miliary dermatitis (Figure 159.7) and/or eosinophilic skin lesions (i.e., eosinophilic plaque) (Figure 159.8), eosinophilic granuloma, and indolent ulcer (Figure 153.9). None of these reaction patterns, however, are pathognomonic for allergic skin disease in the cat. Other causes of pruritus need to be investigated prior to diagnosing atopic dermatitis. This is especially true for eosinophilic lesions (particularly plaques and indolent ulcers) as these are often manifestations of bacterial pyoderma in the cat.

In people, a phenomenon known as the "atopic march" has been described where the disease starts with atopic dermatitis or eczema and progresses to rhinitis and asthma. Although the "atopic march" has not been

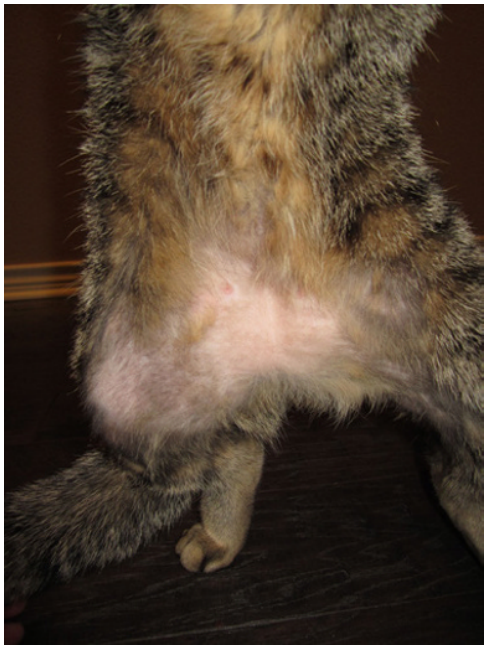


Figure 159.6 Self-induced noninflammatory alopecia on the abdomen of an atopic cat.

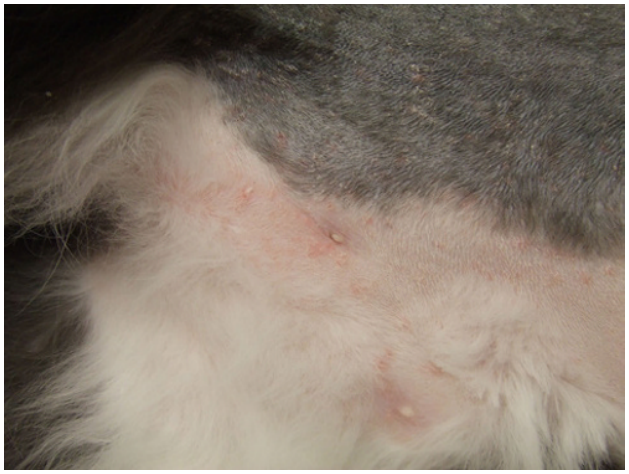


Figure 159.7 Miliary dermatitis lesions (crusted erythematous papules) on the ventrum of an atopic cat. These lesions were readily palpated, but not easily visible until the patient was shaved.



Figure 159.8 Eosinophilic plaque lesions on the ventral abdomen of an allergic cat. Several individual plaque-like lesions coalesced to form the large plaque in the image.



Figure 159.9 Unilateral indolent ulcer on the upper lip of an allergic cat.

reported in dogs, the disease may start off fairly mild with regard to severity of pruritus noted, or be limited to only certain body regions. However, as the dog ages, and particularly if therapeutic intervention is not pursued, the disease will commonly progress. More severe pruritus is generally reported and more body regions become affected over time. Additionally, the seasonality of the disease will often change; what may have begun as very seasonal pruritus will show evidence of extension of season (e.g., signs of atopic dermatitis may have initially been only in the spring, but now extend into the summer and fall) and eventually be present year-round. Seasonal flares or worsening may still, however, be present in these dogs.

Diagnosis

The diagnosis of atopic dermatitis is based on a consistent and fitting history, clinical signs, and exclusion of all other pruritic dermatoses. There is no test which

definitively diagnoses atopic dermatitis (this is true for dogs, cats, horses, and humans); rather, it is a diagnosis of exclusion. This includes ruling out pruritus due to the presence of parasites (fleas, lice, *Sarcoptes*, *Otodectes*, *Cheyletiella*, *Demodex*), infections (staphylococcal pyoderma, *Malassezia* overgrowth, dermatophytosis), flea allergy dermatitis, and cutaneous adverse reaction to food. As pruritus is an additive process, meaning that several contributing factors/diseases can result in the manifestation of pruritus in a given patient, and multiple factors may be present at the same time (e.g., atopic dermatitis with secondary superficial bacterial folliculitis), it is imperative to rule out confounding factors prior to arriving at a diagnosis of atopic dermatitis. Additionally, every patient is slightly different with regard to their "pruritic threshold." Once secondary problems or confounding pruritic dermatoses are identified and addressed, the clinician might note that the patient's baseline level of pruritus is much less severe than what was initially thought.

Recently, a set of criteria has been proposed to aid in the diagnosis of atopic dermatitis in dogs. Granted, the parameters suggested may be seen along with other pruritic skin diseases but if the clinician takes the appropriate steps to rule out parasites and infections, the presence of these criteria strongly supports a clinical diagnosis. The presence of five of the criteria has a specificity of 79% and a sensitivity of 85% to differentiate dogs with atopic dermatitis from those with other chronic and pruritic skin diseases. The presence of a sixth criterion increases specificity to 89%, but sensitivity is decreased to 58%. The criteria (referred to as Favrot's criteria) are as follows:

- Onset of signs before 3 years of age
- Dog living mostly indoors
- Glucocorticoid-responsive pruritus
- Chronic or recurrent yeast infections
- Affected front feet
- Affected ear pinnae
- Nonaffected ear margins
- Nonaffected dorsolumbar area

Once a clinical diagnosis of atopic dermatitis has been made, documentation of IgE involvement may be pursued with either serum or intradermal allergen testing. With allergen serology tests, radioallergosorbent (RAST), enzyme-linked immunosorbent assay (ELISA), or liquid-phase immunoenzymatic assays are used to identify the presence of allergen-specific IgE in the patient's serum via colorimetric, fluorometric, or radiometric analysis. Various commercial laboratories utilize different methodologies for detection of allergen-specific IgE; specificity of the testing reagent (e.g., decreased cross-reactivity with IgG), allergen extracts used, and lack of standardization protocols lead to a great deal of variability between tests. Currently, comparison of tests from different laboratories does not show appreciable correlation.

Intradermal allergen testing is considered to be the "gold standard" for documentation of IgE involvement in atopic dermatitis in the dog. Intradermal injection of various environmental allergens causes mast cell degranulation, extravasation of edema fluid, erythema, and formation of a wheal by IgE binding with sensitized molecules (Figure 159.10). Intradermal testing in cats tends to be more difficult and often frustrating; cats tend to form less distinct wheals and more subtle positive reactions when compared to dogs, although the test can be beneficial in this species as well. This test is best performed by a board-certified veterinary dermatologist; it requires practice with regard to technique and interpretation, and cost of allergen upkeep may be prohibitive for the general practitioner.

It is important to remember that a positive test result must be viewed in light of the animal's history and seasonality of disease. Additionally, these allergy tests can be positive in approximately 50% of animals without a clinical diagnosis of atopic dermatitis so it is imperative that serum and intradermal allergen tests are not used to diagnose disease. Rather, these tests become important considerations if the owner wishes to pursue immunotherapy for their pet (see below). Their importance stems from educated guidance on immunotherapy formulation.

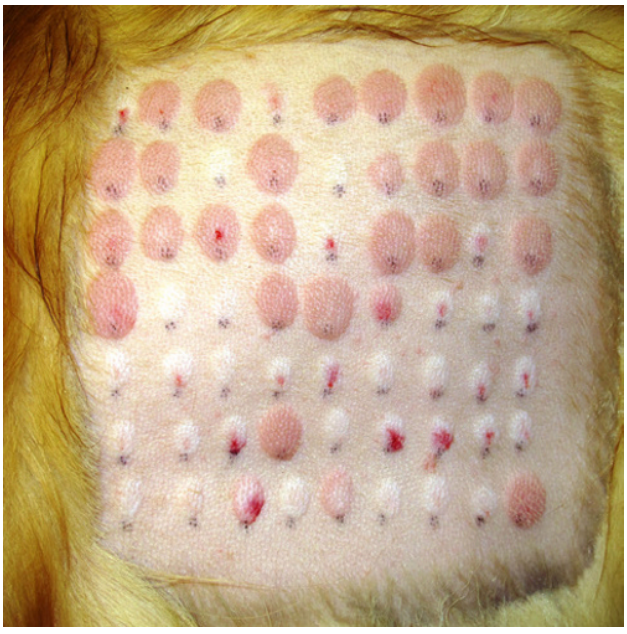


Figure 159.10 Intradermal allergen test showing several positive reactions to various environmental pollens. Positive reactions are demonstrated by the formation of an erythematous wheal.

Several factors can influence the results of allergen testing, including time of year (particularly if seasonal variation is noted), strength of allergens, and significant inflammatory skin disease (either due to atopic dermatitis alone or other concurrent pruritic dermatosis). Additionally, administration of antipruritic pharmacotherapy can dampen or mask "positive" test results. This is especially true for intradermal allergen testing. A recent review proposed optimal and minimal withdrawal times of antipruritic drugs prior to allergen testing. Based on a review of the current literature, antihistamines should be withdrawn for at least seven days, oral and topical glucocorticoids (including otic preparations) for at least 14 days, and a minimum of 28 days for longer-acting injectable glucocorticoids (although many dermatologists recommend at least 4–8 weeks withdrawal) prior to intradermal allergen testing. There was insufficient evidence to make recommendations for medication withdrawal prior to serology allergen testing; these tests may be less influenced by the presence of antipruritic pharmacotherapy but care must be taken with regard to interpretation of results.

Therapy

As with people and other domestic animal species, there is no cure for atopic dermatitis in dogs or cats. However, the disease can be fairly well managed with various therapeutic interventions. Therapy falls into two categories: medical and allergen-specific immunotherapy. Medical therapies aim to primarily address the pruritus and discomfort associated with atopic dermatitis, whereas allergen-specific immunotherapy attempts to "retrain" the immune system, shifting back towards a more "normal" Th1 response as opposed to Th2 dysregulation.

Medical Therapy

With regard to medical therapy for atopic dermatitis, interventions span the spectrum from fairly conservative to more aggressive. Options for conservative therapy include implementation of environmental allergen avoidance, bathing and other topical therapy, antihistamines, and essential fatty acid administration. More potent, "aggressive" medical therapy includes administration of systemic glucocorticoids, ciclosporin, or oclacitinib. Additional/alternative therapies have also been evaluated with variable success.

Avoidance

Avoidance of environmental allergens can be rather difficult, particularly since many dogs and cats with atopic dermatitis show reactions to allergens which cannot easily be avoided or eliminated. Pollens, for example, are essentially impossible to eliminate. Owners will often ask about changing the immediate environment to which the dog or cat is exposed (e.g., removing problematic trees or grasses from the property). However, the spread of aeroallergens can have an approximately 100 mile radius or more, depending on environmental conditions. The statement "if it is not in your own yard, it might be in your neighbor's" holds a large amount of truth.

There is a large market as well for avoidance and reduction of house dust mite allergen (the most common environmental allergen implicated in atopic dermatitis in dogs worldwide). Special air filters, pillow, and mattress covers are designed to reduce the load of house dust mite in the environment, and household cleaning products have been designed to kill and thereby reduce house dust mites in the home. These measures do not completely eliminate allergens from the environment and therefore are insufficient on their own to reduce severity of disease. Decreased exposure, however, may allow for a reduced flare of atopic dermatitis and/or provide benefit as an adjunct intervention with additional therapeutic measures. Additional recommendations for improved allergen avoidance include frequent washing of pet and household bedding, maintained replacement of air filters in the home, avoiding fresh cut grass (for pollen allergens), and frequent bathing.

Bathing and Other Topical Therapy

Along with mechanical removal of environmental allergens, bathing provides additional therapeutic benefit to the atopic dog. Shampoos containing antipruritic ingredients such as colloidal oatmeal, pramoxine (topical analgesic), antihistamine, or glucocorticoids are often recommended as maintenance therapy for the allergic dog; interestingly, however, studies have not documented improvement with any specific ingredient over another. A small study evaluated a lipid and complex sugar-containing shampoo with and without the addition of whirlpool bathing; bathing with the shampoo showed evidence of clinical reduction of pruritus, which was reduced further when a whirlpool was also used. Taken together, the physical act of bathing may be the most important factor for providing relief to the pruritic dog as opposed to a specific ingredient or formulation. The above ingredients, however, are benign and often owners feel their pet experiences more beneficial results when a particular product or ingredient is used.

Bathing is typically recommended once every 1–2 weeks long term. In the face of an allergic flare, more frequent bathing may be beneficial. In dogs where secondary bacterial or yeast skin infections are contributing factors associated with atopic dermatitis, shampoos

containing antiseptic ingredients (e.g., chlorhexidine, miconazole, ketoconazole, ethyl lactate) may be better recommended for maintenance bathing.

Although bathing has historically been considered the "gold standard" adjunct therapy for allergic dogs, newer formulations of products are cropping up with increased frequency. The addition of spray, mousse, and leave-on lotion formulations may increase client compliance due to the decreased effort/time involved in application. These products often are identical to or mimic their shampoo counterparts with regard to active ingredients; depending on the formulation, they may be used to decrease frequency of bathing, or provide longer acting beneficial response after the recommended bath. As many cats are not overly fond of bathing, these alternative formulations may be of added benefit in this species as part of the therapeutic regime.

Application of topical essential fatty acids, lipids, and ceramides has been a newer area of investigation for therapy of canine atopic dermatitis. These products aim to improve the structure and/or function of the epidermal barrier by "normalizing" lipid and ceramide content of the epidermis. Much of the information regarding these therapies has been largely anecdotal; smaller studies indicate that benefits may take several weeks to be apparent (upwards of 12 weeks to see maximal benefit). In the mildly atopic patient, these formulations may be sufficient solely (or with occasional additional conservative therapy) to control disease; however, they are likely to be insufficient on their own to control a more severely affected atopic dog. Their benefit in that case may be as an adjunct therapy, allowing for reduction of more potent therapeutic interventions. As it is still unclear whether all or only some dogs with atopic dermatitis manifest with epidermal barrier dysfunction as part of their clinical disease, the true benefit of these products is largely uncertain.

Particularly when fairly localized pruritus is present in the atopic patient, topical glucocorticoids may provide beneficial results with minimal systemic absorption. These may come in ocular or otic preparations, or in topical lotions, creams, or sprays. The efficacy of various products varies markedly with the potency of the steroid used. Evidence exists in favor of utilization of a 0.0584% hydrocortisone aceponate-containing spray (Cortavance® Virbac, Canada) or 0.025% budesonide-containing leave-on lotion (Barazone®, Dermcare-Vet, Australia) for management of atopic dermatitis in the dog; these products, however, are not necessarily available worldwide (both are currently unavailable in the USA). Depending on formulation and potency of steroid used, side-effects can include some systemic absorption, thinning and decreased elasticity of the skin, phlebectasia, and milia formation.

Similar to topical glucocorticoids, application of topical tacrolimus (Protopic® 0.03% or 0.1% ointment, Astellas Pharma, Illinois, USA) may provide localized control of pruritus in the atopic dog. This calcineurin inhibitor acts similarly to ciclosporin; it more specifically reduces T cell-mediated inflammation without the side-effects of topical glucocorticoid therapy. It does, however, have a much slower onset and may not be beneficial in the face of an acute pruritic flare.

Antihistamines

The benefit of antihistamines in atopic dermatitis is markedly uncertain. As the manifestation of pruritus involves many more inflammatory mediators other than histamine, which may in fact only account for a very small part of itch development in an atopic dog or cat, antihistamine administration by itself may make a negligible difference in the management of the allergic patient. According to a review of the evidence, their benefit has not been convincing, particularly in the case of an acute flare. That said, they may more importantly serve as an adjunct therapeutic intervention, allowing for reduced administration of more potent antipruritic therapy, in particular systemic glucocorticoid administration.

Commonly used antihistamines in the dog include cetirizine (0.5–1 mg/kg PO q24h), hydroxyzine (2 mg/kg PO q12h), diphenhydramine (2.2 mg/kg PO q12h), amitriptyline (1–2 mg/kg PO q12h), chlorpheniramine (0.4 mg/kg PO q8–12h), and loratidine (1 mg/kg PO q12–24h). Additionally, some evidence exists to suggest that fexofenadine (1–2 mg/kg PO q24h) may provide sufficient improvement in pruritus in atopic dogs. In cats, additional options include clemastine (0.25–0.68 mg/kg PO q12h) and cyproheptadine (2 mg/cat PO q12h). It is important to remember that every allergic dog and cat is a bit different; one antihistamine medication may be more effective than another for reduction of pruritus. Serial two-week trials of antihistamine medications may be necessary to arrive at an adequate therapeutic choice.

Essential Fatty Acids and Other Nutritional Supplements

Similar to topical ceramide- and lipid-containing products, systemic administration of essential fatty acids may enhance epidermal barrier function by incorporating more "normal" skin lipids into the epidermis. Although the ideal ratio of omega-3/6 essential fatty acids is unknown, most dermatologists recommend dosing based on eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA). Supplementation of 180 mg/4.5 kg EPA and 120 mg/4.5 kg DHA per day is favored for atopic dermatitis; the daily dose is calculated based on the concentration of EPA and DHA in a particular product. Additional nutritional supplements such as choline,

nicotinamide, histidine, and inositol have been shown to possibly augment barrier function in healthy dogs by increasing production of ceramide skin lipids; whether they have beneficial results in dogs with atopic dermatitis, however, is uncertain. As with some of the other conservative medical therapies, their most important benefit may be in the form of adjunct therapy for the disease, thereby decreasing the need for additional medical interventions.

Glucocorticoids

Glucocorticoids have historically been touted as a mainstay therapy for atopic dermatitis in dogs and cats. Their efficacy in management of pruritus associated with the disease is without question; in fact, excellent response to glucocorticoid therapy can be a key factor in confirming a clinical diagnosis of atopic dermatitis. Strong evidence exists with regard to efficacy, particularly for controlling nonlocalized pruritus associated with atopic dermatitis. Particularly for the acute flare, short-course oral glucocorticoid administration can be highly effective in managing the atopic patient. Recommended dosing for oral glucocorticoids (prednisone, prednisolone, methylprednisolone) is initiation of therapy at 0.5 mg/kg PO q12–24h and then reducing to the lowest possible (ideally alternate-day) dosing which provides sufficient comfort. In cats, it is imperative that either prednisolone or methylprednisolone be prescribed as most cats do not respond as well to the prodrug (prednisone). Additionally, allergic cats often require a higher initial dose (1–2 mg/kg PO q24h) for clinical effect. The use of long-acting injectable glucocorticoids should be avoided for the management of chronic inflammatory diseases such as atopic dermatitis, as they have a much stronger effect on the hypothalamic-pituitary-adrenal axis. Moreover, their antipruritic/antiinflammatory effect is not superior compared to oral short-acting glucocorticoids.

Although highly effective and cost-effective (even for large patients), the side-effects of continued long-term glucocorticoid administration are concerning. Clinicians are encouraged to consider and pursue alternative therapy for atopic dermatitis if glucocorticoid administration is necessary for several months of the year to provide benefit.

Ciclosporin

As with glucocorticoids, there is strong evidence to support ciclosporin administration for management of atopic dermatitis in dogs and cats. This calcineurin inhibitor more specifically targets T cell-mediated inflammation associated with atopic dermatitis. It is important, however, to remember that the modified version of the drug (e.g., Atopica®, Elanco Animal Health, Indiana, USA) must be administered for predicted efficacy. This microemulsion of the parent drug is more predictably absorbed and metabolized in the dog and cat compared to nonmodified formulations.

Dosing is initially recommended to be 5–7 mg/kg PO q24h. Cats, particularly those with indolent ulcers, may require a higher initial dose (7–10 mg/kg PO q24h) to achieve initial beneficial results. When remission is achieved, this dose or frequency of administration may often be decreased while still achieving similar clinical benefit on a long-term basis. Although it is recommended to be given on an empty stomach, administration with food has not been proven to alter clinical improvement. Additionally, drug level monitoring is generally not indicated for the allergic patient; therapeutic drug levels do not typically correlate with clinical improvement. Obtaining ciclosporin drug levels may, however, be beneficial in a dog or cat with a clinical diagnosis of atopic dermatitis that is not responding favorably to therapy.

Compared to glucocorticoids, ciclosporin is generally better tolerated with fewer side-effects, even long term. This is not to say that side-effects do not occur; it is recommended to monitor basic internal health (e.g., complete blood count, serum biochemistry, urinalysis and urine culture and sensitivity) every 6–12 months long term with continued ciclosporin administration. The most commonly reported side-effect is gastrointestinal upset (e.g., vomiting, diarrhea, decreased appetite). These side-effects are typically self-limiting and transient; gastrointestinal upset will typically resolve within 1–2 weeks of initiating therapy. Antinausea medication (e.g., maropitant) may be necessary in the short term to minimize undue patient discomfort.

Other less commonly reported side-effects of ciclosporin include bacterial infections, bone marrow suppression, hirsutism and excessive shedding, gingival hyperplasia, hepatitis, papillomatosis, and seizures. Additionally, in cats, acute and fatal toxoplasmosis has also been documented. It is recommended that cats remain indoors and not be fed a raw diet, be completely restricted with regard to scavenging and hunting, and have serology documenting toxoplasma and feline leukemia virus/feline immunodeficiency virus (FeLV/FIV) status prior to initiating therapy.

Ciclosporin levels in the blood may be influenced by concurrent administration of other medications. Ketoconazole and fluconazole, for example, can increase the circulating ciclosporin levels via competitive binding of the cytochrome P450 enzyme. Although this combination can be clinically useful (e.g., allowing for lowered dose of ciclosporin required to achieve clinical results, thereby decreasing the cost of therapy), it can also increase the chance of side-effects. Care must be taken with other cytochrome P450-associated medications

(e.g., metoclopramide, metronidazole) as concurrent administration may increase side-effects.

As opposed to glucocorticoids, which cause a rapid reduction in pruritus, there is a lag associated with ciclosporin administration and clinical improvement. Maximal benefit is typically noted within about 4–6 weeks. At that time, if the patient is sufficiently comfortable, the medication may be tapered.

Oclacitinib

Oclacitinib (Apoquel® Zoetis, New Jersey, USA) is a novel Janus kinase inhibitor approved for dogs in the USA and Europe to control the pruritus associated with allergic dermatitis in general and, specifically, atopic dermatitis. Oclacitinib rather specifically inhibits production of IL-31 from T cells in the dog.

This targeted therapeutic is similar to other tyrosine kinase molecules which have shown some benefits in the treatment of atopic dermatitis (e.g., masitinib), but the safety profile is markedly enhanced. In a recent study, side-effects were reduced compared to either glucocorticoids or ciclosporin even when the medication was administered long term. Vomiting and diarrhea were the most frequent side-effects reported but were typically transient and self-limiting and did not require additional therapy or withdrawal of medication. Minimal changes were noted on bloodwork and urinalysis, with values remaining typically within the normal range. Decrease in white blood cells was noted in some patients, along with increased cholesterol and lipase in others; however, neither fell outside a normal reference range. Efficacy for control of pruritus associated with atopic dermatitis is considered excellent in most dogs.

Dosing is recommended at 0.4–0.6 mg/kg PO q12h for the first two weeks, and then q24h long term. Increase in pruritus is commonly noted as the frequency of administration is reduced to once daily; however, care should be taken to not administer the dose twice daily longer than the recommended two weeks because of increased risk for concerning, long-term side-effects. The increase in pruritus is likely because the drug has a rather short serum half-life and dividing the once-a-day dose to twice-a-day administration may help control the pruritus flare in some patients. Oclacitinib has a very rapid onset, often markedly decreasing pruritus within the first one to two doses. It has not been extensively evaluated in cats with allergic skin disease and its use in this species is not currently recommended.

Lokivetmab

Lokivetmab (Cytopoint, Zoetis)is the first anti-IL31 monoclonal antibody (mAB) licensed for the treatment of allergic and atopic dermatitis in dogs. The injection is administered subcutaneously at a minimum dose of 2 mg/kg under the direction of the veterinarian. It can provide efficacy within 24 hours and can provide therapy for an average of 4–8 weeks, at which time it may be repeated. This therapy is considered to be safe and is intended for both short- and long-term use. Side effects are minimal; vomiting, diarrhea, injection site discomfort, and lethargy are most commonly reported and tend to be self-limiting in nature. It may be used in dogs of any age, including those with concomitant diseases. There are no drug-drug interactions reported thereby adding to Cytopoint's robust safety profile. As this is a caninized mAB, it should only be administered in dogs.

Miscellaneous Therapies

Many additional therapeutic interventions have been investigated for controlling pruritus associated with atopic dermatitis in the dog. There is some evidence to support administration of recombinant interferons (either recombinant feline INF-omega or recombinant canine INF-gamma); these injections have shown moderate efficacy and a good safety profile in several allergic dogs. However, products are not necessarily available worldwide. Other therapies such as azathioprine, various cyclooxygenase/cyclooxygenase-lipoxygenase inhibitors, and pentoxifylline have been evaluated but have not shown appreciable efficacy in atopic dogs.

Allergen-Specific Immunotherapy

As opposed to addressing strictly the clinical signs associated with atopic dermatitis, allergen-specific immunotherapy aims to address the underlying immunologic dysregulation which is part of the disease pathogenesis. Although the exact mechanism of action is uncertain, successful therapy may lead to a more "normalized" immunologic response to allergen exposure. This was documented in one study where dogs that responded favorably to therapy showed increases in less inflammatory cytokines (IL-10) and regulatory T cells.

Allergen-specific immunotherapy is a "cocktail" of extracts of various environmental allergens based on the results of allergen testing (see above). Although no well-controlled clinical studies have established an ideal treatment protocol, formulation, or administration schedule for immunotherapy, benefits do appear to be noted in some dogs and cats with atopic dermatitis. Efficacy, however, does appear to be less when compared to other options (e.g., glucocorticoids, ciclosporin, oclacitinib). Based on anecdotal reports, approximately 50–75% of dogs and cats with atopic dermatitis show beneficial results with immunotherapy administration. As the therapy aims at changing the underlying immune response, results may take several months to be apparent. Clinical improvements may initially be seen within the first 3–6 months but maximal benefits may not be noted until 12–18 months. Most patients require the addition of

concurrent antipruritic pharmacotherapy during the induction of immunotherapy.

Two formulations currently exist for immunotherapy: subcutaneous injections and sublingual/oral drops. Injections have been available much longer than the oral formulation and so we have much more information regarding their use. Although they are very safe, side-effects may include injection site pruritus, angioedema, or anaphylaxis in a small percentage of patients. Anecdotally, these effects may be more common in toy-breed and very small patients. They are generally well tolerated by cats. Sublingual immunotherapy is a newer option; it is a needle-free way to administer the formulated allergen "cocktail" which may improve client compliance. Although a set protocol has yet to be developed, sublingual immunotherapy is typically administered more frequently (e.g., 1–3 times daily) compared to its injectable counterpart (e.g., q1–3 weeks long term). Although less information is available for the sublingual formulation, trends appear to follow what is seen for immunotherapy injections with regard to time to improvement and percentage of animals experiencing clinical benefit.

There are alternative options for immunotherapy which have been developed more recently. Regional immunotherapy and more generalized formulations eliminate the need for allergen testing prior to formulation. How these less specific options compare to injectable or sublingual allergen-specific immunotherapy has yet to be determined.

Prognosis

Although there is no cure for atopic dermatitis in the dog or cat, the long-term prognosis is considered to be good. Most patients, however, require life-long therapy for the disease and, even with generally good control, flares may periodically occur, necessitating additional therapeutic intervention.

Conclusion

Atopic dermatitis can be extremely frustrating to manage for the practitioner and owner alike. That being said, thorough client education efforts can markedly enhance compliance and, therefore, results long term. It is important to let clients know from the beginning that this is a disease which can be *managed* but never *cured*. Additionally, even with excellent control overall, flares may periodically occur and the animal may still be considered more pruritic than a normal patient. Although we strive for perfection, it is rarely achieved in a dog or cat with atopic dermatitis. Goals for the patient should be to improve their comfort (e.g., reduction of pruritus, decreased frequency of secondary infections) by approximately 80–90% for approximately 80–90% of the time. This may require a combination of therapeutic interventions including bathing/topical therapy along with immunotherapy or various medications. Every patient with atopic dermatitis is different; specific therapy needs to be tailored to the individual based on both patient and client feasibility. Having a client "onboard" with a multimodal approach to atopic dermatitis is imperative for successful management.

Additionally, it is important to remember that rarely does a therapy "stop working" for managing the disease. For example, a dog has been doing fairly well on allergen-specific immunotherapy injections for several months/years and all of a sudden develops moderate to severe pruritus. Prior to jumping to repeating allergen testing/reformulating immunotherapy or abandoning immunotherapy altogether for alternative medications, secondary flare factors such as infections and parasites (particularly fleas and *Sarcoptes*) should be investigated and addressed appropriately. In endemic areas, all patients should be treated year-round with adulticide flea prevention at least every 30 days to minimize the chance of flea infestation leading to an increase in pruritus, thereby exacerbating atopic dermatitis.

Further Reading

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160

Allergic Skin Diseases

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This chapter includes common allergic skin diseases of dogs and cats with the exception of atopic dermatitis and cutaneous adverse food reactions, which are covered in Chapters 159 and 161, respectively.

Urticaria and Angioedema

Etiology/Pathophysiology

Immunologic and nonimmunologic mechanisms are suspected to be involved in the pathogenesis of urticaria and angioedema, causing degranulation of mast cells or basophils which results in vascular dilation and recruitment of inflammatory cells. The inflammation remains limited to the dermis in patients with urticaria, but it extends to the subcutis with angioedema. While the immunologic process is mediated by a predominantly type I or III hypersensitivity reaction (e.g., allergies), nonimmunologic causes (e.g., heat, cold, stress, chemicals) can also trigger mast cell degranulation (Table 160.1).

A hypersensitivity reaction to an offending substance may not result in clinical signs at the first exposure, but will more likely occur with repeated exposures. Repeated exposures may also potentially result in more severe reactions.

Epidemiology

Urticaria and angioedema are rare in cats and uncommon in dogs and have been associated with various triggering factors as described above.

Signalment

Urticaria and angioedema can occur at any age and affect male and female animals equally. A specific breed predisposition has not been established.

History and Clinical Signs

Urticaria and angioedema typically have an acute onset (minutes to a few hours). Urticaria is characterized by erythematous wheals which are small (1–5 cm in diameter) and present in a multifocal to coalescing pattern (Figure 160.1). They are transient and normally fade within 24 hours but new lesions form as long as the animal remains exposed to the triggering factor. Angioedema presents as a locally extensive and ill-defined swelling of the face and ventral neck due to edema in the deep dermis and subcutaneous tissue (Figure 160.2). In severe cases, serum may leak through the skin. Very rarely and only in severe cases, fever, lethargy, and anorexia may be present. Pruritus may or may not accompany urticaria and angioedema.

Diagnosis

The diagnosis is based on the patient's history, clinical presentation, behavior of the skin lesions, diascopy (blanching) and, if necessary, histopathology. Identifying any triggering factor should be a priority. For this reason, a thorough patient history, including vaccination and any drug exposure, should be recorded. Pyoderma and vasculitis are differential diagnoses consistent with urticaria, but the lesions of those diseases will not blanch on diascopy. Mast cell tumor, cutaneous lymphoma, and amyloidosis should also be considered as differential diagnoses for urticarial lesions. Differential diagnoses consistent with angioedema are cutaneous lymphoma, juvenile cellulitis, mast cell tumor, and infectious cellulitis.

Therapy

The triggering cause should be identified and eliminated to evade symptomatic therapy and prevent recurrences;

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Table 160.1 Possible factors for triggering urticaria and angioedema in dogs and cats

Trigger	Remarks
Foods	
Drugs	Penicillin, ampicillin, cephalexin, tetracycline, vitamin K, propylthiouracil, amitraz, ivermectin, moxidectin, vincristine, azathioprine
Vaccines	Panleukopenia, leptospirosis, distemper-hepatitis, rabies, feline leukemia
Insect bites/stings	Bee, hornet, mosquito, black fly, spider, ant
Atopy	Pollen, mold, dust mite
Blood transfusions	
Plants	Nettle, buttercup
Intestinal parasites	Ascarids, hookworms, tapeworms
Infections	Staphylococcal pyoderma, canine distemper
Sunlight	
Excessive heat and cold	
Estrus	
Dermatographism	
Psychogenic factors	
Vasculitis	



Figure 160.1 Five-year-old male neutered mixed-breed dog with multifocal wheals on lateral trunk and hind legs.



Figure 160.2 Three-year-old female spayed mastiff with facial angioedema.

however, this may be challenging and not always achievable. In persistent or severe cases, symptomatic therapy is necessary. Epinephrine (0.1–0.5 mL of a 1:1000 solution SC or IM) combined with injectable glucocorticoids and/or antihistamines may be needed for severe cases. For persistent cases of urticaria, oral glucocorticoids (e.g., prednisone/prednisolone at 2 mg/kg/day PO) as well as oral antihistamines (e.g diphenhydramine, hydroxyzine, each at 2.0 mg/kg twice daily) are given. In mild cases, antihistamines are typically used as sole therapy.

Prognosis

If the cause of the disease can be identified and exposure eliminated, the prognosis is considered good.

Allergic Contact Dermatitis

Etiology/Pathophysiology

Allergic contact dermatitis is a type IV hypersensitivity reaction associated with a cell-mediated allergic response to haptens, which are small reactive lipid-soluble molecules. Although an overlap between irritant and allergic contact dermatitis has been reported in regard to cytokine profile and inflammatory cell activation, allergen-specific CD4+ T cells (CCR10+) and some chemokines (e.g., IP-10) seem to be expressed exclusively

in allergic contact dermatitis, which may represent differences in regulatory mechanisms.

Epidemiology

A wide range of allergens, such as various plants (e.g., dandelion, Asian jasmine, cedar mulch), cement, plastic toys and bowls, household cleaners, and topical drugs (e.g., neomycin, propylene glycol), have the potential to trigger contact hypersensitivity. An overlap of contact hypersensitivity with atopic dermatitis (AD) may also exist, since it is suspected that about 20% of dogs with contact hypersensitivity also suffer from AD.

Signalment

Allergic contact dermatitis is considered to be a rare pruritic condition and has no age or gender predisposition. However, some short-haired breeds such as the boxer, pit bull, dachshund, and Boston terrier appear to be affected more frequently.

History and Clinical Signs

Skin lesions typically occur on sites which are sparsely haired and directly exposed to allergens such as the ventral aspects of the neck, chest, abdomen, tail, digital spaces, muzzle, concave aspects of the pinnae, and scrotum (Figure 160.3). Lesions may also develop in haired areas if the sensitizer is in liquid, powder or aerosol form. The skin lesions are characterized by macules, papules, and erythema which may progress in chronic cases and become lichenified, hyperpigmented, and alopecic. Secondary bacterial and yeast infections are commonly present. Excoriations may also occur due to the associated pruritus. As with other hypersensitivity reactions, previous allergen exposure is necessary for the development of sensitization and resultant clinical signs.

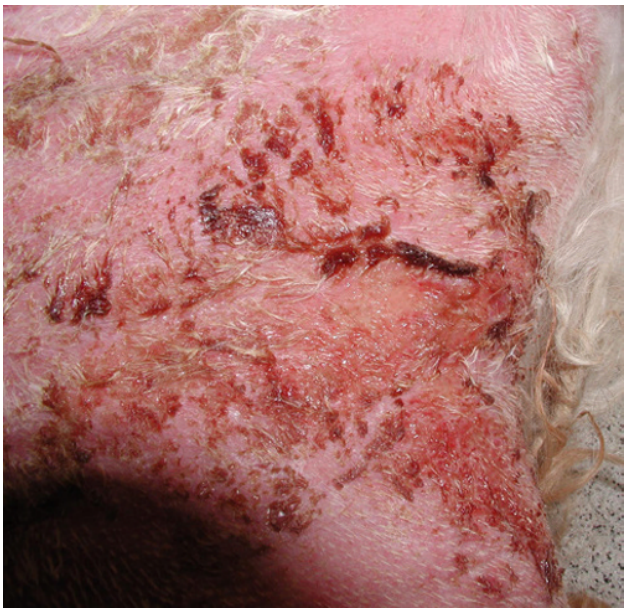


Figure 160.3 Severe contact dermatitis to a plant fertilizer in a 5-year-old golden retriever. Erythema, edema, serosanguinous to purulent exudate, and brownish crusts were present on the ventral abdomen and inner thighs. *Source:* Courtesy of Sheila Torres.

Diagnosis

Allergic contact hypersensitivity is diagnosed based on the patient's history, physical examination findings, resolution of clinical signs after elimination of the offending allergen, provocation of skin lesions with reexposure, and patch testing. The most common differential diagnoses associated with contact hypersensitivity are cutaneous adverse food reaction, atopic dermatitis, scabies, pyoderma, *Malassezia* dermatitis, and insect bite hypersensitivity.

Therapy

The primary goal should be to prevent further exposure to the offending allergen. Symptomatic therapy with glucocorticoids (e.g., prednisone/prednisolone at 0.5–1 mg/kg PO daily) may be attempted where elimination is not feasible; however, response to glucocorticoids occasionally fails. Pentoxifylline (10–30 mg/kg PO 2–3 times daily) has shown some beneficial effect for long-term management and prophylaxis. Patients with a poor response to glucocorticoids may benefit from treatment with ciclosporin (5 mg/kg PO daily).

Prognosis

Prognosis is considered good if the allergen can be eliminated from the patient's environment and good clinical response can be achieved with immunomodulating drugs.

Flea Allergy Dermatitis

Etiology/Pathophysiology

Several allergens responsible for flea allergy dermatitis (FAD) in dogs and cats have been identified in flea saliva. So far, one major allergen, a protein called *Ctef1* from the cat flea *Ctenocephalides felis*, has been associated with flea allergy in dogs.

Epidemiology

The prevalence of FAD varies greatly depending on the climate and geographic location, but it is the most

common hypersensitivity in dogs and cats in flea-endemic areas. Fleas can be a perennial problem in subtropical and tropical climate zones, seasonal in more temperate climate zones, and practically nonexistent in arid, high elevation, or cold climates. Even if fleas are considered to be absent from a particular area, there is a possibility that animal movement or contact may bring fleas into the area.

Signalment

Any dog and cat in a flea-endemic area can become allergic to fleas but no breed or sex predilection has been identified. Although FAD can develop at any age, dogs predisposed to FAD will generally develop clinical signs by 5 years of age.

History and Clinical Signs

The most typical clinical sign associated with fleas is pruritus, but FAD must be differentiated from flea infestation. Clinical signs associated with flea infestation are variable. The pruritus is generally intermittent and an increased number of fleas is common.

The typical predilection sites for FAD in dogs are the lumbosacral area, tail base, and caudomedial thighs, and minimal flea burden is typical. In cats, skin lesions are commonly found on the caudodorsal area, as in dogs, but can also be present on the head and neck. Many dogs and cats suffering from FAD may have concurrent atopic dermatitis and/or cutaneous adverse food reaction which may complicate the clinical presentation and diagnosis.

The most common skin lesions seen in dogs with FAD are erythematous papules and in more severe and chronic cases, self-induced alopecia, lichenification, and seborrhea on the predilection sites (Figure 160.4).

In cats, skin lesions range from miliary dermatitis (crusted papules) to excoriations to self-induced alopecia. Cats also often show skin lesions consistent with eosinophilic granuloma, especially indolent ulcers on the upper lips which can be found in up to 60% of flea-allergic cats (Figure 160.5).

Diagnosis

Any pruritic skin disease should be considered as a potential differential diagnosis for FAD and mainly includes other ectoparasitic disorders, microbial skin infections, or other hypersensitivities. Diagnosis is based on history, clinical signs, and response to therapy. The presence of fleas is not an adequate indicator of FAD and allergy skin testing with flea allergen can show false-negative results. Nevertheless, flea combing should be performed for direct identification of fleas or flea feces.



Figure 160.4 Five-year-old female spayed mixed-breed dog with flea allergy dermatitis exhibiting alopecia, erythema, excoriations, and seborrhea along the caudodorsal aspects of the trunk, tail, and hindlegs.



Figure 160.5 An indolent ulcer in a 4-year-old female spayed domestic shorthair cat with flea allergy dermatitis.

Therapy

The most effective treatment for animals with FAD is avoiding exposure to fleas combined with aggressive flea control. Veterinarians should be aware that none of the current flea preventives have an effective repellent effect. Since fleas in the pupal stage can survive up to 174 days in the environment, it is not unusual for the response to effective flea prevention to take a couple of months. For this reason, it is strongly recommended to maintain regular application of flea products in endemic areas. Fast-acting systemic adulticides are recommended over topically applied flea preventives because they reduce the contact time between the flea and the animal, resulting in faster reduction of irritation and pruritus. Flea preventives with a rapid adulticidal effect act through activation of nicotinic acetylcholine receptors or inhibition of gamma-aminobutyric acid (GABA)-gated chloride channels. Such products are available as oral tablets and topical solutions, and contain either nitenpyram, spinosad, or an isoxazoline (e.g., fluralaner, sarolaner, afoxolaner, lotilaner). Cats are very sensitive to permethrin so parasiticidals containing this product should be avoided in this species.

Despite strict flea prevention and depending on the severity of FAD, dogs and cats may develop episodes of increased pruritus after exposure to a flea. For the symptomatic therapy of pruritus, antiinflammatory dosages of oral glucocorticoids (e.g., prednisone/prednisolone at 0.5–1 mg/kg PO daily) and/or topical therapy (e.g., hydrocortisone aceponate spray [Cortavance®,Virbac], available only in Canada and Europe, or triamcinolone acetonide topical spray [Genesis®, Virbac]) may provide sufficient relief. In dogs, oclacitinib (Apoquel, Zoetis) can be administered at a dose of 0.4-0.6 mg/kg PO BID for up to 2 weeks, then once daily thereafter to alleviate pruritus associated with FAD. Lokivetmab (Cytopoint, Zoetis) is now licensed for the treatment of allergic dermatitis in dogs and, thus, could also be considered as an option for treating pruritus. A minimum dose of 2 mg/kg is administered SC and can be repeated every 4 to 8 weeks as needed. Other important measures include keeping the affected animal indoors and treating all in-contact pets.

Prognosis

Canine and feline FAD tends to worsen with age but with strict flea control, control of other underlying hypersensitivities and other measures which may help to reduce exposure to fleas, the disease can be well controlled.

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161

Cutaneous Adverse Food Reactions

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Etiology/Pathophysiology

Cutaneous adverse food reactions include any skin reactions that are reproducible. Most commonly seen is pruritus, but recurrent pyoderma or edema have also been reported. Food allergy is an immunologically mediated reaction caused by food. Type I hypersensitivity mediated by food-specific IgE antibodies is the most common reaction, but delayed type II (T cell mediated) and type III (where food-specific antibodies and food antigens form complexes) hypersensitivities may also occur.

In veterinary practice, the immunologic basis of food reactions is rarely documented. Thus, technically, the commonly used term "food allergy" is inappropriate, because adverse food reactions may also be nonimmunologically induced (and are then called food intolerances). Food intolerance may be pharmacologic, such as those mediated by pharmacologically active ingredients of the diet (e.g., histamine), toxic (caused by toxins in the food commonly produced by microorganisms in contaminated food stuffs), or metabolic (ingredients in the food are metabolized in the patient to a substance causing the reaction). If none of those mechanisms can be identified, the reaction is idiosyncratic.

However, proving the exact pathogenesis in an individual patient in practice is very difficult. Serum IgE testing for food-specific antibodies in normal dogs without clinical problems is characterized by a high number of false-positive reactions and reliable tests for other types of adverse food reactions are lacking. Thus, in most cases the diagnosis of adverse food reaction is made by response to an elimination diet and deterioration on rechallenge, as described below.

In human medicine, food allergens are typically glycoproteins with molecular weights between 10 and 70 kDa and some typical allergens come from nuts, shellfish, milk, and eggs. In dogs, the most commonly identified food antigens are beef, dairy products, chicken, soy, and wheat – ingredients that are most commonly present in commercial dog foods (Table 161.1). In the cat, beef, dairy, fish, and chicken are the most common reported offending antigens (see Table 161.1).

To what degree related proteins can cause clinical problems via cross-reactivity is not clear. One study evaluating individual rechallenges in dogs with adverse food reactions could not demonstrate evidence of cross-reactivity between, for example, beef and cow's milk. However, a case report of a dog with oral allergy syndrome described cross-reactivity with tomato and cedar pollen. A further *in vitro* study identified bovine IgG as a major antigen in dogs and a potential source of cross-reactivity between beef, cow's milk and potentially mutton (as there is a high homology between bovine and ovine IgG), but whether this is clinically relevant has not been demonstrated convincingly at this point.

History and Clinical Signs

Adverse food reaction is characterized in most cases by a pruritic and nonseasonal dermatitis. The face, feet, ventrum, and perianal area are often affected in the dog (Figure 161.1). Otitis externa is common and may be the only presenting sign in some dogs (Figure 161.2).

The skin may be erythematous; self-trauma quickly leads to alopecia and excoriation and in chronic cases lichenification of affected skin (Figure 161.3).

Papules, pustules, and oily and scaly skin may be due to common secondary infections with bacteria and/or yeast organisms. Concurrent gastrointestinal signs are seen in up to 25% of affected dogs. Beyond vomiting and diarrhea, gastrointestinal signs may include frequent defecation, borborygmi and flatulence, which may in some dogs be the only noncutaneous clinical signs. Recurrent bacterial infection and vasculitis were also reported in

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Table 161.1 Ingredients reported to cause adverse food reaction (AFR) in dogs and cats (in order of reported incidence)

Ingredients causing canine AFRs	Ingredients causing feline AFRs
Beef	Beef
Dairy	Dairy
Chicken	Fish
Wheat	Chicken
Egg	Corn
Soy	Lamb
Lamb	Wheat
Pork	Egg
Fish	
Corn	
Turkey	
Rice	
Duck	



Figure 161.1 Periocular lichenification, crusting, and hyperpigmentation in a 15-year-old, female mixed-breed dog with adverse food reaction.

some dogs. In one dog, erythema multiforme was apparently triggered by an adverse food reaction. Concurrent allergic diseases such as atopic dermatitis due to environmental allergens or flea bite hypersensitivity are seen in 20–75% of patients, depending on the study. Gender predispositions have not been reported.

As adverse food reaction and nonseasonal environmentally induced atopic dermatitis have identical cutaneous signs and are often present concurrently, breeds seemingly overrepresented include West Highland white terriers, Labrador and golden retrievers, American cocker and English springer spaniels, Chinese shar-peis,



Figure 161.2 Erythematous otitis externa in an 8-year-old, female spayed golden retriever with adverse food reaction.



Figure 161.3 Ventral lichenification, ulceration, and crusting in a 7-year-old, male castrated schnauzer with adverse food reaction.

and miniature schnauzers. In a recent study from Switzerland, West Highland white terriers, Rhodesian ridgebacks, boxers, and pugs were predisposed.

In cats, all cutaneous reaction patterns associated with flea allergy or environmental allergy can also be due to an adverse food reaction. Food-induced miliary dermatitis, noninflammatory alopecia, eosinophilic granuloma, and head and neck pruritus have all been reported.

Diagnosis

Although serum testing for food allergen-specific IgE is offered in many countries, there is no evidence that this test has any value in the diagnosis of adverse food reactions. In all previous publications, numerous false-positive and false-negative reactions were detected, when comparing test results with clinical rechallenges. In one recent study, false-negative reactions were less likely. However, at this time there is unanimous agreement amongst dermatologists worldwide that the only reliable way to diagnose an adverse food reaction is an elimination diet with food stuffs previously not fed to the patient.

Choice of Elimination Diet

In dogs, one protein source and one carbohydrate source not previously fed will be used exclusively; in cats, feeding only the protein source increases palatibility and compliance. Thus, it is important to obtain a reliable and detailed feeding history for the patient as well as the ingredient lists of commercial foods fed in the past. Ideally, the food should be home-cooked to assure that only the selected food stuffs are used. This is even more important after evidence has been published that many dog foods may include food sources not listed on the label. However, convincing owners to cook for their pets for several weeks may be more difficult nowadays than it used to be half a century ago. In addition, home-cooked diets are rarely balanced, which typically does not lead to clinical problems in adult dogs on a deficient diet for only a short time such as a month or two. However, if home-cooked diets are fed for extended time periods or if the patient is a young dog or cat still growing, care must be taken to seek advice from a nutritionist and balance the diet to avoid nutritional deficiencies.

To what degree cross-reactivities between related allergens (for example, beef and mutton or cow's milk) are clinically relevant in the dog and cat is currently unclear. One study showed *in vitro* evidence of reactivity of most dog sera with specific IgE antibodies against bovine IgG present in cow's milk and lamb and beef extract. Studies evaluating clinical cross-reactivity are rare and so far have not confirmed those findings. The author prefers to use food sources removed as far as possible from the previously fed antigens; for example, animals fed predominantly meat such as beef, mutton or pork will receive poultry proteins such as duck or goose and pets on a predominantly chicken-based food will be recommended goat, buffalo or reindeer.

If owners cannot be convinced to cook for their pets, commercial diets with selected protein and carbohydrate sources are sold by many companies. Furthermore, hydrolyzed diets are also available. These diets contain hydrolyzed proteins and their small sizes make cross-linking of IgE on the surface of inflammatory cells less likely, and thus these diets can be considered truly "hypoallergenic." Hydrolyzed diets and selected protein diets do not lead to remission in all animals with an adverse food reaction and thus are the second best option for diagnosing the condition. The exact reason for this decreased efficacy is not known at this time, but may relate to the presence of a concurrent allergic condition, cross-reactivities or adverse food reactions that are not immune mediated in the first place. However, these diets are often ideally suited for long-term maintenance, once the diagnosis is made and patients have been shown to tolerate them.

If it is not possible for owners to feed a previously unfed protein or carbohydrate source, either because what is available is simply too costly (which may be relevant for owners of large dogs) or because dogs or cats have been fed a wide variety of foods in the past, then it is sensible to choose the food sources the animals have seen the least or only in the more distant past, when clinical signs were not present. In one Dutch study of dogs with an adverse food reaction being fed three commercial protein diets, no dog responded to all of the diets but almost all dogs responded to at least one of them. Thus, performing two or three commercial diet trials in dogs with a suspected adverse food reaction may be useful.

Duration and Execution of the Diet

The ideal duration of an elimination diet is controversial. In a study evaluating the duration until clinical remission in 51 dogs with adverse food reaction, less than a quarter of the dogs responded within the first three weeks, a further half after 4–6 weeks, 10 dogs after 7–8 weeks, and three dogs after 9–10 weeks. However, although the time to complete remission can be extended, most dogs will start improving within the first 6–8 weeks and if a patient shows no clinical improvement on an appropriate elimination diet within that time, the author considers adverse food reaction ruled out. One has to keep in mind that the longer the trial duration, the higher the likelihood for lack of owner compliance.

In most patients, a gradual switch from the original diet to the elimination diet over a few days will help with compliance as well as gastrointestinal complications, particularly in finicky dogs and in cats. In dogs, owners are the limiting factor for most unsuccessful diet trials. However, cats often prove more difficult and due to the threat of hepatic lipidosis after several days of refusing to accept the diet, particularly in obese cats, it is not uncommon to try a number of feeding options before a suitable diet is identified.

The most important detail to relate to the owners is the need for maximal compliance. Even small amounts of food antigens fed infrequently can trigger pruritus and thus mask improvement, so flavored medications or treats such as rawhide, pig's ears, and others must be

avoided during the time of the diet. In particular, dog owners used to giving treats will often only be able to complete a diet trial if suitable alternatives are agreed on prior to starting the diet. For example, jerky of the meat used for the elimination diet can be home-made or acquired in bigger pet stores as chews or treats. Dogs with a high affinity for scavenging need to be kept on the leash and cats with outdoor access are ideally kept indoors. If those restraints are not possible for whatever reason, then an elimination diet trial may still be attempted but the limitation of these more relaxed elimination diets is that a lack of improvement does not rule out adverse food reaction in that patient, although some patients may still improve when the intake of the offending allergen is limited at least to some degree.

Interpretation of the Outcome of an Elimination Diet

If a reevaluation after 6–8 weeks shows no improvement on an appropriate elimination diet and a secondary infection masking the improvement is not present, then adverse food reaction is ruled out and the diet trial does not need to be extended. If, however, there is some improvement seen, then in some patients it may be necessary to continue the trial for up to 12 weeks. Improvement may be due to the elimination diet, concurrent treatments, seasonal changes or other factors, so a rechallenge with the old diet is absolutely necessary for the diagnosis (although some owners will need some convincing) and leads to deterioration of clinical signs within a few days. If after two weeks on the previous diet there is no deterioration of clinical signs, adverse food reaction is ruled out and improvement was due to other factors. As soon as a deterioration is detected, the elimination diet is fed again and if clinical signs improve again (typically much faster than at the initial introduction of the elimination diet), the diagnosis is confirmed.

Subsequently, there are three choices for the client. The easiest is to stay on the elimination diet long term. However, ideally, one food source after another is introduced again gradually for a few days to weeks, depending on the original rechallenge. If a patient deteriorated after two days on the old diet, then sequential rechallenges for four days each should be sufficient. If the original rechallenge led to deterioration after one week, then sequential rechallenges should probably be performed for two weeks each. This way, offending allergens can be identified and this knowledge permits greater flexibility in feeding, although it requires more effort. And lastly, if a home-cooked diet was used for the diagnosis, a commercial diet can be tried based on the feeding history of the patient.

Therapy

Ideally, avoidance of the offending food antigens is the best way to treat adverse food reactions in dogs and cats. If home cooking is used for long-term management, care should be taken to create a well-balanced diet and advice from a veterinary nutritionist may be useful.

However, if avoidance is not possible or if flares due to inadvertent ingestion of antigens are encountered, medical treatment with antiinflammatory drugs also used for environmental atopic dermatitis may be attempted. Glucocorticoids and ciclosporin are efficacious options for dogs and cats suffering from cutaneous adverse food reactions, although anecdotal evidence indicates that higher doses are needed to achieve remission than with atopic dermatitis due to environmental allergens. Oclacitinib (Apoquel; Zoetis) and lokivetmab (Cytopoint; Zoetis) are also licensed for the treatment of allergic dermatitis in dogs and thus are excellent, alternative options for controlling pruritus in canine patients with cutaneous adverse food reaction.

Prognosis

Once the diagnosis is established and offending allergens are identified, the prognosis is excellent, although some rare dogs and cats will develop a reaction against the new food antigens with time and will have to undergo a repeated change in their diet.

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162

Autoimmune and Immune-Mediated Skin Diseases

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Canine Familial Dermatomyositis

Dermatomyositis (DM) is a hereditary, ischemic dermatopathy and myopathy that occurs most commonly in collies, Shetland sheepdogs, Beauceron shepherds, Belgian tervurens, and Portuguese water dogs. Affected dogs generally develop lesions when they are less than 6 months of age, and either sex can be affected.

Dermatomyositis is characterized by nonpruritic alopecia, erythema, scaling, and mild crusting of the face, ears, distal limbs, digits, tail, and bony prominences (Figure 162.1). Additionally, claws may slough and fragment and ulceration may be rarely present in the oral cavity. Skin lesions may vary in severity depending on the individual. The presence and degree of myositis also vary. Clinical signs of myositis include regurgitation associated with megaesophagus, a high-stepping stiff gait, and atrophy of the masticatory muscles and distal limbs.

The diagnosis of DM is made through history, physical examination, and skin biopsy. Punch biopsies should be taken from the center of an alopecic area of skin. Crusted lesions can also be biopsied. The skin should not be scrubbed or clipped prior to procuring the biopsy. Care should be taken to include only abnormal skin in the biopsy. Histopathology will feature changes characteristic of ischemic dermatopathy.

Benign neglect may be an appropriate treatment approach for minimally affected patients. Avoidance of trauma to bony prominences and avoidance of prolonged sun exposure may also be beneficial. Pentoxifylline, prednisone, vitamin E, omega-3 fatty acids, tetracycline with niacinamide, and topical tacrolimus are therapies that may be used either alone or in combination depending on patient response (Table 162.1).

Complications can include secondary pyoderma for those dogs with more significant skin lesions and aspiration pneumonia for those with megaesophagus. Amyloidosis may rarely occur in chronically affected dogs. Minimally affected dogs may experience spontaneous resolution of skin lesions while other dogs may require lifelong therapy.

Erythema Multiforme

Erythema multiforme (EM) is an inflammatory cutaneous reaction pattern of multifactorial etiology, and dogs and cats of any age, breed or sex may be affected. It is characterized by rarely pruritic, sometimes painful, erythematous macules or papules that coalesce and eventually form a clear center and acquire an annular to arciform shape. Additional skin lesions may include plaques, vesicles and bullae, ulcers, and urticaria. Classic target lesions are present in only about one-third of cases. The axillae, groin, mucocutaneous junctions, pinnae, and footpads are most frequently affected. Oral ulceration may be present in some cases. Erythema multiforme can be classified into various categories based upon severity; however, such classifications are beyond the scope of this chapter.

The disease is diagnosed based on history, physical examination, and skin biopsy findings. Punch biopsies should be taken from the center of an erythematous area of skin. The clinician should biopsy affected skin and avoid ulcerated areas as ulcerated skin may yield a nondiagnostic sample. The skin should not be scrubbed or clipped prior to procuring the biopsy. Care should be taken to include only abnormal skin in the biopsy. Histopathology reveals apoptosis of keratinocytes at various levels of the epidermis combined with lymphocyte satellitosis.

Erythema multiforme has a variable appearance, and therefore many potential clinical differentials. Some differential diagnoses include systemic lupus erythematosus, urticaria, superficial pyoderma, dermatophytosis, demodicosis, bullous autoimmune disease, vasculitis

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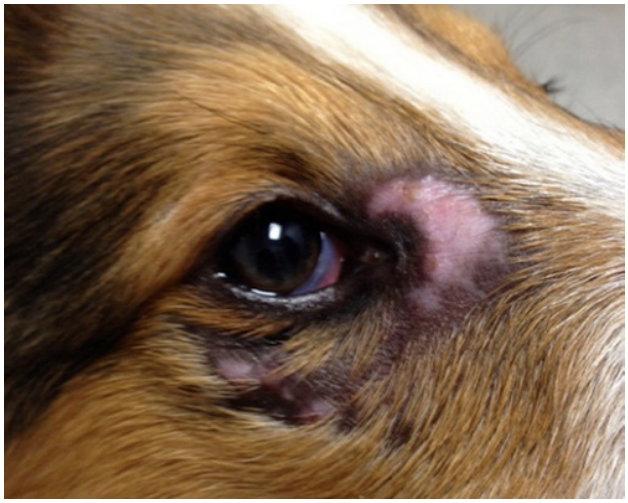


Figure 162.1 Less than 1-year-old, male, intact collie with nonpruritic alopecia associated with dermatomyositis.

and necrotizing dermatoses, superficial necrolytic dermatitis, and zinc-responsive dermatosis.

The identification and removal of the possible underlying cause are important in the management of EM; however, some cases are idiopathic. Triggering causes may include drugs, bacterial infections, *Pneumocystis* pneumonia, parvovirus, food, neoplasia or possibly herpesvirus. Mildly affected individuals may experience resolution of disease without additional therapy. Other patients may need immunosuppressive therapy such as glucocorticoids, azathioprine, ciclosporin, and/or intravenous immunoglobulin therapy (IVIG) (see Table 162.1).

Complications can include secondary pyoderma. The prognosis depends on the severity of the lesions and response to therapy.

Toxic Epidermal Necrolysis

Toxic epidermal necrolysis (TEN) is a severe vesiculobullous disorder affecting the skin and oral mucosa of dogs and cats. Dogs and cats of any age, sex or breed can be affected.

Toxic epidermal necrolysis is characterized by generalized erythematous or purpuric patches, and skin ulceration involving more than 30% of the body. Systemic signs (pyrexia, lethargy, depression, and/or anorexia) typically accompany the skin lesions.

Toxic epidermal necrolysis is often thought of as a severe variation of EM although some clinicians consider the two as separate diseases. It is generally differentiated from EM based on the severity of skin lesions and the percentage of the body that is affected.

The disease is diagnosed based on history, physical examination, and skin biopsy findings. Punch biopsies should be taken from an erythematous area of skin adjacent to an ulcer. The clinician should take care to avoid sampling eroded or ulcerated skin. Ulcerated skin has less diagnostic value. The skin should not be scrubbed or clipped prior to procuring the biopsy. Care should be taken to include only abnormal skin in the biopsy. The histopathology reveals diffuse necrosis of the epidermis with minimal dermal inflammation.

Clinical differential diagnoses include first-degree burn and toxic shock syndrome.

The identification and removal of a possible underlying cause are important in the management of TEN; however, many cases are idiopathic. The most common precipitating factor is drugs. Other less common triggers include vaccination, neoplasia, infections, and pregnancy. Wound care and general supportive care are critical to attempt to prevent sepsis. The use of glucocorticoids is controversial but ciclosporin and IVIG have been used with beneficial results in some cases.

Complications can include severe pyoderma and sepsis. The prognosis is guarded.

Cutaneous Lupus Erythematosus

Discoid Lupus Erythematosus

Discoid lupus erythematosus (DLE) is a fairly common photoaggravated or perhaps even photoinduced, depigmenting autoimmune skin disease. It affects middle-aged dogs, and collies, Shetland sheepdogs, German shepherd dogs, and Siberian huskies are predisposed. One case of generalized DLE has been reported in a Chinese crested dog. DLE has rarely been reported in cats. Sex and age predilections have not been substantiated.

The disease is characterized by depigmentation and loss of cobblestone architecture of the nasal planum (Figure 162.2). Erosions and crusting may also develop. While the nasal planum is most typically affected, lesions may also be found extending proximal to the nasal planum, around the eyes, around the mouth, on the genitals and distal extremities. Oral ulceration may also be present.

Diagnosis is based on history, physical examination, exclusion of systemic involvement, and skin biopsy findings. The clinician should select a site of recent depigmentation for punch biopsy. Lesions with severe crusting, ulceration or scarring should be avoided. The skin should not be scrubbed or clipped prior to procuring the biopsy. Care should be taken to include only abnormal skin in the biopsy. Histopathology reveals lymphocytic interface dermatitis. Direct immunofluorescence can further support the diagnosis.

Table 162.1 Immunosuppressive drug therapy

Drug	Dose	Comments
Pentoxifylline	Dogs: 15–25 mg/kg PO q8–12h	May require 8 weeks for maximum benefit
Tetracycline	Dogs >10 kg receive 500 mg PO q8h Dogs <10 kg receive 250 mg PO q8h	This class of antibiotic combined with niacinamide may require 3 months for maximum benefit
Doxycycline	Dogs: 5–10 mg/kg PO q12h	Can be used when tetracycline is unavailable. Use carefully in dogs with liver disease
Minocycline	Dogs: 5–12.5 mg/kg PO q12h	Can be used when tetracycline or doxycycline is unavailable. May cause more GI upset than other tetracyclines
Niacinamide	Dogs >10 kg receive 500 mg PO q8–12h Dogs <10 kg receive 250 mg PO q8–12h	May cause GI upset
Prednisone Prednisolone Dexamethasone	Dogs: 1–3 mg/kg PO Cats: 2–4 mg/kg PO Dogs: 0.1–0.2 mg/kg PO Cats: 1.5 mg/average sized cat PO	As a general rule, glucocorticoids should be administered q24h until the disease is controlled. Once the disease is controlled, they should be administered q48h or less. A slightly higher dose administered q48h tends to have fewer side-effects than a daily dose, even if the daily dose is lower
Triamcinolone	Dogs: 0.3–1 mg/kg PO Cats: 0.3–1 mg/kg PO	
Methylprednisolone	Dogs: 0.8–2 mg/kg PO or 4 mg/10 lb	
Azathioprine	1.5–2.5 mg/kg PO q24–48h	Dosing q48h reduces side-effects. Monitor CBC/chemistry q2 weeks for initial 3–4 months. May require 2 months for maximum benefit. Do not give to cats
Ciclosporin	Dogs and cats: 5–10 mg/kg PO q24h	Use the modified CSA formulation. CSA blood level monitoring is generally not useful when treating skin disease
Hydroxychloroquine	Dogs: 5 mg/kg PO q24h	
Omega 3 fatty acids	Dogs: 180 mg EPA and 120 mg DHA/10 lb PO q24h	Use as adjunctive therapy. Benefit may not be noted before 8–12 weeks
Vitamin E	Dogs: 200–800 IU PO q24h	Use as adjunctive therapy
Chlorambucil	Dogs and cats: 0.1–0.2 mg/kg PO q24–48h	Monitor CBC/chemistry as for azathioprine
Dapsone	Dogs: 1 mg/kg PO q8h	Monitor CBC/chemistry. Do not give to cats
Tacrolimus 0.1%	Apply topically q12h	
Betamethasone valerate 0.1% Fluocinolone (Synotic®, Zoetis)	Apply topically q12h Apply topically q12h	Topical steroids are useful for focal skin lesions. Dermal atrophy may occur with prolonged use

CBC, complete blood count; CSA, ciclosporin; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GI, gastrointestinal; IU, international units; PO, by mouth (*per os*).

Differential diagnoses include systemic lupus erythematosus, pemphigus foliaceus, pemphigus erythematosus, vitiligo, trauma, and Vogt–Koyanagi–Harada-like syndrome.

Treatment involves sun avoidance, oral and/or topical glucocorticoids, topical tacrolimus, niacinamide with tetracycline, and ciclosporin (see Table 162.1). These therapies can be used alone or in combination, depending on response to therapy. Complications can include secondary pyoderma.

Prognosis is generally good because DLE is limited to the skin. Chronic, untreated lesions may rarely progress to squamous cell carcinoma.

Exfoliative Cutaneous Lupus Erythematosus

Exfoliative cutaneous lupus erythematosus (ECLE) is an autoimmune disease that affects German shorthaired pointers. The disease occurs in puppies and young adults. Sex predilection has not been noted.

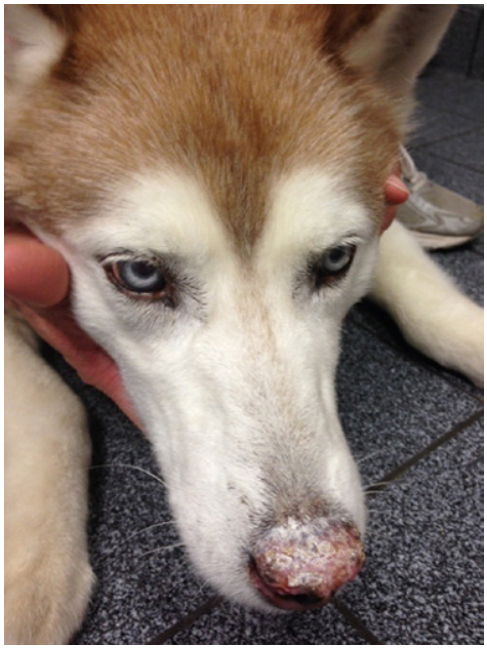


Figure 162.2 Middle-aged, male, neutered Siberian husky with crusting, depigmentation, and loss of cobblestone architecture of the nasal planum associated with discoid lupus erythematosus.

The disease is characterized by widespread scaling, depigmentation, alopecia, ulceration and crusting on the muzzle, pinnae, trunk, and limbs (Figure 162.3). Systemic abnormalities such as lymphadenopathy, intermittent pyrexia, joint pain, infertility, hyperglobulinemia, and thrombocytopenia may also be present. Dogs often assume a hunched stance.

Diagnosis is achieved with history, physical examination, and skin biopsy. The skin should not be clipped or cleaned prior to sampling with a punch biopsy. Multiple specimens should be selected from lesions of varying stages. Histopathology reveals lymphocytic interface dermatitis with marked hyperkeratosis and apoptotic keratinocytes. Destruction of sebaceous glands may also be observed.

Clinical differential diagnoses include primary seborrhea, ichthyosis, and sebaceous adenitis.

Glucocorticoids, ciclosporin, and hydroxychloroquine can temporarily relieve clinical signs (see Table 162.1). Complications may include secondary pyoderma, yeast dermatitis, and otitis.

This disease may wax and wane. Dogs eventually succumb to the disease, but treatment can improve quality of life in some dogs for several months to years.

Vesicular Cutaneous Lupus Erythematosus

Vesicular cutaneous lupus erythematosus (VCLE) is an autoimmune blistering disease that primarily affects middle-aged to older, female Shetland sheepdogs and collies. The disease generally occurs in the spring and summer months, and sparsely haired areas of the skin are most typically affected.

Vesicular cutaneous lupus erythematosus is characterized by transient vesicles that develop into coalescing ulcers with serpiginous borders (Figure 162.4). The abdomen, groin, and axillae are most frequently affected, although lesions may also occur on the mucocutaneous junctions.

Diagnosis is based on history, physical examination, and skin biopsy findings. The skin should not be clipped or cleaned prior to sampling with a punch biopsy. Vesicles or lesional skin adjacent to a fresh ulcer are ideal for sampling. Lesions devoid of epithelium have less



Figure 162.3 One-year-old German shorthaired pointer with exfoliative cutaneous lupus erythematosus. Note the extensive scaling present on the dorsal muzzle, extending to the periocular region and forehead. *Source:* Courtesy of Sheila Torres.



Figure 162.4 Three-year-old collie with vesicular cutaneous lupus. Note the coalescing ulcerative lesions forming a serpiginous pattern. *Source:* Courtesy of Sheila Torres.

diagnostic value. Histopathology reveals interface vacuolation and basal cell apoptosis.

Clinical differential diagnoses include severe erythema multiforme, systemic lupus erythematosus, pemphigus vulgaris, severe dermatomyositis, and bullous pemphigoid.

Treatment involves immunosuppression using glucocorticoids combined with azathioprine or ciclosporin. Pentoxifylline, vitamin E, topical glucocorticoids, or hydroxychloroquine can be used as adjunctive therapy (see Table 162.1). Sun avoidance is potentially important because sun exposure may be part of the disease pathogenesis. Topical and/or oral antibiotics along with general wound care should also be instituted. Complications may include secondary pyoderma and even septicemia. Prognosis is generally good.

Autoimmune Subepidermal Blistering Diseases

This group of diseases is autoimmune in nature and characterized by vesicle formation on various parts of the body. The diagnosis is based on signalment, physical examination, histopathology, and response to therapy. Immunohistochemistry or immunofluorescence is also sometimes required to differentiate among the blistering diseases.

Bulla or vesicles should be sampled via wedge biopsy for diagnostic purposes. If only erosions and ulcers are present, the clinician should obtain a wedge biopsy encompassing both margins of an erosive lesion. It is important to include epidermis in the sample. A biopsy that includes only dermis (e.g., center of an erosion or ulcer) will yield minimal diagnostic information. Samples should be submitted to an experienced dermatohistopathologist to increase the chances of obtaining a definitive diagnosis. Response to therapy and lesion appearance can also guide the diagnosis. Bullous pemphigoid and mucous membrane pemphigoid are fairly glucocorticoid responsive, while epidermolysis bullosa acquisita (EBA) is more glucocorticoid resistant.

The mucous membranes are predominantly affected in mucous membrane pemphigoid. Areas of friction and trauma (i.e., footpads) are predominantly affected in EBA. Vesicular cutaneous lupus erythematosus (discussed above) features extensive abdominal erosions. Bullous pemphigoid and EBA generally feature tense vesicles, while the vesicles of vesicular cutaneous lupus erythematosus are more flaccid.

Bullous Pemphigoid

Bullous pemphigoid (BP) is an autoimmune vesiculobullous disease that more often affects middle-aged dogs. Breed and sex predilections have not been identified.

Initial lesions develop on haired skin and include erythematous macules and patches that progress to turgid vesicles. The lesions evolve to ulcers and crusts. Lesions are not pruritic but can be painful. Pawpads are generally spared and mucosa is less frequently affected than in mucous membrane pemphigoid.

Diagnosis is based on the dermatohistopathologic findings of skin biopsy and immunofluorescence or immunohistochemistry. Refer to the subepidermal blistering diseases introduction for details about biopsy technique and special testing. Histopathology reveals subepidermal bullae.

Clinical differential diagnoses include EBA (although EBA typically features footpad involvement), pemphigus variants, VCLE, and mucous membrane pemphigoid. The presence of nonmucosal involvement is more suggestive of BP than mucous membrane pemphigoid.

Treatment involves topical glucocorticoids, oral glucocorticoids, tetracycline with niacinamide, and/or azathioprine (see Table 162.1). Complications include pyoderma.

Spontaneous remission has been reported although it should be anticipated that life-long therapy could be necessary.

Epidermolysis Bullosa Acquisita

Epidermolysis bullosa acquisita is an autoimmune vesiculobullous disease that affects mostly young adult dogs. Great Danes and male dogs are overrepresented.

Initial lesions include patchy erythema and vesicles of the face, oral cavity, concave pinna, axilla, and groin (Figure 162.5).

Vesicles may be hemorrhagic. Areas of friction tend to have the most obvious lesions. The groin and axilla develop erosions quickly. The oral mucosa and footpads usually feature extensive sloughing. Affected individuals



Figure 162.5 One-year-old Great Dane with epidermolysis bullosa acquisita. Note the ulcers on the buccal mucosa and vesiculation at the lower lip margin. *Source:* Courtesy of Sandra Koch.

may show systemic signs of illness. A localized variant of EBA exists that does not have systemic signs.

Diagnosis is based on the dermatohistopathologic findings of skin or mucosal biopsy and immunofluorescence or immunohistochemistry. Refer to the subepidermal blistering diseases introduction for details about biopsy technique and special testing. Histopathology reveals subepidermal bullae.

Clinical differential diagnoses include bullous pemphigoid, mucous membrane pemphigoid, VCLE, pemphigus vulgaris, severe erythema multiforme, and bullous drug eruptions.

Treatment involves immunosuppressive therapy such as glucocorticoids and azathioprine that can be combined with IVIG in refractory cases (see Table 162.1). Disease complications include lethargy, fever, and sepsis. Anemia and thrombocytopenia were observed in one dog.

Prognosis is guarded to poor because this disease does not respond readily to treatment.

Linear IgA Disease

Linear IgA disease (LAD) is a rare autoimmune disease of dogs. There are no known breed, age or sex predilections. The disease is characterized by ulcerations of the mucous membranes, mucocutaneous junctions, and skin (particularly of the extremities, axillae, groin, and pawpads). The initial lesions are vesicles, but their transient nature means they are rarely observed.

Diagnosis is based on the dermatohistopathologic findings of skin or mucosal biopsy and immunofluorescence or immunohistochemistry. Refer to the subepidermal blistering diseases introduction for details about biopsy technique and special testing. Histopathology reveals subepidermal bullae with mild to moderate inflammation. Clinical differential diagnoses include bullous pemphigoid, mucous membrane pemphigoid, EBA, VCLE, systemic lupus erythematosus, pemphigus vulgaris, severe erythema multiforme, and bullous drug eruptions.

Treatment has not been reported for this rare disease in dogs; however, the same immunomodulatory/immunosuppressive drugs mentioned for the other autoimmune blistering diseases can be tried (see Table 162.1).

Prognosis is guarded due to the paucity of information about this disease in dogs.

Mucous Membrane Pemphigoid

Mucous membrane pemphigoid (MMP) is a rare autoimmune blistering disease of dogs and cats that affects the mucous membranes and adjacent skin. Dogs are affected in adulthood, with no recognized sex predilection. German shepherd dogs may be predisposed.

Lesions are characterized by vesicles that progress to form erosions, ulcers, and crusts. The oral cavity, nasal planum, periocular region, genitalia, footpads, and concave pinnae can be affected. Hypopigmentation and atrophic scarring may occur in some cases. The lesions are nonpruritic, but may be painful. Lymphadenopathy may be present.

Diagnosis is based on the dermatohistopathologic findings of skin or mucosal biopsy and immunofluorescence or immunohistochemistry. Refer to the subepidermal blistering diseases introduction for details about biopsy technique and special testing. Histopathology reveals subepidermal bullae.

Clinical differential diagnoses include bullous pemphigoid, EBA, VCLE, pemphigus vulgaris, erythema multiforme, and bullous drug eruptions. The mucous membranes are markedly affected in MMP. This characteristic can be useful in distinguishing MMP from other blistering diseases.

Treatment involves immunosuppression. Lesions are generally not severe, and tend to respond easily to therapy. Tetracycline and niacinamide should be considered as initial treatment. Glucocorticoids and other immunosuppressants may be considered if the lesions are severe or do not respond readily (see Table 162.1).

Prognosis is good to guarded. Complications include secondary infections of the lesions.

Pemphigus Complex

History, physical examination, impression smears, and histopathology lead to the diagnosis of diseases within the pemphigus complex. The hallmark of diseases in this category is acantholytic keratinocytes (Figure 162.6) and these can be identified on cytology and histology.

Trichophyton mentagrophytes and severe pyoderma are the primary differentials for pemphigus because acantholytic keratinocytes can occur in these conditions as well.

A direct impression smear from under a moist crust or the content of a pustule will reveal numerous nondegenerate neutrophils, acantholytic keratinocytes and sometimes eosinophils. Bacteria may be present if secondary infections occur.

The punch biopsy technique is appropriate for diseases in this category. The skin should not be shaved or cleaned prior to obtaining the biopsy. Crusts should not be removed because they contain acantholytic keratinocytes. With rare exceptions, skin devoid of epithelium should not be biopsied because epithelium is required for a histologic diagnosis. Moist, tightly adhered crusts, pustules, vesicles or the epithelialized edge of an erosion

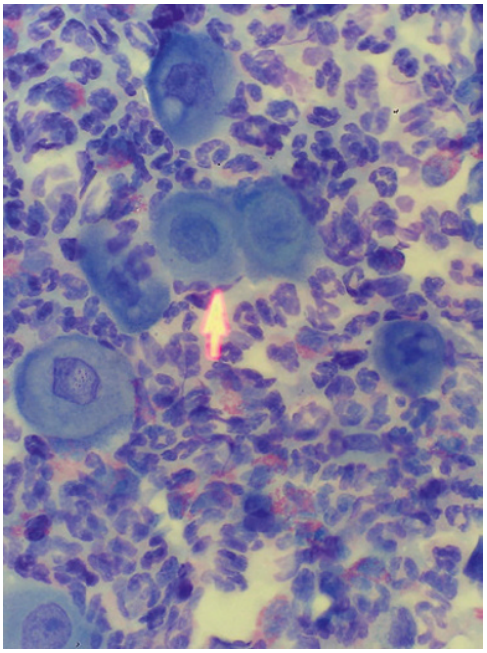


Figure 162.6 Sample collected from a pustule in a case of pemphigus foliaceus. The arrow shows a characteristic acantholytic cell. Also present are large numbers of neutrophils and eosinophils. *Source:* Courtesy of Lisa Reiter.

are the ideal lesions to biopsy. Periodic acid–Schiff (PAS) stain should be requested to evaluate the sample for fungal elements. Immunofluorescence or immunohistochemistry is rarely used to support a diagnosis.

Pemphigus Foliaceus

Pemphigus foliaceus (PF) is a fairly common autoimmune disease that affects many species, including dogs and cats. The disease affects middle-aged to older animals. No sex predilection has been recognized.

Dogs may develop large pustules, erosions and crusts on the face (particularly the periocular region and bridge of the nose), concave aspect of the pinnae, pawpads, and/or trunk (Figure 162.7). Pruritus may or may not be present. Pemphigus foliaceus in cats is characterized by crusting on the pinnae, face, and/or nailfolds. Caseous debris may also be present around the nails (Figure 162.8). Pruritus is usually absent.

The reader is referred to the pemphigus introduction above for details about biopsy technique and special testing. Histopathology reveals broad, subcorneal pustules with acantholytic keratinocytes. Differential diagnoses include superficial pyoderma, pustular dermatophytosis, and drug reactions. Complications include fever, weight loss, lethargy, and anorexia in pets that have widespread lesions. Concurrent dermatophytosis and/or secondary pyoderma may also be present.



Figure 162.7 Cocker spaniel with pemphigus foliaceus. Multifocal to coalescing lesions covered with yellowish crusts localized to the pinna, dorsal aspect of the head and muzzle. Areas of erosion are noted where adherent crusts were removed. *Source:* Courtesy of Sheila Torres.



Figure 162.8 Domestic shorthair cat with caseous debris and erythema of the nailfold associated with pemphigus foliaceus.

Glucocorticoids are generally effective but often need to be combined with azathioprine. Glucocorticoids can also be combined with ciclosporin, chlorambucil, or tetracycline with niacinamide (see Table 162.1).

Topical flea and tick products that contain amitraz have been associated with pemphigus-like disease. The first step in treatment should be to discontinue amitraz-containing flea/tick preventives. Immunosuppressive therapy should then be started.

Prognosis is guarded for pets that do not respond to or cannot tolerate initial therapy with glucocorticoids. Prognosis is good for pets that respond easily to therapy and that can be controlled with low doses of medication.

Pemphigus Erythematosus

Pemphigus erythematosus (PE) is an autoimmune disease with characteristics of pemphigus foliaceus and DLE. Dogs and cats are affected; no breed or sex predilections have been identified.

It is characterized by lesions that are limited to the face and pinnae. Specifically, the nasal planum and sometimes the concave aspect of the ears are affected with pustules, erosions, crusts and sometimes depigmentation. Refer to the pemphigus introduction above for details about biopsy technique and special testing. Histopathology reveals acantholysis and interface dermatitis. Differential diagnoses include dermatophytosis (*Trichophyton mentagrophytes*), DLE, and pemphigus foliaceus. Complications include secondary infections of lesional skin.

Treatment involves immunosuppression with one or a combination of the following: tetracycline/niacinamide, glucocorticoids, azathioprine, ciclosporin, and/or topical tacrolimus (see Table 162.1). Avoidance of intense sun exposure may also be helpful. Prognosis is good. Some cases may be more responsive to therapy than others.

Pemphigus Vegetans

Pemphigus vegetans (PV) is an exceedingly rare autoimmune disease of dogs. Three cases are described in the literature. The disease is characterized by wart-like projections on the pinnae, axillae, and sternum. Additionally, pustules and vesicles may be present on the abdomen and paws, and erosions may be present on mucous membranes. See the pemphigus introduction above for details about biopsy technique and special testing. Histopathology in humans reveals suprabasilar clefting.

Treatment is immunosuppression (see Table 162.1), and prognosis is guarded due to the paucity of information regarding this disease in dogs.

Pemphigus Vulgaris

Pemphigus vulgaris is a rare autoimmune blistering disease of dogs and cats. This disease can occur at any age and male dogs appear to be predisposed but there is no breed predilection.

Characteristic lesions are dramatic and include flaccid vesicles, erosions, and ulcers. Mucosal or mucocutaneous lesions are generally observed first, followed by lesions that may occur on the face and nose (see Figure 162.5). Pressure points, pawpads, and intertriginous areas are also usually affected. Refer to the pemphigus introduction above for details about biopsy technique and special testing. In cases where mucosal erosions predominate, a wedge biopsy encompassing both margins of the lesion may be preferred over a punch biopsy. Histopathology reveals suprabasilar clefting with acantholytic keratinocytes and rounded basal cells.

Differential diagnoses include paraneoplastic pemphigus, mucous membrane pemphigoid, bullous pemphigoid, EBA, erythema multiforme, and epitheliotropic cutaneous lymphoma. Complications include lethargy, anorexia, weight loss, and secondary skin infections.

Treatment involves immunosuppression with glucocorticoids combined with azathioprine or chlorambucil or tetracycline/niacinamide (see Table 162.1). Prognosis is guarded as this disease may be refractory to therapy.

Uveodermatologic Syndrome

Uveodermatologic syndrome or Vogt–Koyanagi–Harada-like syndrome is a rare disease of dogs. The pathomechanism is currently unknown but antibodies directed against melanocytes and pigment-associated proteins have been identified, suggesting that autoimmunity plays a role. There is evidence that genetics participates in disease development in akitas. Uveodermatologic syndrome affects young to middle-aged dogs, and there is no apparent sex predilection. Akitas, Samoyeds, Siberian huskies, Alaskan malamutes, and chow chows are overrepresented, although numerous other breeds have been affected.

The disease is characterized by acute onset of unilateral or bilateral uveitis and concurrent erythema, scaling and depigmentation of the hair, lips, eyelids, nose and occasionally the footpads, scrotum, anus, and hard palate. In most cases, the skin signs are mild with depigmentation being the main lesion. Pruritus may or may not be present.

The diagnosis is based on history, physical (especially ocular) examination, and skin biopsy findings. The clinician should biopsy an area of erythematous and depigmented skin. Histopathology reveals lichenoid granulomatous dermatitis with melanophages. Ocular examination is necessary to diagnose uveitis.

Differential diagnoses include concurrent separate ocular and skin diseases. Uveitis is often an indicator of systemic disease and may be secondary to immune-mediated, infectious, neoplastic, toxic, metabolic, traumatic, or idiopathic processes. Other causes of hair and mucocutaneous skin depigmentation include DLE,

alopecia areata, vitiligo, pemphigus erythematosus, and epitheliotropic cutaneous lymphoma.

Therapy should be directed towards preserving vision. Skin lesions may respond while eye lesions continue to progress. Frequent monitoring of the eyes is important. Topical or intravitreal glucocorticoids, topical cycloplegics, and carbonic anhydrase inhibitors should be instituted along with systemic glucocorticoids combined with azathioprine or ciclosporin (see Table 162.1).

Complications may include secondary glaucoma, cataracts, and blindness. Prognosis is guarded, although better when treatment is instituted early in the disease course. Repigmentation of the skin and hair may or may not occur.

Further Reading

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163

Approach to Alopecia

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Etiology/Pathophysiology

Alopecia or hypotrichosis are common reasons for presentation to a veterinarian. Alopecia implies complete hair loss while hypotrichosis implies thinning of the hair coat. The presentation of alopecia/hypotrichosis may be localized or generalized and focal, patchy or diffuse, depending on disease severity, duration, and the cause of the hair loss. Alopecia may be traumatically induced, with the patient scratching or licking the hair off, or due to hair falling out or failing to regrow following normal shedding.

Trauma-Induced Alopecia

Trauma-induced alopecia is most often secondary to pruritus. Common causes include allergies, ectoparasites, bacterial skin infections, and *Malassezia* dermatitis. Less common causes in older animals include neoplastic diseases such as epitheliotropic lymphoma or mast cell tumor and paraneoplastic syndromes.

Inflammation-Induced Alopecia

Alopecia not associated with trauma may be due to an inflammatory condition, such as pyoderma, follicular demodicosis, dermatophytosis, or sebaceous adenitis (Table 163.1).

Sebaceous adenitis is an immune-mediated destruction of the sebaceous glands and is associated with scaling and alopecia. Breed predilections include the standard poodle, Samoyed, akita, and vizsla. In short-coated dogs, these conditions present as a patchy or "moth-eaten" pattern of alopecia (Figure 163.1).

The lesions might not overtly appear inflammatory; however, the multifocal pattern of the alopecia should make you suspicious of an inflammatory cause. Hairs may epilate easily from the periphery of these inflammatory alopecic sites but not from other locations on the body. While pruritus can be associated with these diseases and may even be directed at the lesions, it is not the cause of the alopecic spots.

Vasculitis from immune-complex deposition secondary to infectious or immune-mediated diseases may cause multifocal alopecia due to local ischemia. Clinically, the lesions may resemble dermatophytosis in that they are circular and alopecic; however, they appear noninflammatory, lacking erythema and crusting with thin rather than thickened skin, unless cutaneous necrosis and ulceration occur (Figure 163.2).

A common example of focal ischemic alopecia is rabies vaccination-induced vasculitis. Vasculitis may also be seen with drug reactions, tick-borne diseases, and systemic lupus erythematosus. Dermatomyositis is an inherited (autosomal dominant with variable penetrance) disorder that primarily affects collies and Shetland sheepdogs. Vasculitis and ischemic dermatitis are thought to be part of the pathogenesis of the disease.

Autoimmune/immune-mediated diseases such as alopecia areata or pseudopelade and neoplastic conditions such as epitheliotropic lymphoma could result in areas of inflammatory alopecia. Alopecia areata is an immune-mediated attack on the hair bulb while pseudopelade is an immune-mediated attack on the follicle wall, resulting in focal to multifocal alopecia. Clinically, the areas of alopecia may not show evidence of erythema, suggesting a noninflammatory mechanism; however, the pattern of alopecia necessitates investigation into inflammatory differentials.

Paraneoplastic alopecia occurs in association with internal neoplasia. This is a presumed inflammatory alopecia although the pathomechanism of the alopecia is unknown. Paraneoplastic alopecia has been described in cats in association with pancreatic and biliary carcinoma. The alopecia is acute and progressive with easy epilation of hair and smooth thin skin.

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Table 163.1 Differential diagnoses for inflammation-induced alopecia

Common	Less common	Uncommon
Pyoderma Demodicosis Dermatophytosis Sebaceous adenitis	Idiopathic vasculitis Vaccination-induced vasculitis Drug reaction Systemic lupus erythematosus Dermatomyositis	Paraneoplastic alopecia Alopecia areata Pseudopelade

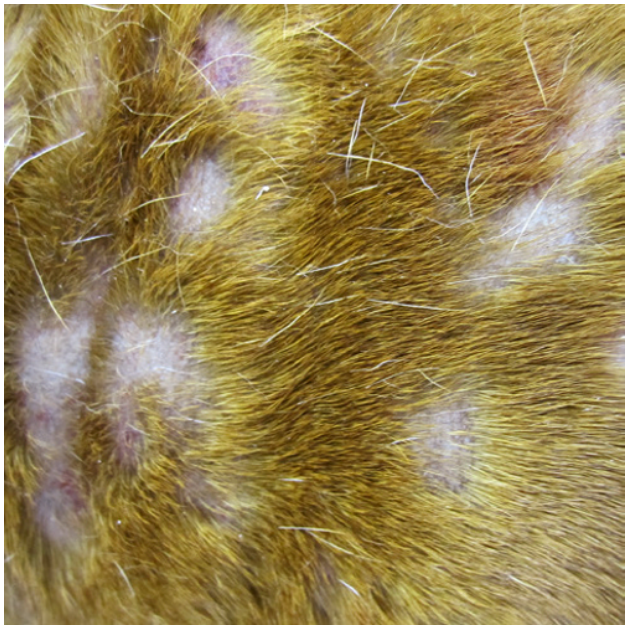


Figure 163.1 A 3-year-old male castrated English bulldog with patchy alopecia of the trunk associated with sebaceous adenitis.

Noninflammatory Alopecia

Alopecia may also occur as a consequence of abnormal hair cycling or hair development. These are grouped under noninflammatory causes of alopecia and include endocrine diseases as well as congenital/hereditary and idiopathic causes of alopecia. To understand these conditions, it is important to understand the hair cycle. Briefly, the anagen phase of the hair cycle is when the hair is actively growing. In most dogs and likely all cats, this is a relatively short phase lasting at most a few months until the hair reaches its maximum length. The length of the anagen phase, and thus the length of hair, is genetically determined and may be of different durations for different regions of the body. From anagen, the hair goes through a short catagen phase in which it reverts into a nongrowing or telogen hair. The hair can remain in telogen for a prolonged period of time before a new cycle is started. For some breeds such as the malamute, this may be a few years. The telogen hairs are well anchored and do not epilate easily. Thus, the presence of telogen hairs is not necessarily pathologic. Dogs that require frequent hair clipping, such as poodles, have a hair cycle more similar to people in that they have a prolonged anagen phase with fewer hairs in telogen at any point in time. These dogs are more likely to develop alopecia from chemotherapeutic agents which inhibit actively dividing cells. Shedding, or exogen, is separate from the hair cycle and is independent of whether a new hair cycle is starting.



Figure 163.2 Adult male castrated toy poodle with focal alopecia secondary to rabies vaccination-induced vasculitis. Dog was referred for nonresponsive dermatophytosis because of the circular lesion.

Alopecia Associated with Abnormal Hair Growth

Abnormalities in hair growth occur during the anagen phase of the hair cycle. There are only a few conditions that fall into this category and they include follicular dysplasias, congenital hypotrichosis, color dilution alopecia, and black hair follicular dysplasia. Follicular dysplasias, where abnormal follicles fail to produce healthy anagen hairs, are most often associated with alopecic breeds (e.g., Chinese crested dog, Mexican hairless dog, and the Sphynx cat) in which the alopecia is a breed characteristic. Congenital hypotrichosis is poorly described in small animals. The hypotrichosis/alopecia occurs either at birth or within the first six months of life and may be associated with other ectodermal defects. Color dilution alopecia and black hair follicular dysplasia are color-restricted alopecias that begin

gradually in the first three years of life (Figure 163.3). The alopecia involves a defect in melanosome migration and/or transfer, which occurs during the anagen phase of the hair cycle.

Alopecia Associated with Hair Cycle Arrest

Alopecia associated with abnormal hair cycling typically occurs because the hairs remain in telogen and a new anagen cycle is not initiated. With time, the telogen hairs are shed but are not replaced, resulting in a diffuse, often symmetric alopecia. Areas of wear such as the neck, pressure points, and tail may become alopecic first as these hairs are removed by friction.

There are many conditions that appear to be associated with hair cycle abnormalities. These include hypercortisolemia, hypothyroidism, hyperestrogenism, alopecia X, patterned alopecia of various breeds, cyclic flank alopecia, postclipping alopecia, and anagen/telogen defluxion. Some of these conditions are associated with a temporary alopecia (postclipping alopecia, anagen/telogen defluxion), some may be seasonal (cyclic flank alopecia), and others are likely permanent with variable response to treatments (alopecia X, patterned alopecia). The cutaneous changes associated with endocrine dermatoses may also occur with other hair cycle abnormalities, including diffuse alopecia often sparing the head and distal extremities, seborrhea, comedones, hyperpigmentation, and cutaneous infections. In addition, many of the histologic characteristics associated with endocrine dermatoses (telogen hairs, follicular keratosis, hyperkeratosis, excess trichilemmal keratinization [flame follicles], thin epidermis, and thin dermis) may also be seen with other hair cycle abnormalities. It is important to realize that, with a few exceptions, histopathology cannot differentiate endocrine diseases from other causes of hair cycle arrest.



Figure 163.3 Neck region of a 9-year-old female spayed gray and white Italian greyhound with long-standing color dilution alopecia. The white hairs are normal. The area which had gray hairs is seborrheic and lichenified.

Specific Noninflammatory Alopecic Disorders

Alopecia X

Alopecia X is a hair cycle arrest that affects primarily plush-coated breeds but also toy and miniature poodles (Table 163.2). It is presumed to be hereditary because of the strong breed predilections although the specific defects or mode of inheritance have yet to be determined. Dogs affected are usually young adults but alopecia X can affect any dog between 1 and 10 years of age. There is no sex or neuter status preference with this condition. Clinically, dogs present with progressive symmetric alopecia that spares the head and distal extremities (Figure 163.4).

The alopecia is often associated with hyperpigmentation of the skin. Because of the similarity of this condition with endocrine dermatoses, it is important to rule those conditions out before a diagnosis of alopecia X can be made. A unique feature of this disease is hair regrowth at the site of biopsy or surgical trauma.

Table 163.2 Common breeds associated with noninflammatory alopecic syndromes (not inclusive)

Alopecia X	Patterned alopecia	Cyclic flank alopecia	Color dilution alopecia	Other
Chow chow	American water spaniel	Airedale	Chihuahua (blue)	Chesapeake Bay retriever
Keeshond	Boston terrier	Boxer	Dachshund (blue)	Labrador retriever (silver)
Malamute	Dachshund	English bulldog	Doberman pinscher (blue and fawn)	Schipperke
Pomeranian	Greyhound	French bulldog	Weimaraner	
Samoyed	Irish water spaniel		Yorkshire terrier	
Siberian husky	Portuguese water dog			
Spitz				
Toy/miniature poodle				



Figure 163.4 Adult male castrated Pomeranian dog with alopecia X. Note that the alopecia spares the head and distal extremities, similar to hypercortisolemia.

Patterned Alopecia

Patterned alopecia is a tardive hypotrichosis that often starts at less than 1 year of age. Many syndromes have been described that are breed restricted. These include pinnal alopecia of dachshunds, ventral and caudal alopecia of dachshunds and Boston terriers (Figure 163.5), alopecia of the ventral neck, flank, and caudal regions of water spaniels, and alopecia of the caudal thighs of greyhounds. The actual mechanism of the alopecia is not known. Because some dogs can regrow normal hair at these sites, it is thought not to be a follicular dysplasia but more likely a hair cycle abnormality, although multiple etiologies are possible. The breed associations suggest a genetic component.

Cyclic Flank Alopecia

Cyclic flank alopecia is a seasonal or cyclic truncal alopecia that usually occurs during or just after short day-length period. The alopecia affects the flanks, lateral thorax, and sometimes caudodorsum and nose bridge (Figure 163.6).

There are often bizarre patterns to the alopecia and the skin may be intensely hyperpigmented. Less common presentations include hypotrichosis and hair pigment changes without overt alopecia, also in strange patterns. The alopecia may not recur each year or in some cases may be permanent. Age of onset is 1.5–4.5 years. Breeds reported to be affected by this condition include boxers, English and French bulldogs, and Airedales (see Table 163.2).

Postclipping Hair Follicle Arrest

Postclipping alopecia or hair follicle arrest refers to failure of hair regrowth following close clipping, usually in preparation for surgery (Figure 163.7).

It may occur more frequently in plush-coated breeds and there are two theories as to why this occurs. The first



Figure 163.5 Patterned alopecia in a young adult female spayed Boston terrier with alopecia of the lateral thorax and ventrum.



Figure 163.6 Alopecia of the lateral thorax and flank in a male castrated boxer with cyclic flank alopecia.



Figure 163.7 Adult male castrated mastiff with postclipping alopecia secondary to receiving an epidural injection.

is that the clipping/surgical preparation causes a hair cycle arrest, possibly because of a temperature change with vasoconstriction to the skin surface. The other theory applies primarily to the plush-coated breeds. It is thought that these dogs may have been clipped during a time when their hair is in a prolonged telogen phase and not able to initiate a new anagen cycle. It is also possible that the clipping uncovered an endocrine or other noninflammatory alopecia condition. The hairs are not cycling because of an underlying disease such as hypercortisolemia or alopecia X but alopecia has not yet occurred. The clipping simply hastened the alopecia. With postclipping hair follicle arrest, the hairs should spontaneously resume normal cycling within 7–30 months, often following a strong stimulus for hair cycling such as shortening day length.

Anagen/Telogen Defluxion

Anagen or telogen defluxion involves hair loss following an illness. Telogen defluxion occurs more commonly in small animals. The illness causes an abrupt cessation of anagen, synchronizing all hairs in telogen. In 1–3 months following the illness, large numbers of telogen hairs are shed synchronously as a new anagen hair cycle begins. Hairs epilate easily during this time. Anagen defluxion occurs more commonly in large animals. The illness causes a generalized disturbance of the anagen stage of the hair cycle resulting in a sudden loss of coat. In contrast to telogen defluxion, hair loss occurs within two days to one week following the illness. In both of these conditions, hairs regrow normally.

Signalment

The breed and age of onset should aid in the initial differential list (see Table 163.1). Congenital/hereditary alopecias are more likely to occur within the first few years of life while endocrine dermatoses and neoplastic diseases occur in middle-aged to older animals. Depending on the trigger, immune-mediated dermatoses can occur within a wide age range and affect many breeds and their crosses.

History and Clinical Signs

When evaluating the dog or cat for alopecia, a thorough history and physical examination are in order. Determining the presence or absence of pruritus and the distribution and pattern of hair loss will help determine the ultimate cause of the alopecia.

Clinically, pruritus-induced alopecias are characterized by broken hairs where the animal has been scratching. Microscopic examination of the tips of the hairs (trichogram) will show a blunted or fractured tip instead of a tapered tip if the animal is inducing the alopecia secondary to trauma. This technique is not helpful if dogs are groomed and clipped regularly, as all of their hairs will be blunted. Evidence of excoriations supporting pruritus may also be observed in the alopecic areas.

Onset of Alopecia

If the onset of alopecia is rapid, infectious or paraneoplastic conditions need to be considered. Also, a recent history of systemic illness could be the cause of a rapid onset of alopecia.

Ease of Epilation

Easy epilation of hairs is more often associated with inflammatory causes of alopecia such as pyoderma, dermatophytosis or demodicosis but can also be seen with conditions that result in rapid progression of alopecia such as anagen/telogen defluxion.

Distribution and Pattern of Alopecia

Distribution and pattern of the alopecia may be key to identifying the underlying diagnosis or formulating your differential diagnosis list but requires careful observation. If the alopecia is color restricted, likely this is color dilution alopecia or black hair follicular dysplasia. If the

alopecia is patchy throughout the coat, an inflammatory cause is likely, whereas if the alopecia is diffuse and symmetric, a noninflammatory cause is more likely.

Diagnosis

Minimum Dermatology Database

A minimum dermatology database consisting of skin scrapings, fungal culture, and surface cytology should be performed on all cases of alopecia. If infections are suspected by clinical presentation (patchy alopecia) or detected by the dermatology database, then treatment should be pursued and alopecia reassessed before further diagnostics are performed.

Trichogram

Trichogram involves the plucking of hairs and examination under the microscope. The tips of the hairs can be examined to determine if the alopecia is traumatically induced (see above). The shafts of the hairs can be examined to look for abnormal clumping of melanin and distortion of the hair shaft, suggestive of color dilution alopecia. This method is not useful for black hair follicular dysplasia, as the hair is too pigmented to allow for this observation. The bulbs of the hairs can be examined for evidence of a preponderance of telogen hairs, which might suggest telogen defluxion when coupled with ease of epilation and supportive history.

Histopathology

Histopathology will help rule out many of the inflammatory causes of alopecia (e.g., folliculitis, sebaceous adenitis, vasculitis, alopecia areata, pseudopelade, neoplasia, or paraneoplastic dermatitis) but, as stated before, it seldom allows differentiation of endocrine diseases from other noninflammatory causes of alopecia such as alopecia X or patterned alopecias. It is helpful to first treat any infections that are identified prior to performing a biopsy as inflammation associated with the infection could mask other causes of alopecia.

Endocrine Testing

If noninflammatory alopecia is first occurring in a middle-aged dog, further investigation into a possible endocrinopathy is warranted. This may include basic bloodwork and urinalysis to screen for abnormalities consistent with an endocrinopathy. However, even if all laboratory parameters are within normal limits, endocrine testing may still be indicated.

Table 163.3 Treatment options for select inflammation-induced alopecic conditions

Disease	Treatment options
Sebaceous adenitis	Vitamin A, synthetic retinoids, ciclosporin, glucocorticoids
Vasculitis	Tetracyclines/niacinamide, pentoxifylline, glucocorticoids
Alopecia areata/ pseudopelade	Glucocorticoids, ciclosporin

Additional Diagnostic Tests

If an older dog or cat first develops alopecia, screening for neoplasia becomes very important. Diagnostics in this case may include basic bloodwork, urinalysis, histopathology, and imaging.

Therapy

Treatment depends on the cause of the alopecia. Table 163.3 lists treatment options for some of the inflammation-induced causes of alopecia.

For many of the noninflammatory causes of alopecia associated with hair cycle arrest (alopecia X, patterned alopecia, cyclic flank alopecia, and postclipping alopecia), melatonin therapy may result in hair regrowth. The recommended dosage is 3 mg q12h for small dogs and 6–12 mg q12h for larger dogs. Side-effects are minimal, with the most common one being sedation. It is possible that melatonin causes insulin resistance so it should be used with caution in diabetic animals. Recently, medroxyprogesterone acetate injections were shown to be marginally effective for treating some Pomeranian dogs with alopecia X.

Prognosis

Alopecia in itself is seldom a life-threatening condition although, in some instances, it may be a cutaneous marker for a systemic disease that could carry a guarded to grave prognosis. Most alopecia caused by pruritus or inflammation can be managed or treated once the underlying cause is identified. If follicular destruction occurs secondary to severe inflammation or ischemia, alopecia could be permanent. In addition, immune-mediated conditions such as alopecia areata and pseudopelade may fail to respond to treatment.

Many congenital/hereditary alopecias have a guarded prognosis for hair regrowth. Once the diagnosis has been determined, it becomes of cosmetic concern only. While some treatments may result in varying degrees of hair regrowth for these individuals, the veterinarian and client must decide if the risks of the treatment are warranted for the disease.

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164

Canine Sterile Papular and Nodular Skin Diseases

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This chapter will review the etiology, pathogenesis, diagnosis, management, and prognosis of the most common canine sterile papular and nodular dermatoses, including histiocytic disorders, sterile nodular panniculitis, sterile granuloma/pyogranuloma syndrome, and juvenile cellulitis.

Canine Histiocytic Disorders

Canine histiocytic disorders include canine reactive histiocytosis (cutaneous and systemic) and histiocytic sarcoma complex (localized and disseminated histiocytic sarcoma).

Canine Reactive Histiocytosis

Canine reactive histiocytosis includes systemic histiocytosis (SH) and cutaneous histiocytosis (CH). Both forms are characterized by reactive proliferation of activated dermal dendritic cells. They affect mainly the skin and subcutaneous tissue, but in the systemic form other organ systems can be involved, including lymph nodes, eyelids, sclera, nasal cavity, lungs, spleen, and bone marrow.

Cutaneous Histiocytosis

Etiology/Pathophysiology

The etiology and pathogenesis of CH are unknown. Since infectious agents have not been identified and the disease responds to immunosuppressive therapy, immune-dysregulatory mechanisms are likely involved. This disease is characterized by specific morphologic and immunohistochemistry criteria. According to Affolter and Moore, CH originates from CD1+, CD11c+, MHC II+, CD4+, and Thy-1+ (CD90) activated dermal dendritic antigen-presenting cells, admixed with T lymphocytes and neutrophils. The cellular phenotype has become the basis for definitive diagnosis (see diagnosis section below).

Epidemiology

Age at the time of diagnosis ranges from 3 to 9 years and males and females can both be affected, but one study showed male predilection. Collies and Shetland sheepdogs may be predisposed.

Clinical Signs

Cutaneous histiocytosis is characterized by multiple hairless, erythematous dermal to subcutaneous nodules localized predominantly to the face, neck, nasal mucosa, perineum, scrotum, and feet (Figures 164.1 and 164.2). The lesions are not pruritic or painful, but larger lesions may become ulcerated and cause discomfort. The lesions wax and wane, with older lesions spontaneously regressing as new ones form. The disease is usually slowly progressive and, in some cases, may spontaneously resolve.

Diagnosis

The clinical differential diagnoses include other nodular skin diseases such as neoplasia (e.g., multiple cutaneous histiocytomas, mast cell tumors, cutaneous lymphoma), infectious granulomas, sterile nodular panniculitis, and cutaneous sterile granuloma and pyogranuloma syndrome.

Diagnosis is based on the patient's history, clinical signs, cytologic findings, and primarily histopathologic findings. Immunohistochemistry may be required to confirm the diagnosis.

Cytologic examination shows large numbers of histiocytes with abundant cytoplasm; binucleated and multinucleated cells can be seen. Variable numbers of other inflammatory cells can be present.

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Figure 164.1 Two-year old Bernese mountain dog with cutaneous histiocytosis. Nodular lesions are present on the lips and planum nasale.



Figure 164.2 Close-up of the lesions on the lips of the dog in Figure 164.1. Note the multiple, crusted, erosive to ulcerative nodules.

Histologically, the skin lesions are characterized by a nodular to diffuse infiltrate that extends from middermis to the subcutaneous tissue. The infiltrate is perivascular and periadnexal. Early lesions have a linear or nodular configuration, but it may become diffuse in chronic cases. The infiltrate can invade the wall of blood vessels, causing focal or multifocal areas of ischemic necrosis. Important differential diagnoses for histopathology include sterile granuloma and pyogranuloma syndrome, multiple cutaneous histiocytomas, and cutaneous lymphoma. Immunohistochemistry may be required to differentiate cutaneous histiocytosis from these conditions.

It is recommended to contact veterinary diagnostic laboratories for availability and tissue submission requirements for immunohistochemistry. Because a limited number of markers are available to be used on formalin fixed specimens, the submission of fresh tissue samples may be necessary. Canine cutaneous histiocytosis has been characterized by proliferation of CD1+, CD11c+, MHC II +, CD4+, and Thy-1+ (CD90) activated dermal dendritic cells.

Therapy

Immunosuppressive drugs have been used with mixed results. Most cases respond completely or partially to immunosuppressive therapy with glucocorticoids, but require long-term or intermittent therapy to induce remission and prevent reoccurrence. Up to 50% of cases respond to prednisone as sole therapy. Azathioprine, ciclosporin, and leflunomide have also been shown to be effective, and can be helpful in cases not responding to glucocorticoid therapy. Tetracycline/niacinamide treatment has been found to be effective as maintenance therapy to avoid recurrence. Since tetracycline has been unavailable in the US market, doxycycline or minocycline can be substituted for tetracycline.

Prognosis

Prognosis is guarded. Up to one-third of patients have reoccurrence of skin lesions and thus long-term therapy is required. Dogs with nasal involvement may be more likely to have recurrence.

Systemic Histiocytosis

Systemic histiocytosis is considered a disseminated form of cutaneous histiocytosis. In addition to the skin and mucocutaneous junctions, lesions may be found in the lungs, spleen, liver, lymph nodes, eyelids, sclera, and bone marrow.

Etiology/Pathophysiology

The etiology and pathogenesis of SH are currently unknown. As for CH, since infectious agents have not been identified and the disease responds to immunosuppressive therapy, immune-dysregulatory mechanisms are likely involved.

Signalment

Systemic histiocytosis was first recognized in Bernese mountain dogs, but since then has been described in several other breeds. In one report including 26 dogs, Bernese mountain dogs were overrepresented (11/26),

followed by Rottweilers (4/26), and golden and Labrador retrievers (3/26). The age at the time of diagnosis varies from 1 to 9 years. Males seem to be more frequently affected in Bernese mountain dogs. No sex predisposition was observed in other breeds.

Clinical Signs

Systemic histiocytosis differs from CH in the extent of lesions present and the multiorgan involvement. Lesions affect the skin, with high prevalence for mucocutaneous junctions; other organs commonly involved include the nasal cavity, eyes, spleen, lymph nodes and testicular tissue. Bone marrow, liver, lungs, and gingiva can also be affected. In a recent study, 2/26 dogs had hypercalcemia. The clinical signs vary depending on the organs affected and extension of the lesions. Anorexia, weight loss, conjunctivitis, and stertorous respiration are commonly seen. The disease waxes and wanes and dogs are asymptomatic between clinical episodes. The clinical episodes can increase in severity and respond less effectively to therapy with chronicity.

Diagnosis

Clinical differential diagnoses include neoplasia, infectious and sterile granulomas, cutaneous histiocytosis, and cutaneous sterile granuloma and pyogranuloma syndrome. The diagnosis is based on history, clinical signs, cytology, histopathology, and ruling out infectious causes.

Cytologic findings are similar to CH, consisting mainly of large numbers of histiocytes, with occasional bi- or multinucleated giant cells. Histopathologic findings are identical to those observed with CH, composed of multifocal nodular infiltrate affecting the deep dermis and subcutaneous tissue. The cellular infiltrate consists mainly of histiocytes, lymphocytes, and neutrophils. The infiltrate is angiocentric and may invade the blood vessels, causing destruction of the vascular wall, thrombosis, and ischemic necrosis. Invasion of the blood vessel wall has been observed more consistently in cases of SH. The infiltrating histiocytes express CD1+, CD11c+, MHC II+, CD4+, and Thy-1+ (CD90), consistent with activated dermal dendritic cells.

Therapy

The clinical signs wax and wane, and some dogs can undergo long periods of remission, but most cases require long-term immunomodulatory therapy. The experimental use of thymosin, which modulates T lymphocyte effector and regulatory function, has shown promising results; however, further use of this treatment has not been documented. Good response has been seen with leflunomide and ciclosporin, both of which have an inhibitory effect on T lymphocytes. The good response to these drugs suggests an important role of T lymphocytes in the pathogenesis of canine reactive histiocytosis. Ocular lesions may be more difficult to treat and often require the use of ophthalmic ciclosporin preparations. The use of high doses of glucocorticoids and cytotoxic agents has shown poor response.

Prognosis

The prognosis is guarded; the clinical course waxes and wanes but it is usually prolonged. Most cases are euthanized due to relapse of clinical signs or poor response to therapy.

Histiocytic Sarcoma Complex

Previously known as malignant histiocytosis, this complex includes localized and disseminated histiocytic sarcoma (HS). Histiocytic sarcoma is a highly aggressive neoplasm. It may develop as a localized tumor or a widely disseminated disease; animals with initially localized disease often develop metastasis. The disease is characterized by infiltration of neoplastic proliferation of cells of the histiocytic lineage, including dendritic antigen-presenting cells and macrophages. The presence of macrophages has been documented only in cases of hemophagocytic HS, in which the histiocytes are markedly erythrophagocytic. Histiocytic sarcoma is highly breed specific, with Bernese mountain dogs, Rottweilers, and flat-coated and golden retrievers having a high prevalence. Immunohistochemistry plays an important role in differentiating histiocytic tumors from other neoplasias with similar histopathologic findings such as lymphoma, poorly differentiated mast cell tumors, and malignant fibrous histiocytoma.

Pathogenesis

Histiocytic sarcomas are characterized by localized or disseminated infiltration of malignant histiocytes. Expected immunohistochemical expression pattern for HS in snap-frozen tissue samples is CD1+, CD4-, CD11c+, CD11d-, MHC II+, ICAM1+, Thy -1+/-. Hemophagocytic HS expresses MHC II, beta-2 integrin, and CD11d. The disease is familial in Bernese mountain dogs in which an oligogenic mode of transmission has been proposed.

Signalment

Histiocytic sarcoma affects mainly Bernese mountain dogs, Rottweilers, flat-coated and golden retrievers with a median age at presentation of 8 years. The tumor has been found to have a male predisposition in Bernese mountain dogs and flat-coated retrievers.

Clinical Signs

Localized HS is reported to be most common in the bone, appendicular joints, and skin. Distant metastasis

to the lungs, lymph nodes, and abdominal viscera has been reported in up to 91% of cases. Affected dogs are usually presented for lameness or a soft tissue swelling. In dogs with disseminated HS, the clinical signs are vague and include anorexia, lethargy, and weight loss. Pulmonary involvement is common and dogs may show evidence of dyspnea at the time of initial presentation. Neurologic abnormalities, including ataxia and paraparesis, are also common. Other organs often affected include the liver and spleen. Although clinicopathologic findings are nonspecific, anemia, thrombocytopenia, and hypoalbuminemia were consistently reported in cases of hemophagocytic HS. Diffuse splenomegaly with ill-defined masses was also consistently present in these cases.

Diagnosis

The diagnosis is based on clinical signs, signalment, and cytologic and histopathologic findings. The main clinical differential diagnoses are other neoplasias and systemic histiocytosis. Both localized and disseminated HS have the potential for highly aggressive behavior so complete staging to determine disease extent is recommended to determine possible treatments and prognosis. Cytologic finding include large round cells with foamy cytoplasm and multinucleated giant cells admixed with spindle-shaped cells. Histopathologically, the tumors are poorly demarcated and the neoplastic infiltrate consists of pleomorphic mononuclear cells and multinucleated giant cells. Phagocytosis of neutrophils and erythrocytes is not uncommon. Marked anisokaryosis and anisocytosis with high mitotic rate are also present. The histopathologic findings and the use of immunohistochemical staining help differentiate these tumors from other round cell tumors.

Recently, a screening program has been proposed for early detection of disseminated HS in Bernese mountain dogs. The program suggests screening of Bernese mountain dogs over 4 years of age every six months, including diagnostic imaging and measurement of ferritin as a blood-borne marker of the disease.

Therapy

For cases of localized HS, improved outcome has been reported with the use of localized therapy, including surgery and radiation therapy. Unfortunately, the rate of metastasis is very high (up to 91%) so the use of adjuvant systemic therapy may be beneficial. The disseminated form of the disease usually has poor sensitivity to chemotherapy. Lomustine, doxorubicin, and vincristine have been used with variable success. The use of bisphosphonates has been proposed to increase the effectiveness of chemotherapy against HS cells. The use of a multiple drug protocol including cyclophosphamide, vincristine, and prednisone has also been reported to induce a temporary response.

Prognosis

In general, the prognosis is poor. Dogs with localized HS receiving aggressive localized treatment and systemic chemotherapy may have a better prognosis with a median survival time of 568 days. The median survival time for dogs with disseminated HS receiving chemotherapy is 106 days. The presence of distant metastasis or disseminated disease worsens the prognosis. Many dogs are euthanized at the time of diagnosis because of poor clinical condition and poor prognosis.

Sterile Nodular Panniculitis

Panniculitis refers to inflammation of the subcutaneous fat and it may be associated with a variety of conditions. Sterile nodular panniculitis (SNP) refers to sterile inflammation of the subcutaneous fat tissue of unknown origin. Clinical signs include single or multiple subcutaneous nodules, intermittent fever, and anorexia.

Concurrent inflammation of the fat in other organs can be seen in cases of SNP. Skin lesions can be solitary or multiple and multiple lesions can be associated with systemic signs including fever, lethargy, and anorexia.

Pathogenesis

Sterile nodular panniculitis has been documented in association with systemic lupus erythematosus, pancreatitis and pancreatic tumors, rheumatoid arthritis, and lymphoplasmacytic colitis. In people, a deficiency of alpha-1-antitrypsin, a protease inhibitor, has been suggested to be a predisposing factor. In dogs, this association has not been made with certainty. In one dog with panniculitis in which alpha-1-antitrypsin was found to be low, a *Bartonella* infection was present, making it difficult to determine the cause. In one retrospective study, 37% (16/43) of the patients had prior surgery with lesions developing at the surgery site.

Signalment

A large retrospective study did not identify any age, breed or sex predilection; however, others suggest 3–5 years as the most common age of onset and dachshunds, miniature poodles, and collies as the breeds at increased risk for SNP. In two studies, the most affected dogs were neutered, suggesting no gender predilection.

Clinical Signs

Clinically, SNP manifests as single or multiple subcutaneous nodules varying in size from a few millimeters to several centimeters in diameter. Lesions can be of normal skin color or be erythematous or bluish in color. Initially, the nodules are firm but they may liquefy and become soft. Some lesions regress while others develop draining tracts and become ulcerated (Figure 164.3).

Well-delineated ulcers are characteristic. Draining lesions discharge an oily, clear to yellowish brown material, which may also be hemorrhagic (Figure 164.4).

Nodules may heal with scarring and are more commonly found on the trunk but can occur anywhere. Fever, lethargy, and anorexia are commonly seen in dogs with multiple lesions; these signs occur simultaneously or just before the beginning of nodule formation. Other systemic signs reported include peripheral lymphadenopathy, joint effusion and pain, vomiting, and abdominal pain.



Figure 164.3 Multifocal areas of ulceration on the lateral thorax of a Labrador retriever with sterile nodular panniculitis.



Figure 164.4 Oily, hemorrhagic discharge from an ulcerated nodule in a Weimaraner with sterile nodular panniculitis. *Source:* Courtesy of Dr Melanie Hnot.

Diagnosis

Sterile nodular panniculitis must be differentiated from other forms of panniculitis and other diseases with similar clinical presentation, including infectious diseases such as bacterial, fungal or mycobacterial infection, sterile granuloma and pyogranuloma syndrome, foreign bodies, injection site reaction, insect bite, drug reaction, and neoplasia. Sterile nodular panniculitis is diagnosed based on the patient's history and clinical signs, exclusion of other causes of panniculitis, and cytologic and histopathologic findings. It can be a cutaneous marker of a concurrent disease process so a systematic diagnostic approach is needed to help identify a possible etiologic factor.

A complete history, physical examination, and minimum database including hemogram, chemistry profile and urinalysis can serve as guides in deciding which additional test(s) will be useful in the diagnosis. In a recent study, neutrophilia, increased alkaline phosphatase (ALP), mild hypoglycemia, and hypoalbuminemia were present in over 50% of cases with systemic involvement. Cytologic evaluation of aspirates from intact lesions can vary in appearance from suppurative to pyogranulomatous or granulomatous with fat droplets or cells present and no microorganisms. Aspirates from deep firm nodules may show spindle cells that resemble neoplastic cells. The definitive diagnosis can be based only on histopathologic findings. Wedge biopsies should be performed to collect samples that include the epidermis, dermis, and subcutaneous tissue. The sample should be collected aseptically if submitted for fungal, bacterial (aerobic/anaerobic), and mycobacteria cultures. Bacterial and fungal cultures of intact nodules yield no growth. Special stains of biopsy samples can be used to help eliminate bacteria and fungi as causative agents. Some organisms are difficult to culture or identify with routine methods, and molecular studies like polymerase chain reaction (PCR) are necessary. This is particularly true for mycobacteria and *Leishmania*.

Therapy

Surgical excision of solitary masses can be curative. Dogs with multiple lesions are treated with immunosuppressive drugs. In dogs, oral prednisone or prednisolone is usually effective at 2 mg/kg/day for two weeks; then, the patient should be reevaluated. If remission is achieved within that time, the dose should be decreased by 25% every seven days until the lowest effective dose is given

every 48 hours. Regression of the lesions may take 2–8 weeks. If remission has not been achieved after four weeks of daily immunosuppressive doses of glucocorticoids, the case may require combination therapy with other immunosuppressive drugs such as azathioprine or ciclosporin. Topical and intralesional corticosteroids have been effective in some cases, and may be the treatment of choice when systemic immunosuppressive therapy is contraindicated. In addition to immunosuppressive treatment, vitamin E and potassium iodide have been recommended, but their efficacy is unknown.

Prognosis

The prognosis is usually good, with most cases showing a good response to treatment. Some cases may require prolonged immunosuppressive therapy.

Sterile Granuloma/Pyogranuloma Syndrome

Sterile granuloma/pyogranuloma syndrome (SGPS) is an uncommon disease presenting clinically with cutaneous papules, nodules or plaques of unknown origin. The lesions may be solitary or multiple, and localized or generalized.

Pathogenesis

Sterile granuloma/pyogranuloma syndrome is an idiopathic canine skin disorder. The pathogenesis is unknown, but the inflammatory nature of the infiltrate, failure to demonstrate infectious agents, and the good to excellent response to immunomodulating drugs support it being an immune-mediated disorder. However, it has been hypothesized that SGPS may be related to an immune response against persistent endogenous or exogenous antigens, such as *Leishmania* spp. or *Mycobacterium* spp. organisms or incomplete clearing of associated antigens, causing a granulomatous/pyogranulomatous inflammatory reaction. The presence of *Leishmania* spp. DNA has been documented in cases of SGPS in Spain and Italy. The finding of antigenic fragments or organisms may become possible as we advance our diagnostic techniques.

Signalment

Sterile granuloma/pyogranuloma syndrome can affect dogs of any age and gender, but in a retrospective study 24/29 cases were male. It is seen more frequently in the Great Dane, boxer, golden retriever, collie, dachshund, English bulldog, and Weimaraner.

Clinical Signs

The clinical signs are characterized by firm, hair-covered to partially alopecic, erythematous papules, nodules, or plaques. Lesions develop more commonly on the head and distal extremities, and less commonly on the pinnae, eyes, trunk, and abdomen. Lesions involving the tongue and prepuce have been seen in individual dogs. In most cases, the lesions are multiple and are not associated with pain or pruritus. Occasionally, draining tracts and ulceration can be observed, especially on lesions localized to the feet (Figure 164.5).

Lymphadenopathy was present in 31% of the cases in a review including 29 dogs. Systemic signs associated with this syndrome have not been reported. The condition may resolve spontaneously or take a waxing and waning course.

Diagnosis

Clinical differential diagnoses include bacterial and fungal infections, foreign bodies, SNP, cutaneous eosinophilic granulomas, and cutaneous neoplasms. Diagnosis of SGPS is based on its clinical appearance, histopathologic findings, and failure to document the presence of microorganisms. Wedge biopsies should be performed to collect samples that include the epidermis, dermis, and subcutaneous tissue. The samples should be collected aseptically if they are being submitted for cultures. Histopathologically, SGPS is characterized by multifocal, nodular to diffuse pyogranulomatous/granulomatous dermal infiltrates. Special stains on biopsy samples are negative. Aerobic and anaerobic bacterial cultures and fungal culture from fresh tissue samples are also negative. Some organisms are difficult to culture or identify with routine methods, and molecular studies such as



Figure 164.5 Partially alopecic, erythematous and ulcerated nodule present in the interdigital space of digits 4 and 5 in a dog with sterile granulomatous pyogranulomatous syndrome. *Source*: Courtesy of Dr Wendy Lorch.

PCR are necessary. This is particularly true for mycobacteria and *Leishmania*.

Therapy

Surgical excision can be curative for solitary nodules or plaques. Systemic treatment is often needed for multiple lesions, including immunosuppressive doses of glucocorticoids or other immunomodulating agents. The use of tetracycline and niacinamide combination was shown to be effective for long-term management in a case of SGPS. A trial with this combination is warranted before more potent immunosuppressive drugs are used. Tetracycline/niacinamide is used at 250 mg of each for dogs less than 10 kg, and 500 mg of each in dogs more than 10 kg q8–12h. If tetracycline is unavailable, doxycycline at 5 mg/kg q12h can be used. If shortage of doxycycline occurs, minocycline can be substituted for doxycycline.

Prednisone or prednisolone can be used at 2.2–4.4 mg/kg q24h PO until resolution of the skin lesions (usually 10–14 days), then the medication can be tapered to the minimal effective dose (see treatment for sterile nodular panniculitis). Most cases require long-term alternate-day glucocorticoid therapy to avoid reoccurrence. Refractory cases may require the addition of other immunomodulating agents like ciclosporin or azathioprine.

Prognosis

The prognosis is good. The condition may resolve spontaneously or take a waxing and waning course. Most cases required prolonged use of immunomodulatory drugs.

Juvenile Cellulitis

Canine juvenile cellulitis, also known as juvenile pyoderma, puppy strangles, or juvenile sterile granulomatous dermatitis and lymphadenitis, is an uncommon lymphocutaneous disease. It is characterized by a sterile granulomatous or pyogranulomatous dermatitis and lymphadenitis and usually affects young puppies.

Pathogenesis

The cause of juvenile cellulitis is unknown. Cytologic examination of aspirates of affected lymph nodes and skin lesions does not reveal infectious agents, and culture results of intact lesions are always negative for bacterial and fungal growth. In addition, the condition responds dramatically to treatment with glucocorticoids, suggesting an immune dysfunction. There may be a heritable component as it has been documented more frequently in certain breeds and within litters. Vaccine reactions have been postulated as the cause of juvenile cellulitis, but the role of vaccine or other viruses in the disease development remains unclear. A nonviral infectious etiology has also been considered but attempts to isolate bacteria and fungi have not been successful.

Signalment

Most cases are young puppies less than 4 months old, with a few reported cases in older dogs. No sex predilection has been reported. Breeds that appear to be predisposed include golden retrievers, dachshunds, Gordon setters, and Weimeraners. Other breeds reported include the Labrador retriever, Siberian husky, miniature poodle, Chesapeake Bay retriever, Lhasa apso, and mixed-breed dogs.

Clinical Signs

Early clinical signs consist of edematous moist dermatitis affecting mainly the eyelids, lips, and muzzle. The affected skin rapidly develops papules and pustules. Lesions are characterized by severe edema, fistulation, and drainage with copious purulent discharge and crust formation. Purulent otitis externa and conjunctivitis are also common; the pinnae are often severely swollen and may develop ulcerative lesions. Affected skin is usually painful. Submandibular and prescapular lymphadenopathy is commonly present. Concurrent neurologic signs and orthopedic problems have been reported preceding or associated with the signs of juvenile cellulitis. The patient may be lethargic and depressed and older dogs may present with more severe systemic signs and pyrexia.

Diagnosis

Clinical differential diagnoses include angioedema in acute cases and as lesions progress; staphylococcal pyoderma, demodicosis, and adverse cutaneous drug reaction should also be considered. Other less likely differential diagnoses include neoplasia (cutaneous lymphoma, mast cell tumor) or infectious causes such as nocardiosis, actinomycosis, mycobacterial infections, and subcutaneous opportunistic mycoses. Diagnosis is often based on characteristic clinical presentation, but can be confirmed by cytologic or histopathologic findings. Tests may include fine needle aspirates of lymph nodes, impression smears or skin scraping, cytology or skin biopsy. Cytology from fine needle aspirates of affected lymph nodes reveals a sterile granulomatous or pyogranulomatous inflammation. Histopathologic findings usually reveal granulomatous or pyogranulomatous dermatitis which may extend into the panniculus.

Furunculosis and suppurative inflammation have also been reported in advanced cases.

Therapy

Treatment consists of immunosuppressive doses of glucocorticoids. Initial treatment should be aggressive, as scarring can be severe if the disease is not controlled quickly. Oral prednisone or prednisolone can be given at 2 mg/kg/day until lesions resolve, usually 2–4 weeks, and then slowly tapered off completely over the next few weeks. Some dogs may respond better to oral dexamethasone at 0.2 mg/kg/day (initial dose). Antibiotics should be given if secondary bacterial infections are present. Oral cephalexin can be given at 25–30 mg/kg q12h for the duration of the corticosteroid treatment. Ciclosporin has also been effective in cases refractory to glucocorticoids. Griseofulvin was used with good results in six puppies at the dose range of 14.2–34 mg/kg q12h. All cases were completely recovered within three weeks. The authors postulated that griseofulvin could induce downregulatory signals within the lesions.

Prognosis

The prognosis is good. Most cases respond well to treatment and relapses are uncommon.

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165

Parasitic Skin Diseases

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Demodicosis

Canine Demodicosis

Etiology/Pathophysiology

Canine demodicosis is currently known to be caused by three species of mites: *Demodex canis*, *D. injai*, and *D. cornei*. *Demodex canis* and *D. injai* are thought to be two separate species. However, *D. cornei*, a short-bodied mite, is believed to be a morphologic variant of *D. canis*. *Demodex canis* and *D. injai* live within the hair follicles or sebaceous glands, and *D. cornei* lives on the stratum corneum.

Recent studies using real-time polymerase chain reaction (PCR) have validated the widely held belief that all dogs, healthy and diseased, harbor *D. canis* mites in their skin. Puppies are believed to acquire *D. canis* from their mothers at birth. However, the mode of transmission of *D. injai* and *D. cornei* is currently not known.

Demodex canis mites have a life cycle involving four stages. They begin as fusiform eggs. These eggs develop into six-legged larvae, then eight-legged nymphs, followed by the adults. The life cycle of *D. cornei* and *D. injai* has not been investigated but it is likely to mirror the life cycle of *D. canis*. Adult *D. injai* mites are much longer than the *D. canis* species (Figure 165.1). Adult *D. cornei* mites have a short tail (Figure 165.2).

Demodicosis caused by *D. canis* can occur in juvenile (≤18 months) or adult dogs (>4 years). Older dogs that develop demodicosis may have another disease process leading to an immune dysfunction that allows the mites to multiply and cause disease. Some examples include hyperadrenocorticism, hypothyroidism, diabetes mellitus, or malignant neoplasia. Immunosuppressive therapy can also result in a proliferation of mites. This includes topical and oral corticosteroids and oclacitinib maleate (Apoquel® for dogs; Zoetis). Allergic dermatitis is often a concurrent diagnosis. Often, no cause is identified for the development of adult-onset demodicosis. *Demodex injai* has only been reported in adult dogs.

The reason for development of demodicosis in some dogs versus others is not precisely known. We do know that certain breeds develop disease more commonly than others, suggesting the influence of genetics. Breeds more commonly diagnosed with demodicosis caused by *D. canis* include the shih tzu, West Highland white terrier, English bulldog, and Boston terrier. In the author's experience, pit bull terriers and Yorkshire terriers also seem overrepresented. Demodicosis caused by *D. injai* has been noted at greater frequency in terriers and shih tzus.

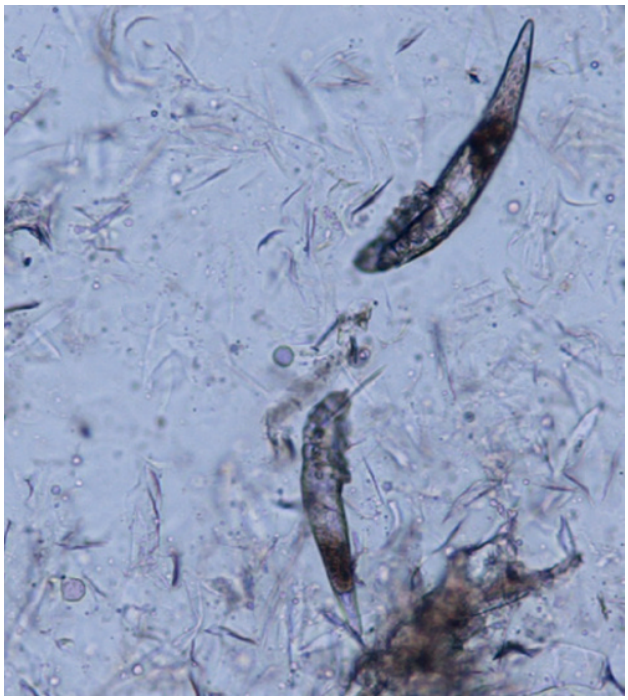
Other factors suggested to play a role include parasitism, inadequate nutrition, and stress. However, many affected patients do not have these problems. Various *ex vivo* studies have investigated the immune response of dogs with juvenile-onset generalized demodicosis caused by *D. canis*, but a defect has yet to be identified. Nevertheless, the current belief is that these dogs inherit an immune dysfunction of variable severity linked to a subset of T cells capable of recognizing specific mite antigens and keeping the mites in small numbers. This theory, however, needs to be validated. Overexpression of the Toll-like receptor 2 gene may result in the clinical findings associated with demodicosis.

History and Clinical Signs

There are two types of infestations of *Demodex* mites: localized and generalized. The localized variant consists of one or more lesions usually on the face and forelegs. These cases typically self-resolve and affect puppies. An infestation is considered generalized when large body areas, several localized lesions, an entire body region, or two or more paws are affected. This form primarily begins at the puppy stage and may resolve, but typically progresses without treatment as the puppy ages.

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(a)



(b)



Figure 165.1 (a) Adult *Demodex canis*. (b) Adult *Demodex injai*. *Source*: Courtesy of Dr Linda Frank.

Demodex canis infestation can cause a variety of signs. Lesions seen can include alopecia, erythema, scales, papules, and pustules. If hair follicles rupture (i.e., furunculosis), severe inflammation associated with tracts draining serosanguineous to purulent exudate is noted (Figure 165.3).

Lymphadenopathy and/or fever may occur in these cases especially if large areas of the body are affected. Follicular casts and comedones are very typical lesions. Pruritus may or may not be present and is usually noted when secondary infection or seborrhea occurs. Secondary superficial or deep bacterial infection is often present in



Figure 165.2 Adult *Demodex cornei*.



Figure 165.3 Juvenile-onset generalized demodicosis caused by *Demodex canis*. Diffuse alopecia, erythema, and edema are noted. Hemorrhagic crusts on the lateral aspect of the face correspond to areas of furunculosis.

the generalized form of the disease and may aggravate lesions, resulting in crusts, pustules, thickened skin, and hyperpigmentation. Paws rarely are affected alone and lesions can be similar to the ones described. Bullae

and fistulous tracts are also present on paws when furunculosis develops (Figure 165.4).

Demodex cornei mites have been found in demodicosis caused by *D. canis*, suggesting that these mites are a morphologic variant of *D. canis* and not a separate species.

Demodex injai typically manifests with dorsal and occasionally facial seborrhea oleosa (Figure 165.5). In these areas, hypotrichosis is present. Pruritus may also be noted.

Diagnosis

Diagnosis of *D. canis* infestation involves performing multiple deep skin scrapings. As mites live in the hair follicles and sebaceous glands, the lesional area is squeezed before scraping in an attempt to extrude the mites. The scraping should be deep enough that capillary bleeding occurs. Multiple adult mites and/or immature forms are diagnostic. Mites should be easy to find if skin scrapings are performed adequately. If only a few mites are found after multiple skin scrapings in an animal with clinical signs suggestive of demodicosis, consider this finding important. This scenario is typically encountered in cases of juvenile, localized demodicosis.



Figure 165.4 Feet of a dog with juvenile-onset generalized demodicosis caused by *Demodex canis*. Multiple tracts draining serosanguineous exudate correspond to areas of furunculosis.



Figure 165.5 Excessive oil along the dorsum of a West Highland white terrier with demodicosis caused by *Demodex injai*.

Similar technique should be applied when *D. injai* infestation is suspected; however, mites can be harder to find because they are present in small numbers and often in sebaceous glands, making their extrusion difficult. Superficial scrapings should be adequate for *D. cornei* but mites are typically not easy to find.

Trichoscopy may also reveal mites in severe cases of demodicosis caused by *D. canis*. Various hairs are plucked from affected areas, placed in mineral oil on a glass slide and covered with a cover slip before microscopic evaluation. These may or may not be positive in affected dogs. Acetate tape impressions of affected squeezed skin have recently been shown to reveal mites in 100% of samples. Mites can also be found on cytology of exudate collected from draining tract lesions. Mites may also be identified using a zinc sulfate centrifugal fecal flotation technique. It is important to emphasize that sensitivity of these tests is generally lower than that of deep skin scrapes adequately performed. Biopsy may be needed in Chinese shar-peis or dogs with fibrotic lesions especially affecting the paws. Mites can be found in the stratum corneum, hair follicles, and on occasion the sebaceous glands. Inflammation may present as an interface mural folliculitis, nodular dermatitis, or a suppurative folliculitis and furunculosis.

Therapy

Affected dogs should be treated with appropriate systemic antibiotics, if indicated. Supportive care may be needed in severe cases. Underlying disease processes should be addressed. Localized cases are typically self-limiting and resolve without treatment in about 6–8 weeks. Generalized cases should be treated for one month beyond two negative consecutive skin scrapings. Skin scrapings are recommended monthly to assess progress. Numbers of live versus dead mites and their life stages can help assess response to therapy.

The most effective treatments are amitraz, macrocyclic lactones, and isoxazolines. The only treatment currently licensed in the United States is amitraz. Labeled treatment is a 0.025% amitraz (Mitaban®; Zoetis) solution used as a dip every 14 days. Variations of this therapy protocol, such as weekly applications at 0.025%, 0.05%, 0.075% or 0.1%, can be considered for more difficult cases. Removal of follicular debris, crusts, and hair that prevents penetration of the solution into the hair follicle is an important part of this treatment regimen; therefore, medium to long hair coats should be clipped and crusts removed prior to dipping. This chemical is a monoamine oxidase inhibitor as well as an alpha-2-adrenergic agonist. Potential side-effects include lethargy, ataxia, vomiting and diarrhea, polyuria and polydipsia, bradycardia, depression, and hyperglycemia. The person providing treatment should

not directly contact the solution or inhale it. Application in a well-ventilated area is important.

Ivermectin is a therapy that is often very efficacious in treating demodicosis. Herding breeds should be assessed for a mutation of the ABCB1 (formerly MDR1) gene which encodes for the cell membrane transporter P-glycoprotein. This mutation can lead to severe toxicosis with avermectins. Some of the breeds reported to be predisposed to this mutation include collies, border collies, Shetland sheepdogs, Australian shepherds, Old English sheepdogs, white Swiss shepherds, long-haired whippets, McNab, and silken windhound. This mutation is still possible in any dog breed, but less likely. The genetic test for the mutated gene can be done through Washington State University College of Veterinary Medicine.

Possible side-effects associated with ivermectin toxicosis include lethargy, vomiting, diarrhea, anorexia, mydriasis, and ataxia. In severe cases, seizures, coma, and death can result. Side-effects can also occur in dogs that carry a normal ABCB1 gene and are often less severe and may resolve by lowering the dosage. Due to possible side-effects, an incremental dose increase is strongly suggested. The dosage range is 0.3–0.6 mg/kg once a day PO. The author determines dosing by calculating the dose desired in this range and starting at one-third this dose. This is given for one week, followed by two-thirds the final dose for one week, then ending at the final dose desired.

Other macrocyclic lactones that can be used are moxidectin and doramectin. Moxidectin is dosed at 0.2–0.5 mg/kg/day PO. Again, gradual dosing is indicated. Possible side-effects include those listed for ivermectin. Moxidectin is also available as a topical product in combination with imidacloprid (Advantage Multi® for dogs; Bayer). This is an approved European treatment applied weekly for demodicosis. It is labeled for monthly usage in the United States but has shown better results when applied every 1–2 weeks, primarily for juvenile-onset cases and mild forms of demodicosis. Doramectin can be given at 0.6 mg/kg subcutaneously (SC) or PO once a week. The SC administration has resulted in better outcomes.

Milbemycin oxime (Interceptor® for dogs; Elanco) is another efficacious product. This can be used at 0.5 mg/kg PO once daily increasing by 0.5 mg/kg every seven days to a final dosage of 2.0 mg/kg/day. This medication is generally well tolerated. Mild neurologic side-effects have been noted. Breeds that do not tolerate ivermectin, including collies, may tolerate this medication but care is recommended to ensure no adverse side-effects ensue, as neurologic effects are still possible. Ataxia has been noted in dogs homozygous for the ABCB1 gene mutation at a dosage of 1.5 mg/kg/day PO.

The newest available therapies are in the isoxazoline class. These drugs are not labeled for treatment of *Demodex* sp. but have been found to be very efficacious. These include lotilaner (Credelio® for dogs; Elanco) at 20 mg/kg PO, and sarolaner (Simparica® for dogs; Zoetis) given at 2 mg/kg PO. These products are labeled for monthly usage for flea and tick prevention and treatment. Fluralaner (Bravecto® for dogs; Merck) given once at a minimum dosage of 25 mg/kg PO has also been found to be very efficacious at treating demodicosis. This product is labeled for administration every 12 weeks for the prevention and treatment of flea and tick infestations in dogs. Afoxolaner (Nexgard®; Merial) given at the minimum dosage of 2.5 mg/kg PO every 14 days for two months has been found to be very effective. However, only one dose may result in deep negative skin scrapings. It is labeled for monthly usage for flea and tick control and can be used in dogs 8 weeks of age and older, whereas fluralaner and sarolaner can only be used in dogs at least 6 months of age. Lotilaner, like afoxolaner, may be used in dogs as young as 8 weeks of age. These parasiticides act by blocking insect GABA- and glutamate-gated chloride channels and are generally very safe but should be used with caution in dogs with a history of seizures. Possible side-effects include vomiting and diarrhea. Sarolaner may cause tremors, unsteadiness, or seizures. Fluralaner may cause seizures in patients which do not have a history of seizures, but is labeled as safe for use in breeding, pregnant, and lactating dogs, and in those with the ABCB1 gene mutation. Lotilaner may also cause an increase in blood urea nitrogen. Afoxolaner should be used with caution in dogs with a history of seizures.

Females or males that have been treated should be neutered due to the potential for passing the predisposition to develop demodicosis to offspring. In addition, females should be spayed because the stress of a heat cycle or pregnancy could worsen the disease.

Prognosis

Overall, prognosis is good. Recurrence of disease can occur, so following the treatment recommendation of 30 days past two consecutive negative skin scrapings can help prevent recurrences. Life-long therapy may be needed in some cases. Long-term glucocorticoids are not recommended in patients with demodicosis or that have had demodicosis. The author believes that any glucocorticoids or oclacitinib maleate (Apoquel; Zoetis) should be used with great caution. A dog is not considered cured until one year after treatment is completed. With the advent of isoxazolines as maintenance flea and tick preventtives, the likelihood of recurrence or even development of demodicosis will probably diminish.

Feline Demodicosis

Etiology/Pathophysiology

Three species of demodectic mites have been implicated in feline demodicosis. These include *D. cati*, *D. gatoi*, and an uncommon, unnamed, morphologically distinct *Demodex* mite. *Demodex cati* spends its life cycle in the

hair follicles and sebaceous glands. This mite is slightly narrower than *D. canis*. *Demodex gatoi* has a shortened abdomen and spends its life cycle on the epidermal surface. The length of the unnamed mite is between *D. cati* and *D. gatoi*.

Demodicosis due to *D. cati* is typically associated with an underlying disease or immunosuppressive therapy. Concurrent diseases that may be present include feline immunodeficiency virus, feline leukemia virus, diabetes mellitus, squamous cell carcinoma *in situ* or other neoplastic disorders, toxoplasmosis, systemic lupus erythematosus, and hyperadrenocorticism. It has been reported to be more common in the Burmese and Siamese breeds.

Demodex gatoi, unlike *D. cati*, is not generally associated with an underlying disease. However, it has been identified in scrapings along with *D. cati* in cats positive for feline immunodeficiency virus. This mite is more commonly located in certain geographic areas. In the United States, it is more often found in the south, especially in the Gulf of Mexico area.

Little is currently known about the unnamed *Demodex* mite. The published reports have found this mite in cats diagnosed with other concurrent illnesses or had recently recovered from illness.

History and Clinical Signs

Demodex cati can cause either a localized or generalized infestation, both of which are rare. Localized demodicosis is primarily located around areas on the head, including in the ears, causing a ceruminous otitis externa, particularly in feline immunodeficiency virus-positive cats. Pruritus is variable but typically not present. Other signs include alopecia, erythema, and the presence of scales and crusts. Generalized cases often affect the head but lesions are also found elsewhere on the body. Presentation is similar to the localized form, but may include hyperpigmentation.

Demodicosis caused by *D. gatoi* is more common than the disease caused by *D. cati*. It is contagious between cats and pruritic. Clinical signs are typically fitting with the degree of pruritus. Traumatic alopecia often results from the severe pruritus on the sides of the thorax, abdomen, and the medial aspect of the legs. Other signs include erythema, scale, excoriation, and hyperpigmentation. A common clinical presentation is self-induced, clinically noninflammatory, symmetric alopecia (Figure 165.6). Some cats can be asymptomatic carriers.

Diagnosis

Skin scrapings should be performed in cases where feline demodicosis is suspected. Broad, superficial scrapings are performed to detect *D. gatoi* (surface mite), whereas deep skin scrapings must be done to diagnose *D. cati* (follicular). *Demodex gatoi* mites are typically more difficult to find due to their small size and low numbers as cats ingest these mites during grooming. Therefore, scraping areas where the cat cannot groom may increase the chances of finding mites. Fecal flotation may be another means of finding *D. gatoi*. Cellophane tape impressions viewed under the microscope may help to reveal the mites. A negative test does not rule out this infestation so diagnosis in many cases may only be made based on history and response to a therapeutic trial. The unnamed mite has been found via trichoscopy and skin scrapings.



Figure 165.6 Self-induced, clinically noninflammatory, symmetric alopecia on the dorsum and thighs of a cat with demodicosis caused by *Demodex gatoi*.

Therapy

Underlying causes leading to the development of demodicosis caused by *D. cati* should be evaluated. This disease when localized may resolve spontaneously if underlying diseases have been controlled. Amitraz (Mitaban; Zoetis) at concentrations of 0.0125–0.025% applied weekly may help. Cats are sensitive to this product and it is not recommended in cats with diabetes. A generally safe option is lime sulfur applied as a 2–4% solution every week. Unfortunately, therapy may need to be continued long term as relapses are possible. Other treatment options include doramectin administered weekly at 0.6 mg/kg SC and ivermectin at 0.2–0.3 mg/kg PO daily to every other day. Cats should be monitored for side-effects such as neurotoxicity. The off-label use of the oral isoxazoline fluralaner (Bravecto) for the treatment of demodicosis has been reported in cats. A single oral dosage of 28 mg/kg resolved *D. cati* in one case report. No side-effects were noted. Topical fluralaner, which is available for cats, may cause vomiting and diarrhea, decreased appetite, or lethargy. It may also cause alopecia or crusting. While a single topical treatment has been shown to be efficacious for the treatment of *Otodectes cynotis* in cats, there are

currently no studies evaluating it's use in the treatment of feline demodicosis. Independent of the parasiticidal chosen, treatment should be continued for 30 days past two consecutive negative skin scrapings performed 4–6 weeks apart.

Options for *D. gatoi* include the above treatment protocols described for amitraz or lime sulfur dips. Treatment typically is needed for 6–8 weeks. In-contact cats should be treated as well. Application of a moxidectin/imidacloprid (Advantage Multi for cats; BayerDVM) spot-on product every week to two weeks for up to three months has been anecdotally reported to work well in some cases. It has also been shown to be efficacious in one case report, applied weekly for 10 doses. Also, ivermectin at 0.2–0.3 mg/kg PO every 24–48 hours may be effective. The extra-label use of oral fluralaner (Bravecto) at 26–34 mg/kg given once has recently been shown to be another efficacious treatment option.

No specific treatment recommendations exist for the unnamed mite, but concurrent daily ivermectin at 0.3 mg/kg PO and 8 oz/gal of diluted lime sulfur rinses twice weekly for 6–8 weeks has been used. Also, SC ivermectin at 0.6 mg/kg daily for four weeks has been used.

For all types of feline demodicosis, isoxazolines may prove to be efficacious. Also, topical fluralaner may be a viable option as opposed to oral administration. More studies are needed in this area.

Prognosis

The prognosis of feline demodicosis varies, especially in cases of *D. cati* where underlying systemic disease is likely present. Overall, prognosis varies from good to guarded.

Scabies

Canine Scabies

Etiology/Pathophysiology

Sarcoptes scabei var. *canis* causes canine scabies, or sarcoptic mange. This is a highly contagious mite that is transmitted between dogs as well as foxes and coyotes. Fomites can also be a source of transmission. The female burrows into the stratum corneum to lay eggs. The larvae travel to the skin surface and develop into nymphs, which may live on the skin surface or in the molting pocket that may also be inhabited by larvae. The mites prefer areas with less hair, so they are more commonly found on the pinnae, elbows, hocks, and ventrum. They typically live 17–21 days. Depending on the humidity and temperature, females and nymphs can survive 4–21 days away from the host. These mites can cause disease at any time of year. Other animals including cats, humans, and foxes can be affected. Humans are usually only transiently affected.

Description of mite characteristics is important in differentiating canine scabies from the feline Sarcoptidae mite, *Notoedres cati*. *Sarcoptes scabei* mites are ovoid and small, with two anterior pairs of short legs with long unjointed stalks and suckers. There are two pairs of rudimentary posterior legs that do not extend beyond the body wall of the mite (Figure 165.7). The anus is terminal.

Research suggests that young dogs of any breed and of both sexes are more likely to become infested with the mites, suggesting that age-related immunity plays a role in pathogenesis. Nutritional status and oxidative stress also play a role in development of infestation. Specifically, alterations in the oxidant and antioxidant balance and greater apoptosis of peripheral leukocytes may contribute to a dog's susceptibility to infestation.

History and Clinical Signs

Scabies causes an intense pruritus. It is important to question if other pets or humans in the same household are also pruritic as this is a valuable diagnostic clue. However, some dogs can be asymptomatic carriers. As previously mentioned, this mite typically affects specific body regions but any body region can be affected. Corticosteroids may be beneficial in some patients at the beginning of therapy to reduce pruritus.

Early signs include papules and scales. Excoriations may also be present. With chronicity, self-induced alopecia, hyperpigmentation, hyperkeratosis or keratinous crusts, and lichenification may develop. The crusts may become thick and yellow (Figure 165.8). Peripheral lymphadenopathy may be present. Some dogs only develop erythema and excoriations.

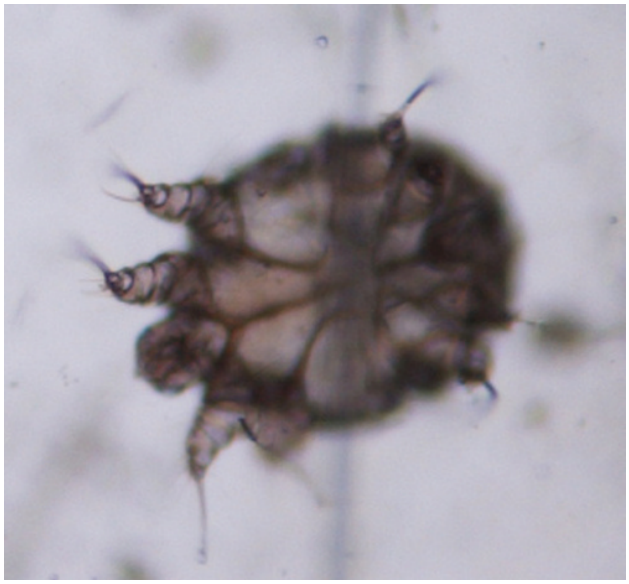


Figure 165.7 Adult *Sarcoptes scabei* var. *canis*.



Figure 165.8 Alopecia and thick yellowish crusts covering the ear margin of a dog with scabies.

Cats that become infested with *Sarcoptes scabei* var. *canis* can develop dermatitis of the face and pinnae. Papules and crusts are present. Dermatitis of the paws as well as claw abnormalities may develop. Some cats may also develop crusting and scaling over the body. Pruritus is a variable finding. Such infestations are uncommon and rare cases have been noted in indoor cats not cohabiting with dogs.

Diagnosis

Infestations with this mite are often diagnosed based on history, clinical signs, and response to therapy. Multiple superficial skin scrapings are required for diagnosis. Unfortunately, as few as 20% of skin scrapings may reveal mites or eggs. Finding even one is diagnostic of canine scabies. It is suggested to scrape the aforementioned areas that are generally affected even in the absence of lesions, as well as areas with papules and yellow crusts. Large numbers of mites are typically found on scrapings from cats infested with *Sarcoptes scabei* var. *canis*.

An additional supportive test is to demonstrate the pinnal-pedal reflex. This test entails scratching the pinnal edge with a resultant ipsilateral leg making a scratching motion. Most dogs with scabies mites have this reflex (sensitivity of 81.8%); however, it can be rarely positive in other diseases (specificity of 93.8%).

Laboratory testing utilizing an enzyme-linked immunosorbent assay (ELISA) is available in certain countries. This test has high specificity and sensitivity, but false-negative results are possible.

Therapy

Affected as well as in-contact dogs should be treated. Area treatments containing pyrethrins, permethrins or a combination of these are available for use in the home environment, keeping in mind that high concentrations of permethrins (>0.1%) are toxic to cats. Discarding bedding is advised. In the United States, a licensed treatment is selamectin (Revolution® for dogs, Zoetis) applied topically every 30 days for two doses; however, for better results most dermatologists recommend administering it every two weeks for 3–4 treatments. Lime sulfur dips at a 2–3% concentration every week for 4–6 weeks is another option. Ivermectin at 0.2–0.4 mg/kg can be given PO every seven days or SC every 14 days for 4–6 weeks. Milbemycin given orally at 2 mg/kg every week for 4–6 treatments has been shown to be effective. An imidacloprid/moxidectin combination product (Advantage Multi) is approved for the treatment of scabies in dogs and is applied topically every 30 days for two doses. Amitraz (Mitaban) solution at 0.025–0.03% applied over the whole body every two weeks for three treatments or weekly for 4–6 treatments should be effective. Fipronil spray applied to the entire body every two weeks for three applications is another treatment option. Doramectin can be given at 0.2–0.6 mg/kg SC every seven days for 4–6 weeks.

Many of these patients have secondary infections which should also be identified and addressed. Isoxazolines have been shown to effectively treat scabies as well. One dose of fluralaner (Bravecto) at a minimum of 25 mg/kg orally or topically has been shown to eliminate scabies mites. Afoxolaner (Nexgard) given at a minimum dosage of 2.5 mg/kg PO for 1–2 monthly doses should also eliminate these mites. Sarolaner (Simparica) can also be used at approximately 2 mg/kg PO for two monthly doses. There are no current publications relating to lotilaner (Credelio) and scabies mites, but the author suspects it, too, would be efficacious at resolving sarcoptic mange. Antiinflammatory doses of corticosteroids given for approximately one week may also help in alleviating the pruritus caused by the mites.

The treatment protocols detailed under "Feline scabies" are also recommended for cats infested with *Sarcoptes scabei* var. *canis*. However, three applications of the moxidectin/imidacloprid (Advantage Multi) compound product applied every two weeks has been shown to be more efficacious in five cats with sarcoptic mange than weekly ivermectin at 0.2 mg/kg SC for four weeks or selamectin (Revolution) administered every two weeks for two treatments.

Prognosis

Most dogs with scabies are cured with treatment. Rare cases have been noted to be refractory to ivermectin and selamectin. The selamectin cases may have been related to poor application on densely coated dogs. In some cases, the author finds it beneficial to keep the patient on monthly selamectin or an isoxazoline (unless it is fluralaner which is given every 3 months) when reinfestation is considered possible.

Feline Scabies

Etiology/Pathophysiology

Feline scabies or notoedric mange is caused by *Notoedres cati*. This mite can also affect foxes, dogs, rabbits, and humans. The lesions on humans are transient. It commonly affects other cats in multiple cat residences as it is very contagious. This mite typically occurs epizootically in endemic areas.

Notoedres cati follows the same life cycle as *Sarcoptes scabei* var. *canis*. Morphologically, it is similar to the canine scabies mite but is smaller, the unjointed stalk is of medium length, more striations are present on the body, and the anus is dorsally oriented.

History and Clinical Signs

Notoedres cati causes intense pruritus predominantly of the facial region. The skin becomes thickened with folds (Figure 165.9). Crusts are yellowish and tightly adherent. Excoriations and partial alopecia may develop. Lesions begin on pinnal edges and spread over the face and neck. The paws and perineum may be affected and peripheral lymphadenopathy may occur.

Diagnosis

Microscopy of superficial skin scrapings of affected cats typically reveals several mites. Diagnosis is also achieved by identifying the eggs or fecal pellets.

Therapy

Affected and in-contact cats should be treated. Safety must be considered in choosing treatments. Weekly 2–3% lime sulfur dips for 4–8 weeks are beneficial. Treatment should continue until negative skin scrapings and resolution of lesions are obtained. Ivermectin at 0.2–0.3 mg/kg may be given PO or SC every 1–2 weeks for 3–4 treatments. Doramectin can also be given at a dose of 0.2–0.3 mg/kg SC once. Selamectin (Revolution) applied topically once or twice every 14–30 days is another option. The moxidectin/imidacloprid (Advantage Multi) topical product has been shown to be effective after one application.



Figure 165.9 Thick crusts on the convex aspect of the pinna of a cat with chronic notoedric mange. *Source:* Courtesy of Dr Clarissa Pimentel de Souza.

Cheyletiellosis

Etiology/Pathophysiology

Cheyletiella, also known as walking dandruff, is a mite that generally results in a dermatitis of varying severity. *Cheyletiella parasitovorax*, *C. blakei*, and *C. yasguri* are the species of most concern in dogs and cats, with *C. yasguri* more likely to be found on dogs and *C. blakei* more likely to be found on cats, although these species are not entirely host specific. All species are contagious, and humans in contact with animals carrying the mite can become transiently affected.

These nonburrowing mites produce ova that attach to the dog or cat hairs. They are large mites that live in the keratin on the surface of the skin. They have four pairs of legs with combs and their mouthparts have characteristic hooks (Figure 165.10).

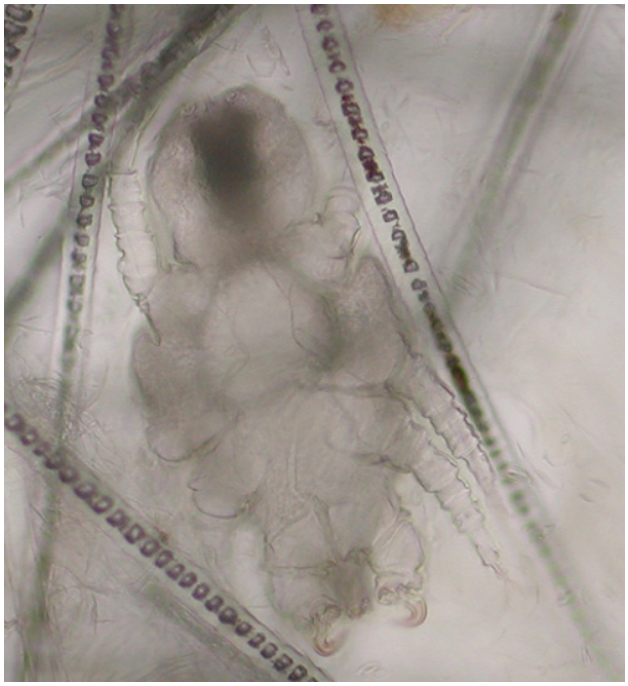


Figure 165.10 *Cheyletiella yasguri* mite; note the characteristic hooks of the accessory mouthparts.

The mites complete their life cycle on the host but mites and eggs attached to the hair shaft can contaminate the environment, creating a source for reinfestation. The adult females can also live off the host for approximately 10 days.

History and Clinical Signs

This mite infestation may result in varying levels of pruritus and severity of clinical signs. Any breed may be affected, but an increased incidence in cocker spaniels and boxers has been anecdotally reported. The resultant dermatitis manifests as dry scales along the dorsum (Figure 165.11). This often worsens over time with hair loss and an increase in pruritus. Cats can also develop miliary dermatitis.

Diagnosis

To diagnose *Cheyletiella*, material is collected from affected areas by acetate tape impressions, flea combings, or superficial skin scrapes. This material can be directly examined by visual inspection (often utilizing a magnifying glass) or using a microscope. If available, evaluate material in a Petri dish in mineral oil utilizing a dissecting microscope. Fecal examinations may also reveal the mite as many pruritic animals will ingest the offending parasite in the process of licking, biting or chewing the affected areas. Two other means of garnering material for examination include a vacuum sample of the affected area or performing a trichoscopy of affected hairs. Some dermatologists find that scraping papules (which are usually rare or absent) and microscopically examining the sample with mineral oil increases the chances of finding the mite. However, none of these diagnostic tests is 100% sensitive so a treatment trial may be necessary to confirm a presumptive diagnosis.



Figure 165.11 Cocker spaniel with cheyletiellosis showing excessive scaling along the dorsum.

Therapy

Fortunately, cheyletiellosis typically responds well to therapy. Options include weekly applications of lime sulfur or amitraz (Mitaban) dips, or pyrethrin shampoos and sprays for 3–4 treatments. However, amitraz and especially permethrins are not generally recommended for cats due to drug sensitivities. Fipronil in the spray form every two weeks for 3–4 treatments or topical concentrated solution every 30 days for three treatments are other options. Selamectin (Revolution) can be applied monthly or every two weeks for 4–6 weeks. Ivermectin at 0.2–0.3 mg/kg can be given PO weekly for 3–6 treatments or by SC injection every 14 days for three treatments. Doramectin is an option at 0.2–0.4 mg/kg SC every seven days for 4–6 weeks. One other treatment is milbemycin oxime (Interceptor) given at 2 mg/kg PO weekly for 3–4 doses. Because this is a highly contagious mite, all animals in the home should be treated.

Lynxacarus radovsky

Etiology/Pathophysiology

This mite, otherwise known as the cat fur mite, is found worldwide, typically in warm humid climates, such as in Australia, Brazil, and Puerto Rico. In the United States, it has been reported in Hawaii, Florida, and Texas. This mite is specific to the cat, but has been found on a dog. Cats acquire this mite through direct contact, but fomites must also be considered.

History and Clinical Signs

Clinical signs include a dull, unkempt coat giving the hair a "salt-and-pepper" appearance (Figure 165.12). Lesions may include alopecia, papules, and crusting and are typically present along the dorsum. Heavily infested cats or those with a long-term infestation can have exfoliative lesions. Pruritus is not typically present and when noted, a search for fleas or other external parasites is warranted.

Diagnosis

Diagnosis of *L. radovsky* infestation is accomplished by identifying the mite with microscopy. Trichoscopy and tape impressions are the ideal diagnostic methods. The

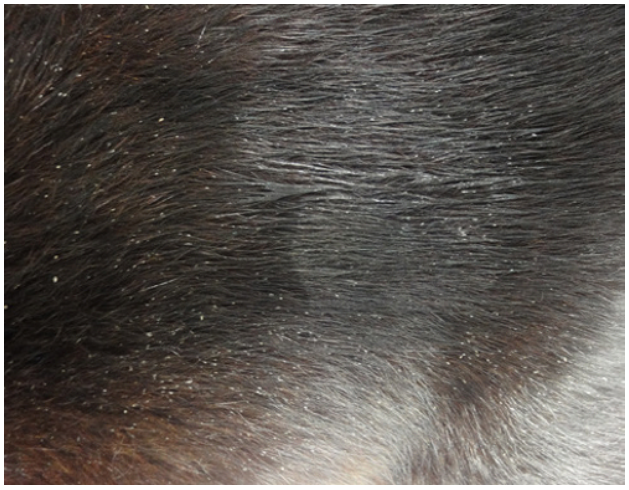


Figure 165.12 Cat with *Lynxacarus radovsky* infestation showing a "salt-and-pepper" hair coat appearance. *Source:* Courtesy of Dr Clarissa Pimentel de Souza.

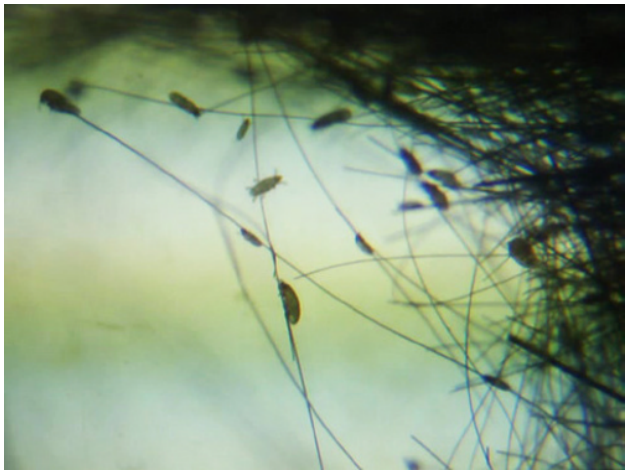


Figure 165.14 Trichoscopy from a cat with *Lynxacarus radovsky* infestation. Note multiple mites attached to the hair shaft. *Source:* Courtesy of Dr Clarissa Pimentel de Souza.

mites have a long body and ventrally oriented head. Sternal extensions attach to the host's hair and the legs have terminal suckers (Figure 165.13). These mites are visualized attached to the hairs (Figure 165.14).

Therapy

Most parasiticidal treatments are effective. More efficacious options include lime sulfur dips or insecticidal sprays such as fipronil, applied weekly to biweekly for 3–4 treatments. Ivermectin or doramectin can also be given at 0.2–0.3 mg/kg SC every 1–2 weeks for 3–4 treatments. Ivermectin can also be given at this dosage orally. Fluralaner (Bravecto) given off-label at a single dosage of 25–50 mg/kg PO or two topical applications of moxidectin/imidacloprid (Advantage Multi for cats) spot-on product two weeks apart has been shown to eradicate the mites. Care must be taken when treating cats with certain parasiticidal topicals, especially those that contain >0.1% permethrin, as this compound is toxic to cats. It is suggested that in-contact cats also be treated.



Figure 165.13 *Lynxacarus radovsky* mite. *Source:* Courtesy of Dr Clarissa Pimentel de Souza.

Dermanyssus gallinae

Etiology/Pathophysiology

This mite primarily affects poultry but is contagious to other animals including dogs, cats, and humans. It is a vector of many significant diseases. Other names are the poultry mite or red mite. These mites spend most of their life span off the fowl host, residing in cracks, crevices, and nests within the poultry house. They feed at night and once fed and engorged, they develop the red coloration. Poultry mites are resilient and can survive up to eight months away from fowl.

History and Clinical Signs

Dogs and cats can be attacked by these mites when in contact with poultry houses or from wild birds that enter and nest in houses. This mite can cause severe pruritus along with papules and crusts. Most cases present with lesions on the limbs and dorsum.

Diagnosis

Finding the mite is best achieved by performing skin scrapings. Mites may also be visualized microscopically on samples collected with cellophane tape impressions.

Therapy

These mites generally respond well to almost all parasiticidal treatments. It is also recommended to treat the surrounding premises to prevent reinfestation.

Pediculosis

Etiology/Pathophysiology

Pediculosis refers to a dermatitis caused by lice. Two types affect dogs, Anoplura, or sucking lice, and Mallophaga, or chewing lice. *Linognathus setosus* is the sucking louse of dogs and *Trichodectes canis* the chewing louse. Cats are parasitized only with a chewing louse, *Felicola subrostratus*. The eggs are deposited on the hairs of the host. The lice typically stay on one host but can be transmitted by close contact. They are species specific. The chewing lice survive primarily on epidermal debris and hair but some species also take blood. The canine chewing louse may carry *Dipylidium caninum*, or tapeworms. Sucking lice solely feed on the blood of the host and can result in severe anemia.

History and Clinical Signs

Pediculosis is relatively uncommon, but more likely to be noted in young and uncared-for animals. Chewing lice on the dog typically affect the dorsum, head, and tail and can cause severe pruritus. In the cat, the face, ears, and back are most commonly affected. Lesions on the dog typically consist of trauma-induced alopecia, seborrhea, and excoriations. Papules and crusts may also be present. Cats can present with no clinical signs or have intense pruritus. The coat may be matted with scale, crust, and alopecia. Sucking lice are primarily present on the pinnae and dorsum, and can result in weakness from the ensuing anemia. Pruritus with resultant excoriations and alopecia may also occur.

Diagnosis

Lice can be distinguished based on the morphology of the head and associated mouthparts. Sucking lice have an elongated, narrow head, whereas chewing lice have a broader head with mouthparts adapted for chewing. They can sometimes be found with direct visualization of the mite or the nit (egg). Microscopy can be utilized to view acetate tape impressions of hair and scale.

Therapy

Treatment should target the affected animals as well as those in contact. Clipping of matted hairs is recommended. Topical sprays and soaks such as lime sulfur can be utilized twice two weeks apart. However, most insecticidal therapies are efficacious. These include but are not limited to ivermectin at 0.2 mg/kg PO or SC twice two weeks apart, selamectin (Revolution) every two weeks for 2–4 treatments, or spot-on fipronil (Frontline®) or spray every two weeks. One application of fipronil or selamectin may work as well for chewing lice. Doramectin can also be used at 0.2–0.4 mg/kg SC weekly for 3–4 weeks. Imidacloprid (Advantage) spot-on alone for one application to treat chewing or sucking lice or the combination with moxidectin (Advantage Multi) applied topically once for chewing lice should be effective. Fluralaner (Bravecto) given once PO has been shown to eliminate *Linognathus setosus*. Appropriate supportive care may be required for anemic animals. Premises should be treated as lice can survive 1–2 days off the host.

Trombiculosis

History and Clinical Signs

Trombiculosis is a dermatitis caused by chigger mites. The larval forms can cause infestation of dogs and cats.

Eutrombicula alfreddugesi, a mite found in the southeast and south central United States, and *Neotrombicula autumnalis*, a mite more commonly found in Europe, are notably orange-red in coloration (Figure 165.15). They typically affect patients in late summer and fall. The larval forms attach to the skin.

Lesions often occur in body regions that contact the ground. However, in cats they are most commonly noted around the eyes, mouth, and base of the pinnae. The larvae pierce the skin and produce pruritic papules and crusts. Scaling and alopecia may also be present. Some animals are asymptomatic.

Walchia americana is a chigger mite that has been reported in cats. It has been found in the southwestern and eastern United States. These mites preferentially affect the ventrum, dorsum, and ears but have been noted on the medial legs and interdigital spaces. Reported lesions include nodules, papules, and wheals with scales and yellow exudate. Swollen paws and cracked claws have been noted.

Straelensia cynotis has been noted on dogs in some European countries. It too causes infestation primarily in



Figure 165.15 *Eutrombicula alfreddugesi* larva. *Source:* Courtesy of Dr Erica Toledo.

late summer and early autumn. This mite is found in the follicular ostia. It causes papules and nodules typically over the dorsum and head. Alopecia, scale, and erythema have been noted. Pruritus appears to be dependent on the presence of secondary infections.

Diagnosis

Diagnosis can be made with visualization of the reddish colored mite attached to the skin. Definitive diagnosis can be made by placing the mites obtained by skin scraping on mineral oil and examining the sample microscopically.

Diagnosis of *Walchia americana* is generally made with skin scrapes. Biopsy can be helpful as well. Unfortunately, skin scrapings are unrewarding with *Straelensia cynotis*. The mite can be found within the hair follicle on biopsy. Also, the histopathology is unique in that it shows a pseudoepitheliomatous follicular hyperplasia and perifollicular mucinosis.

Therapy

Treatment of *Eutrombicula* or *Neotrombicula* usually consists of 1–2 applications of topical parasiticidal agents or dips. Otic products that have parasiticidal properties can also be efficacious. Studied products include 0.25% fipronil spray applied to the entire body monthly for 1–4 months. Another evaluated option is a permethrin-pyriproxyfen topical spray or spot-on for dogs for 1–2 treatments. Systemic glucocorticoids may be indicated to alleviate pruritus and antibiotics may be of benefit if secondary superficial pyoderma is present.

Treatment of *Walchia americana* consists of the same parasiticidal products used for the treatment of *Eutrombicula* and *Neotrombicula*. Treatment of *Straelensia cynotis* has been suggested with macrocyclic lactones or fipronil.

Ticks

Ixodid (hard) ticks and argasid (soft) ticks both can affect cats and dogs. The ixodid ticks, which have a chitinous shield, can serve as vectors of rickettsial, protozoal, and viral diseases. They may also cause a hypersensitivity reaction from their bite, and can sometimes result in tick paralysis. The types of ixodid ticks of importance will not be elaborated on in this section.

Argasid ticks do not have the chitinous shield, or scutum. *Otobius megnini* can inhabit the ear canal in dogs and cats. The larvae and nymphs of this tick can lead to otitis externa. They can cause a severe irritation. Treatment includes manual removal of the ticks. Oil-based ear treatments may smother the tick. Prevention is key to help reinfestation. Many topical and oral parasiticidal treatments offer tick prevention.

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166

Bacterial Pyodermas

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Etiology/Pathophysiology

Pyodermas are bacterial infections of the skin and commonly involve coagulase-positive staphylococci. Indeed, staphylococcal pyoderma is one of the most common conditions treated in clinical practice. For this reason, this chapter is focused exclusively on staphylococcal pyodermas. Staphylococcal infection opportunistically arises secondary to dermatologic or systemic diseases that prompt cutaneous physical or immunologic function insults. These may include hypersensitivity, endocrine, conformational, and keratinization disorders, as well as an immunocompromised status. Clinical presentations are diverse, and mimic a multitude of other dermatopathies. In the current era of antimicrobial resistance, optimal outcomes for staphylococcal pyoderma are achieved via correct diagnosis, rational treatment and follow-up, and management of the inciting cause(s).

Staphylococcus pseudintermedius, previously identified as *Staphylococcus intermedius*, is the most common etiologic agent in canine pyoderma. *Staphylococcus aureus*, *Staphylococcus schleiferi* subsp. *coagulans*, and coagulase-negative staphylococci such as *Staphylococcus schleiferi* subsp. *schleiferi* are isolated at a lesser frequency on healthy or inflamed skin.

Staphylococcal pyoderma is less prevalent in cats than dogs. Feline keratinocyte adhesion of *S. aureus* and *S. pseudintermedius* is inferior compared to human and dog keratinocytes, perhaps a reflection of inferior host adaptation. *S. pseudintermedius*, *S. schleiferi*, and *S. aureus* are most frequently isolated; *S. aureus* is isolated at a higher frequency than in dogs.

Pyoderma Classifications and Presentations

Pyodermas are often categorized based on the depth of infection (surface, superficial or deep) and the site involved, particularly when describing a pyoderma that affects a specific body region (e.g., interdigital pyoderma, nasal pyoderma). These categorizations are useful, particularly the depth of infection because it dictates the methods and duration of therapeutic interventions.

Surface Pyodermas

Acute Moist Dermatitis

Acute moist dermatitis, also known as pyotraumatic dermatitis and commonly referred to as a "hot spot," is characterized by the rapid development of a focal, erythematous, erosive, and exudative lesion that develops due to intense pruritus and self-trauma (Figure 166.1).

Acute moist dermatitis is typically initiated by hypersensitivity disorders, including cutaneous adverse food reaction, atopic dermatitis, and flea bite hypersensitivity, or pruritogenic parasitic diseases such as pediculosis, sarcoptic mange, and cheyletiellosis. Surface staphylococcal overgrowth is concurrently present in nearly all cases of acute moist dermatitis. Cytology of exudate obtained via surface impression smear reveals neutrophils and intracellular and extracellular cocci. Superficial bacterial folliculitis lesions (see "Superficial bacterial folliculitis" section below) observed at the periphery of the self-trauma suggest a longer duration of staphylococcal involvement and that the staphylococcal folliculitis itself

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Figure 166.1 Acute moist dermatitis in a golden retriever dog with atopic dermatitis and superficial staphylococcal folliculitis.

may be the inciting cause of the acute moist dermatitis. This scenario is termed "pyotraumatic folliculitis."

Patients may present on an emergency basis due to rapid, severe progression. Lesions can be painful. Sedation may be required prior to clipping of the coat for optimal examination and initial topical treatment. A thorough examination of the entire coat and obtaining a detailed history are critical, as diagnosis and appropriate management of the underlying pruritic disease are very important, particularly in recurrent cases.

Initial treatment involves cleansing of the lesion with an antimicrobial. A 2% aluminum acetate solution (Domeboro® solution, Bayer) may be used as a topical nonirritating drying and antimicrobial agent. At-home therapy involves daily application (1–3 times/day) of a topical antimicrobial and/or drying agent; use of a topical anesthetic (e.g., pramoxine, lidocaine) or corticosteroid may be additionally beneficial. Limit daily topical corticosteroid use to no more than one week to avoid cutaneous side-effects, such as demodicosis, comedones, cutaneous atrophy, and ulceration.

Application of an Elizabethan collar or breathable physical barrier is recommended in the first 3–7 days of treatment to prevent self-trauma. Oclacitinib (Apoquel®, Zoetis), lokivetmab (Cytopoint®, Zoetis), or systemic corticosteroid treatment is often required to provide rapid relief of pruritus, and, for severe presentations, may be required for several days before topical therapy is attempted at home. Concurrent systemic antimicrobial therapy is required for pyotraumatic folliculitis (see also "Treatment of pyodermas" section below). The patient should be rechecked in 7–14 days to assess response to antimicrobial and antiinflammatory therapies.

Intertrigo

Increased warmth and humidity of the environment, friction, and the protected cutaneous microenvironments of skinfolds are predisposing factors for staphylococcal intertrigo. The aforementioned factors result in surface maceration of the stratum corneum and bacterial overgrowth, predominantly with staphylococci. Concurrent *Malassezia* overgrowth is common, and gram-negative bacteria may also contribute. It is largely a condition in dogs, particularly in the context of hypersensitivity, and is rare in cats. Intertrigo is typically pruritic. Locations affected include abdominal, inguinal, vulvar, lip, tail, and facial folds, with the latter two locations overrepresented in English bulldogs and pugs. Moist erythematous skin, purulent exudate, and in advanced cases ulcerative dermatitis are observed (Figures 166.2, 166.3, and 166.4).

Cytology of exudate obtained via surface impression smear confirms the presence of cocci and may also involve yeast and rods. Neutrophils are variably present. Topical antimicrobial and drying agents are indicated.



Figure 166.2 Mildly erythematous and greasy *Staphylococcus* and *Malassezia* nasal fold dermatitis with crusting staphylococcal folliculitis in a pug with atopic dermatitis.



Figure 166.3 Dorsal interdigital moist erythema with *Malassezia* and *Staphylococcus* overgrowth in a 5-year-old Rottweiler with atopic dermatitis.



Figure 166.4 Severe, purulent tail fold intertrigo with mixed bacterial overgrowth and crusting staphylococcal superficial bacterial folliculitis in an English bulldog with atopic dermatitis. Surgery was ultimately required for control of the dermatitis.

Surgical correction of redundant folds may be indicated for severe, recalcitrant presentations.

Superficial Pyodermas

Impetigo

Impetigo, also referred to as "puppy pyoderma," occurs in puppies and juveniles less than 1 year old. It is typified by subcorneal, often grossly large, pustules caused by staphylococci, most commonly *S. pseudintermedius*. The pustules do not necessarily involve the hair follicles and are typically located in the axillary and inguinal areas. The pustules progress to crusts and epidermal collarettes. Patients are not typically pruritic nor painful. Cytology of pustules reveals degenerated neutrophils and intracellular cocci.

Impetigo is often idiopathic in otherwise healthy puppies. It may also occur in immunocompromised patients suffering from parasitic or infectious diseases, or suboptimal nutrition and housing conditions.

Impetigo is expected to self-resolve in otherwise healthy patients. Use of topical antimicrobial therapy may hasten resolution and may be required for resolution in immunocompromised patients. Treatment options include daily to alternate-day shampoo treatment with a nondrying, antimicrobial shampoo including chlorhexidine or ethyl lactate. Alternatively, for focal lesions, consider convenient antimicrobial wipes, sprays, foams, and ointments/creams applied once or twice daily. Continue topical therapies until lesion resolution. For severe cases or cases that do not respond to topical therapy, systemic antibiotics are indicated. Systemic antimicrobial treatment should continue for one week past resolution of lesions. Resolution of lesions is expected to occur within 14 days.

Superficial Bacterial Folliculitis

Superficial bacterial folliculitis is the most common presentation of pyoderma and, as stated previously, opportunistic *S. pseudintermedius* is the most common etiologic agent. Infection of the hair follicle and epidermis produces characteristic follicular-oriented papules, pustules, and epidermal collarettes (Figure 166.5) progressing to crusts, "moth-eaten" alopecia, and hyperpigmentation (Figures 166.6 and 166.7).

In short-coated dogs, well-demarcated areas of raised hair resemble urticaria from afar. Papular crusting dermatitis (i.e., miliary dermatitis) is most frequently observed in cats. Distribution is dependent on cause, and pruritus is variable.

Differential diagnoses for folliculitis include, but are not limited to, dermatophytosis, demodicosis, pemphigus foliaceus, and, in cats, hypersensitivity syndromes. Systemic and topical treatment is indicated for patients



Figure 166.5 Epidermal collarettes with macular erythema and hyperpigmentation on the abdomen of a terrier mix with superficial staphylococcal folliculitis, atopic dermatitis, and iatrogenic hypercortisolism.



Figure 166.6 Well-circumscribed partial alopecia, crusting and moist erythematous skin of the periocular and perioral regions due to superficial staphylococcal folliculitis in a 7-year-old domestic shorthair cat with atopic-like dermatitis.

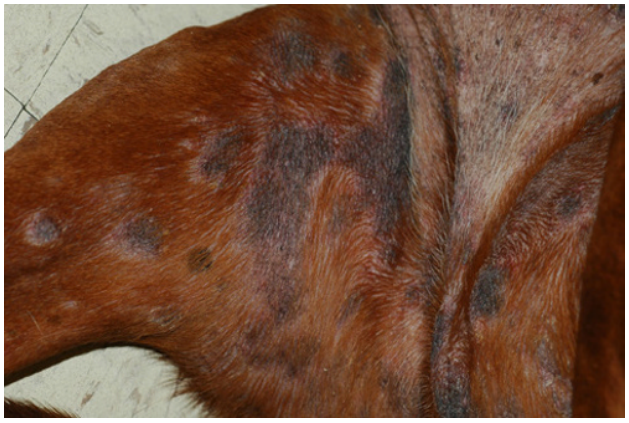


Figure 166.7 Hyperpigmentation and well-circumscribed "moth-eaten" alopecia caused by superficial staphylococcal folliculitis in a 10-year-old redbone coonhound.

with regional or generalized superficial pyoderma. Focal, mild presentations may resolve with daily topical therapy alone.

Diagnosis is achieved via cytology of exudate obtained by rupture of a pustule or avulsion of crusts. The presence of extracellular cocci or phagocytosed cocci confirms the diagnosis. If cytology is negative, culture and/or histopathology are required to make a definitive diagnosis. Superficial pyoderma is commonplace, so it is rational to empirically treat cytology-negative cases of folliculitis to assess for response, particularly if demodicosis and dermatophytosis have been ruled out.

Mucocutaneous Pyoderma

Mucocutaneous pyoderma, a crusting, erosive and depigmenting condition of the canine nasal planum and lip margins, may be an inflammatory response to staphylococci, although the etiopathogenesis remains unknown (Figure 166.8). It may occur alone or in the context of cutaneous hypersensitivity.

Less commonly, lesions may involve the prepuce/vulva, anus, or eyelids. Of note, the German shepherd dog is overrepresented. Differentials for this condition include discoid lupus erythematosus, pemphigus foliaceus, and epitheliotropic lymphoma. Mucocutaneous pyoderma may occur secondary to these conditions, and the histopathologic findings of mucocutaneous pyoderma are similar to that of discoid lupus erythematosus. Thus, diagnosis of mucocutaneous pyoderma is typically made via clinical response to antimicrobial therapy; cytology of exudate may not confirm the presence of cocci. Treatment involves antimicrobial systemic and topical therapy. Empirical or culture-based antimicrobial for a minimum of three weeks prior to biopsy of the aforementioned lesions is recommended to assess for responsiveness and optimize likelihood of a diagnostic biopsy reflective of the primary disease process.



Figure 166.8 Mucocutaneous pyoderma with multifocal labial and perioral depigmentation and erythema with multifocal depigmentation and erosions of the nasal planum in a German shepherd dog.

Canine Chronic, Recurrent Pyoderma

Recurrent pyoderma is characterized by the chronic reemergence of superficial bacterial folliculitis after successful treatment and confirmed clinical and cytologic resolution. This syndrome is most commonly associated with atopic dermatitis, cutaneous adverse food reaction and hypothyroidism, and is typically pruritic when lesions are present. Treatment of this syndrome includes not only topical and/or systemic antimicrobial therapy to treat active infection, but also identification and control of the underlying dermatosis to prevent recurrence.

Patients with idiopathic recurrent pyoderma are euthyroid, fail to respond to a proper elimination diet trial, and have no other signs of atopic or cutaneous disease other than pyoderma typically associated with pruritus. Such patients may be managed via use of frequent application of antimicrobial shampoos, wipes, or sprays to limit chronic use of systemic antibiotics. The immune response to staphylococci, perhaps a true hypersensitivity, may play a role in idiopathic recurrent pyoderma, and in canine patients with atopic dermatitis. Indeed,

subcutaneously injected commercial *S. aureus* phage lysate antigens (Staphage Lysate®, Delmont Laboratories) may be used as maintenance therapy to reduce or eliminate recurrence of pyoderma. This treatment is indicated in patients with idiopathic or atopic recurrent pyoderma cases failing to respond to topical maintenance therapy.

Deep Pyodermas

Generalized Deep Pyoderma

Generalized deep pyoderma arises due to furunculosis (follicular rupture) and foreign body response directed at the liberated hair shafts in the dermis. Lesions include nodules, hemorrhagic bullae, ulcers, draining tracts and crusts with variable pain and pruritus (Figures 166.9 and 166.10).

In cats, deep pyoderma most commonly presents in the context of chin acne. In short-coated breeds with atopic dermatitis or cutaneous adverse food reaction, cystic hemorrhagic, bullous lesions are often observed on the chin and interdigital areas. Staphylococci represent the predominant organism but deep pyoderma may also be accompanied by infection with *Enterococcus*, *Pseudomonas*, and *Proteus* species as well as *Escherichia coli*. Differentials include dimorphic and opportunistic mycoses, pythiosis, lagenidiosis, neoplasia, foreign body, sterile pyogranulomatous dermatitis, and other bacterial etiologies, including species in the genera *Mycobacterium*, *Actinomyces*, and *Nocardia*. Cytologic presence of numerous extracellular cocci or phagocytosed cocci supports the diagnosis. Given the diverse clinical differentials and requirement for prolonged treatment, bacterial culture (aerobic and anaerobic) and sensitivity, fungal culture, and histopathology are recommended for definitive diagnosis and appropriate treatment.



Figure 166.9 Nonblanching, hemorrhagic, nodular, deep staphylococcal pyoderma in a 5-year-old Rottweiler with atopic dermatitis.

Canine Acne

This disease is typified by deep folliculitis and furunculosis affecting the chin and perioral margin, and is a focal form of deep pyoderma. Chin acne usually manifests in young dogs between 3 and 12 months of age although it often persists throughout adulthood and may be complicated by concurrent atopic dermatitis or cutaneous adverse food reaction. Breeds with a short, coarse hair coat are predisposed, including boxers, English and French bulldogs, and Boston terriers.

Lesions consist of papules and nodules that often become erosive and ulcerative with resultant draining tract formation. Hemorrhagic bullae are also common (Figure 166.11).

Demodicosis should be ruled out by performing deep skin scrapes. Juvenile cellulitis is a differential diagnosis; however, classic submandibular lymphadenopathy as well



Figure 166.10 Erythematous nodules with ulcers due to deep *Pseudomonas* pyoderma on the lateral hindlimb of a 3-year-old Rottweiler mix.

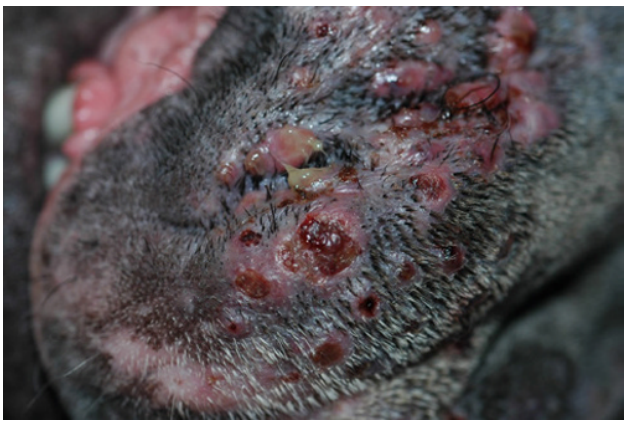


Figure 166.11 Nodular, ulcerative, and purulent deep staphylococcal pyoderma on the chin of a cane corso dog with atopic dermatitis.

as generalized muzzle, periocular, and pinnal involvement clinically differentiate it from chin acne in many cases (see Chapter 164 for a more thorough discussion of juvenile cellulitis). Chin acne is supported by the presence of cocci and a mixed population of inflammatory cells on cytologic evaluation.

Treatment involves systemic antimicrobial therapy, ideally based on aerobic culture and sensitivity testing (see "Treatment of pyodermas" section below), with adjunct topical antimicrobial therapy. Benzoyl peroxide gel, silver sulfadiazine cream, clindamycin cream, and mupirocin (reserved for resistant staphylococcal infections), are often well tolerated when applied to the facial area. Because furunculosis and subsequent deep pyoderma are frequently present, treatment for a minimum of six weeks may be required. Treatment should be continued for two weeks past clinical and palpable resolution.



Figure 166.12 Dorsal interdigital nodule with hemopurulent exudate due to furunculosis and deep staphylococcal pyoderma in a cairn terrier.

Interdigital Pyoderma

Interdigital pyoderma has a diversity of presentations and therefore terms commonly used include canine pododermatitis, pedal folliculitis/furunculosis, and interdigital "cysts." Lesions may include interdigital erythema, salivary staining of hairs, papules, nodules, hemorrhagic bullae, and draining tracts. Clinical signs may include licking and biting of the feet, and lameness. Staphylococci are common bacterial etiologic agents of pododermatitis and infection often occurs concurrently with *Malassezia* and gram-negative bacterial organisms. Interdigital pyoderma is a multifactorial disorder consisting of predisposing abnormal conformation, primary etiologies, and secondary infections that perpetuate the dermatitis.

Abnormal weight bearing as a result of abnormal conformation, musculoskeletal disease, and/or obesity are predisposing factors for the development of interdigital pyoderma. In such cases, rather than generalized interdigital involvement, focal dorsal or ventral dermatitis is often recurrent in one or several interdigital spaces. Short-coated dogs such as Labradors and English bulldogs appear to be predisposed.

Hypersensitivity, autoimmune, and inflammatory conditions are primary etiologies; secondary bacterial and yeast surface overgrowth and/or bacterial folliculitis perpetuate the dermatitis. Occasionally, hypothyroidism and hypercortisolism may result in interdigital bacterial or yeast overgrowth.

A conformation-related disorder involving ventrally oriented cystic follicles, primarily on the forelimbs, has been described. These dilated follicles may be grossly visible as comedones and milia. The cystic follicles rupture in the dermis. The subsequent foreign body response clinically manifests as dorsal interdigital nodules, hemorrhagic bullae, and edema (Figure 166.12). Draining tracts and deep secondary bacterial infection frequently ensue. Treatment of this condition may include multiple carbon dioxide (CO_2) laser ablations of the ventral cystic lesions in addition to antimicrobial therapy as described subsequently in this chapter (see "Treatment of pyodermas").

Diagnosis involves obtaining a thorough history and performing a physical examination to identify possible primary causes. Deep skin scrapes or hair plucks for demodicosis must be performed, as demodicosis may demonstrate all the aforementioned clinical manifestations. In some cases of pododemodicosis, biopsy may be required for diagnosis.

Perform multiple surface cytologic preparations of erythematous interdigital spaces to confirm the presence of bacterial organisms as well as *Malassezia*. Consider aspiration of nodules and hemorrhagic bullae to assess for secondary bacterial infection and other causes of nodular dermatitis, including neoplasia. Consider the possibility of a foreign body, particularly in the context of a solitary nodular lesion with mixed inflammation. Culture and sensitivity of tissue biopsies or aspirates of nodular lesions should ideally be performed with confirmed or suspected bacterial involvement, as such lesions indicate deep pyoderma and require prolonged therapy. Avoid culture of draining tracts as they may not be reflective of the relevant bacterial organisms within the tissue.

Pedal pruritus (licking and biting of the feet) with generalized dorsal or ventral interdigital involvement persisting despite resolution of secondary infection is suggestive of cutaneous adverse food reaction or atopic dermatitis.

Topical antimicrobial therapy is ideal for secondary surface bacterial and yeast overgrowth. Chlorhexidine, benzoyl peroxide, or ethyl lactate-based shampoos may be used as a soak, particularly for painful feet, every 24–48 hours initially. Aluminum acetate solution (Domeboro)

may be similarly used as a foot soak for drying and antimicrobial effects. Antimicrobial wipes and sprays may be considered, but acid- and alcohol-based products should be avoided in erosive and ulcerative presentations (see "Treatment of pyodermas" section for additional treatment recommendations).

Focal nodular staphylococcal or mixed bacterial lesions may be treated with silver sulfadiazine cream, clindamycin ointment, or mupirocin (reserved for resistant staphylococcal infections). Application of dimethyl sulfoxide (DMSO) just before or after application of the topical antimicrobial may improve its penetration and provide additional antiinflammatory effects. Topical corticosteroid treatment (as the sole ingredient or a combination product) may be helpful for additional antiinflammatory benefits, particularly for hypersensitivity. Topical corticosteroids should be avoided in the presence of comedones and milia, as they may exacerbate these lesions. Systemic antimicrobial therapy is indicated for nodules, draining tracts or severe bacterial surface pyoderma (see "Treatment of pyodermas" section). Deep pyoderma (draining nodules, crusts, ulcerations) typically require a minimum of six weeks of systemic antimicrobial therapy, and should be continued four weeks beyond cytologic and clinical resolution (including palpation).

Acral Lick Dermatitis

Although commonly encountered in canine practice, acral lick dermatitis (ALD) is a challenging condition to manage given its multifactorial genesis and chronic nature. Optimal control is achieved via identification and control of contributing factors. Acral lick dermatitis is characterized by repetitive licking, typically of the distal limbs. Lesions, commonly known as lick granulomas, take the form of erosive to ulcerative nodules or plaques with purulent and/or hemorrhagic exudates (Figure 166.13).



Figure 166.13 Acral lick granuloma with erosive surface on the carpus of a 9-year-old Labrador mix; deep staphylococcal pyoderma and atopic dermatitis were contributing factors.

The most common primary factors are atopic dermatitis and cutaneous adverse food reaction, as well as concurrent behavioral etiologies. Importantly, the most common perpetuating factor is secondary deep staphylococcal pyoderma. This must be treated to reduce lesion size and severity. Common bacterial genera concurrently isolated from ALD lesions include *Pseudomonas* and *Enterobacter*. Importantly, methicillin-resistant and multidrug-resistant staphylococcal infections are common in ALD. Cultures obtained from the surface of the lesions do not accurately represent the organisms within the lesion. Thus, tissue biopsy for culture and sensitivity is indicated to select antibiotic therapy, as treatment required is typically in excess of eight weeks.

Methicillin-Resistant and Multidrug-Resistant Staphylococci

Antimicrobial resistance in veterinary medicine has rapidly evolved in recent years from a mere theoretical possibility to an unwelcome reality. Of concern, methicillin-resistant (MR) and multidrug-resistant (MDR) staphylococci pose a risk of difficult-to-treat nosocomial infections and, to a lesser extent, zoonotic infection. To best serve our community and patients in the present era of antimicrobial resistance, critical examination of infection control and antimicrobial prescribing practices as individuals and as a profession is essential.

Methicillin-resistant staphylococci possess the *mecA* genetic element, encoding penicillin binding protein 2a (PBP2a). Beta-lactam antibiotics cannot bind to PBP2a, rendering them ineffective. The *mecA* gene is present within staphylococcal chromosomal cassettes (SCCs) that are also horizontally transferred amongst *Staphylococcus* spp. Staphylococcal chromosomal cassettes may contain other antimicrobial resistance genes, imparting multidrug resistance in nearly all strains of MR staphylococci encountered in veterinary practice. Of note, beta-lactam antimicrobial use selects for survival of MR staphylococci, but does not create, *de novo,* spontaneous resistance.

Cutaneous MR staphylococcal infection and colonization are a worldwide phenomenon, recognized in the dog, cat, horse, cattle, and swine. In years past, MR staphylococcus appeared to be very rare to absent in the canine and feline population but a remarkable increase in frequency of methicillin resistance in the canine and feline population was noted early in the 21st century. The rapid rise of MR staphylococcal infection in veterinary patients is thought to have

occurred via acquisition of the *mecA* gene from human staphylococci and subsequent selection of resistant strains via widespread use of beta-lactam antimicrobials. Methicillin-resistant canine and feline cutaneous infections and colonization have been subsequently reported worldwide, with MR *S. pseudintermedius* most commonly seen. Prevalence varies by geographic location.

Frequent antimicrobial treatment is a risk factor for canine MR staphylococcal pyoderma and carriage of MR staphylococci in healthy dogs and cats. Risk factors associated with MR *S. aureus* infection in the dog and cat include frequent antimicrobial courses, frequent veterinary visits, multiple days of hospitalization, and the presence of surgical implants.

Recognition of Methicillin Resistance

Methicillin-resistant and MDR staphylococcal pyoderma cases do not typically possess unique clinical features. Rather, the first indication of resistance is lack of response to empirical antimicrobial therapy. Therefore, to ensure appropriate response, all patients must be reexamined prior to conclusion of antimicrobial treatment. If resistance is suspected, perform a cytologic evaluation to assess for the presence of cocci, as well as bacterial culture and sensitivity. A sterile needle is used to rupture a pustule or lift the edge of an epidermal collarette or crust to reveal exudate. The sample is collected with a sterile swab. For cases of papular or nodular pyoderma, punch biopsies are recommended for culture.

Although "methicillin resistance" is the accepted term, the more stable oxacillin is used as a surrogate in the laboratory for methicillin susceptibility. Resistance to oxacillin is a strong indicator of *mec*A acquisition and resistance to all beta-lactam antibiotics. Upon interpreting antibiograms, it is important to recognize that oxacillin-resistant staphylococci may show *in vitro* sensitivity to other beta-lactams. Thus, interpretation of staphylococcal antibiograms should first involve noting oxacillin susceptibility, rather than simply searching for reported susceptible antimicrobials. If a bacterial strain is resistant to oxacillin, it should be considered resistant to all beta-lactam antibiotics.

Direct the laboratory to perform extended antimicrobial panels for suspected resistance. Additionally, species identification of staphylococci is useful, as MR *S. aureus* has a more significant zoonotic implication given that it is host-adapted to humans. Methicillin-resistant, coagulase-negative staphylococci, including *S. schleiferi* subsp. *schleiferi*, are clinically significant and should not be disregarded.

Treatment of Pyodermas

Appropriate management of staphylococcal pyoderma is an active area of investigation, which may result in future changes in systemic antimicrobial dose and duration.

Systemic Therapy

Systemic antimicrobial therapy is indicated for regional, generalized or severe superficial bacterial folliculitis, mucocutaneous pyoderma, and forms of deep staphylococcal pyoderma. For milder presentations, expected time of resolution with systemic therapy is 14–28 days. Duration of therapy may be longer and treatment for one week beyond clinical resolution is recommended. For deep pyoderma, treatment may take 6–12 weeks to achieve visual and palpable resolution. For severe presentations of deep pyoderma, consider continuation of antimicrobial therapy four weeks beyond palpable resolution to prevent relapse. Importantly, all patients receiving antimicrobial therapy for staphylococcal pyoderma must be periodically rechecked (every 2–4 weeks) prior to conclusion of antimicrobial treatment to ensure appropriate response.

Empirical and Culture-Based Therapy

Rational antibiotic options for empirical treatment of staphylococcal pyoderma include cephalexin (22–30 mg/kg PO q12h), amoxicillin/clavulanate (13.75 mg/kg PO q12h), cefpodoxime (5–10 mg/kg PO q24h), and cefovecin (8 mg/kg SC q14 days). Lincomycin (15–25 mg/kg PO q12h) and clindamycin (5.5–10 mg/kg PO q12–24h) are considered first-line choices, but their conservation is recommended as some MR and MDR staphylococcal strains retain susceptibility to these antimicrobials. For cases of resistant pyoderma, clindamycin should be used with reservation if the laboratory has not tested for inducible resistance (D-test). This test should be requested if erythromycin resistance is present. If this test is not available and the bacterial strain is resistant to erythromycin but susceptible to clindamycin, do not prescribe the latter.

Culture and sensitivity-based selection of a systemic antimicrobial is indicated for patients that fail to clinically respond to empirical therapy, have evidence of deep pyoderma, or have a chronic history of antimicrobial use with unknown or lackluster response. Empirical treatment is not recommended in these cases as staphylococcal antimicrobial resistance patterns are unpredictable. Dwindling rational systemic treatment options for MDR staphylococcal pyoderma present a global practical challenge. A 2010 study examining 103 isolates of MRSP in North America reported that nearly 90% of isolates were

resistant to ciprofloxacin, clindamycin, erythromycin, and trimethoprim sulfa (TMS); 69.9% were resistant to tetracycline and gentamicin, and 57.3% were resistant to chloramphenicol.

If resistant superficial bacterial folliculitis is present with limited therapeutic options, consider daily topical therapy prior to use of amikacin, rifampin, or chloramphenicol, as this may be sufficient to resolve the problem with minimal risk to the patient. Chloramphenicol may be used with success in resistant cases, but vomiting and diarrhea can be frequent, and transient bone marrow suppression is possible but apparently rare. Reversible weakness (often seen in the hindlimbs) may occur in dogs. Clients must also wear gloves to prevent rare but fatal aplastic anemia of humans. At present, resistance to rifampin is rare. Although it is often stated that a secondary antimicrobial is required with use of rifampin, successful treatment with monotherapy has been documented with *S. aureus* and, therefore, this long-held concept may not apply to treatment of staphylococcal pyoderma. Hepatotoxicity can be life-threatening and biochemistry values must be monitored every seven days during administration. Given the potential for renal failure, amikacin is reserved for patients with severe, deep, resistant pyoderma with no other rational systemic treatment options. When used, frequent urinalysis and monitoring for casts are recommended.

Although susceptibility to vancomycin, linezolid, synercid (quinupristin/dalfopristin), and teicoplanin may be provided in antibiograms, use of these antibiotics is strongly discouraged. These are drugs of last resort used for human MRSA patients with life-threatening infections and selection for further resistance must be avoided.

Topical Therapy

Adjunct topical therapy is indicated in all forms of pyoderma and may be used as the sole treatment for surface pyodermas such as acute moist dermatitis and intertrigo, as well as with superficial pyodermas, including impetigo and superficial bacterial folliculitis. The use of topical therapy may shorten the duration of systemic therapy, and thus reduce antibiotic selective pressures. The choice of topical ingredient(s) and formulation is dependent upon lesion location, distribution, type, and compliance of the client and the animal.

Shampoo therapy is ideally performed 2–3 times weekly as an adjunct for all forms of pyoderma. Active ingredients include chlorhexidine 2–4%, benzoyl peroxide 2.5%, and ethyl lactate 10%. Benzoyl peroxide can be drying and is best used for patients with greasy or purulent dermatitis. A contact time of 5–10 minutes is generally recommended. When instituted as a sole therapy for superficial bacterial folliculitis, daily use is recommended.

Wipes and sprays are convenient for frequent use, and are a convenient sole therapy for intertrigo. These preparations may include acids, such as acetic acid 2% or boric acid 2%, and alcohols for antimicrobial and drying effects. These drying ingredients are particularly helpful for intertrigo, but are painful if applied to ulcerative lesions. Chlorhexidine (2–4%) is commonly found in wipe and spray preparations, and nisin is found in wipe preparations. Of note, chlorhexidine is appropriate for both gram-positive and gram-negative bacteria, whereas nisin is most appropriate for treatment of staphylococci alone. For sole therapy, apply every 12–24 hours; for adjunct therapy, application every 24–72 hours is appropriate.

Hypochlorous acid is available in a convenient, commercial spray formulation (Vetericyn VF®, Innovacyn). It can be used solely once to twice daily for localized superficial and deep pyoderma or as an adjunct to other topical and systemic therapies for more generalized conditions. Hypochlorous acid is the sodium salt of sodium hypochlorite (household bleach). Dilute bleach rinse solutions (0.005–0.01%) are used by human and veterinary dermatologists, particularly for treatment of allergy-induced recurrent and resistant staphylococcal pyoderma. The author uses a dilution of 2 tablespoons of household bleach per gallon of water as a rinse. This effective and affordable therapy can be used after bathing or applied directly to a focal area as frequently as daily as a sole therapy or as infrequent as twice weekly as an adjunct therapy. The patient is patted dry. Note that this solution must be reconstituted daily. It is nonirritating, and there are some data to suggest it is antiinflammatory as well.

Creams, ointments, and gels are most appropriate for focal presentations. Many commercial antibiotic preparations (neomycin, polymyxin B, gentamicin) are available combined with antifungal and corticosteroid ingredients. Concurrent use of a topical corticosteroid may obscure interpretation of antimicrobial response, and chronic use may result in cutaneous atrophy and ulceration. Creams and ointments containing an antimicrobial as the sole ingredient are therefore preferred. Active ingredients include silver sulfadiazine, benzoyl peroxide, fusidic acid, hydrogen peroxide, and mupirocin. Of note, mupirocin ointment should not be used routinely, as mupirocin resistance has been documented, and it is used for decolonization of methicillin-resistant *S. aureus* of humans. For sole therapy, apply every 12–24 hours; for adjunct therapy, application every 48–72 hours is appropriate.

Staphylococcus aureus Phage Lysate Therapy

Subcutaneously injected commercial *S. aureus* phage lysate antigens (Staphage Lysate) may be used as maintenance therapy to reduce or eliminate recurrence of pyoderma in canine patients with idiopathic recurrent pyoderma or atopic dermatitis, and can be used in combination with maintenance topical therapy once active pyoderma has been resolved.

Subcutaneous injection of 0.5 mL is administered twice weekly for a trial period of 10–14 weeks. Topical and/or systemic antimicrobial therapy is required at the initiation of treatment if an active bacterial infection is present. If beneficial, frequency may be tapered to the least frequent administration required to increase the interval between recurrences or prevent recurrences, typically every 7–14 days.

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167

Otitis

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Otitis Externa

Etiology/Pathophysiology

Otitis externa is inflammation of the external ear canal. The microscopic structure of the external ear canal is similar to that of the interfollicular epidermis of the skin. It is a stratified cornified epithelium with adnexal organs such as hair follicles and their associated sebaceous and ceruminous glands. The epidermis lining the canal is only a few layers thick and is punctuated by hair follicles. Therefore, any disease that affects the skin can also affect the external ear canals. Those diseases that cause otitis externa are referred to as primary causes, the most important of which are listed in Box 167.1.

It is crucially important that the primary cause is identified and managed adequately in all cases of otitis externa. Failure to do so leads to recurrence of the problem and progression of the disease to produce a chronically damaged ear. Primary disease initially causes inflammation within the canal which leads to an increase in epidermal turnover and hyperplasia of the canal wall with narrowing of the lumen. As the disease process progresses, sebaceous glands become hyperplastic, often with dilation of their ducts. This is followed more chronically by dramatic changes in the ceruminous glands and ducts which become enormously enlarged, leading to further loss of lumen diameter. Chronic change drives the disease process once it has been established, causing perpetuation of the otitis. Where this is not resolved, effective therapy is difficult and disease perpetuation or recurrence is inevitable. Where the disease process becomes chronically irreversible, the lumen may be completely obliterated and in some of these cases, ossification of the soft tissue may also take place. Once the damage to the ear has become this extensive, medical therapy is rarely effective. Progressive pathologic changes lead to alterations in the microclimate within the external ear canal, causing an increase in temperature and humidity, surface maceration, and an increase in microbial colonization within the ear (Figure 167.1).

Infection is secondary to the inflammatory process and although effective therapy is essential, if other factors are not managed, recurrence is likely.

Signalment

Age

In young dogs, allergy, especially atopic dermatitis, is the most common trigger of otitis. In cats, especially kittens, *Otodectes cynotis* is more important, accounting for about 80% of all cases of feline otitis externa. Otic demodicosis is an uncommon cause of ear disease in the dog and is very rare in the cat. Juvenile-onset disease is seen in animals less than 3 years of age. Adult-onset disease is seen in those older than 3 years.

Other examples of primary causes affecting young animals include primary idiopathic seborrhea and immune-mediated diseases such as juvenile cellulitis. In older animals, systemic disease such as canine hypothyroidism is important although hepatic, renal, and pancreatic diseases may also predispose animals to otic infection. Rare primary causes for otitis externa that can occur in animals of any age include keratinization disorders such as sebaceous adenitis and autoimmune diseases such as pemphigus foliaceus and discoid lupus erythematosus.

Breed

Primary disease triggered by atopic dermatitis is most commonly seen in the West Highland white terrier, Staffordshire bull terrier, Labrador retriever, German shepherd dog, and boxer. Otitis due to cutaneous adverse food reactions is most common in the Labrador

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Box 167.1 Primary causes for otitis externa

Allergy – atopic dermatitis, cutaneous adverse food reaction, contact allergy

Endocrine disease – hypothyroidism (dog), hyperthyroidism (cat), hyperadrenocorticism (dog and cat)

Ectoparasites – *Otodectes cynotis*, *Demodex* spp., *Otobius megnini*

Autoimmune/immune-mediated disease – pemphigus foliaceus, discoid lupus erythematosus, erythema multiforme, juvenile cellulitis, drug reactions, vasulitis

Keratinization disorders – sebaceous adenitis, zinc-responsive dermatosis, primary idiopathic seborrhea

Foreign bodies – grass awns, ceruminoliths (accumulations of cerumen due to failure of epithelial migration)

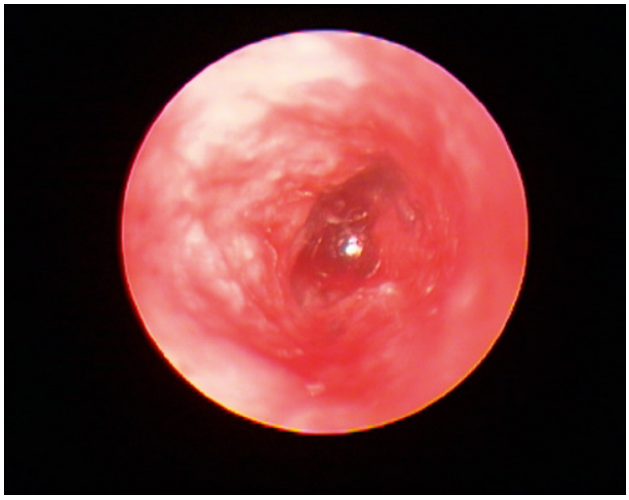


Figure 167.1 Ulcerated ear canal in a case of *Pseudomonas* otitis.

retriever. Juvenile-onset demodicosis is frequently seen in the shih tzu, American Staffordshire terrier, English bulldog, and boxer. Hypothyroidism is commonly recognized in giant breeds such as the dogue de Bordeaux and Newfoundland, as well as hunting dogs such as spaniels and retrievers. Keratinization disorders are often breed linked (e.g., sebaceous adenitis in the akita and standard poodle; primary seborrhea in the cocker spaniel and Persian cat; zinc-responsive disease in the Siberian husky and malamute).

There are many breed characteristics that predispose to the development of disease. Dogs with hairy ear canals, such as the cocker spaniel which has compound hair follicles within its canals, are at increased risk of developing disease. Other dogs with hirsute canals include the poodle and old English sheepdog. Dogs with pendulous pinnae such as spaniels, basset hounds, and bloodhounds are predisposed to disease, as are breeds such as the shar-pei which have narrowed canals.

Box 167.2 Predisposing factors in otitis externa

Conformation of the ear – narrowed canal (shar-pei), hairy external ear canal (spaniels, poodles), hairy concave pinna (spaniels), large pendulous pinnae (basset hounds, bloodhounds)

Inappropriate cleaning, irritant treatment – use of astringent, low-acidity topical products or potent ceruminolytic cleaner when not appropriate

Wetting of the ear – swimming dogs, water-based cleaners, topical medication mixed in water

Obstructive ear disease – polyps, ceruminous gland adenomas, other neoplasia

Box 167.3 Perpetuating factors in otitis externa

Chronic changes – epidermal and glandular hyperplasia, stenosis, failure of epidermal migration, calcification of ear canals, ulceration

Otitis media

History and Clinical Signs

The key aims of history taking are to try to establish the primary cause for the otitis and any predisposing, perpetuating or secondary factors that may be contributing to the disease. Primary causes (see Box 167.1) should be identified in all cases of otitis. Successful management of these triggers is particularly important in chronic disease. Predisposing factors, which are listed in Box 167.2, contribute to ear disease but do not cause it. Perpetuating factors, listed in Box 167.3, and secondary factors which are infections, listed in Table 167.1, are those that drive the process once it has been established. They need to be managed to ensure a complete resolution of disease is achieved without danger of relapse.

In order to identify the primary causes and the other contributory factors, a carefully taken history should include all aspects of the dog's general health and lifestyle. Dogs with atopic dermatitis usually demonstrate a seasonal exacerbation of otitis, pollen-allergic dogs being worse in the spring and summer and house dust mite-allergic dogs being worse in the fall and winter. Allergic dogs that swim commonly develop signs of "swimmer's ear." Hypothyroid dogs may have more generalized systemic signs such as lethargy and a poor exercise tolerance. Where otitis has an acute onset and the disease progresses rapidly to become severe, immune-mediated

Table 167.1 Secondary causes in otitis externa

Infectious organism		Acute disease	Chronic disease
Bacteria (most common isolates)	Gram-positive bacteria	*Staphylococcus* spp. *Streptococcus* spp.	*Enterococcus* spp. *Corynebacteria* spp.
	Gram-negative bacteria	Uncommon	*Pseudomonas* spp. *Proteus* spp. *Escherichia coli*
	Anaerobic bacteria	Uncommon	*Bacteroides* spp.
Yeast (most common isolate)		*Malassezia pachydermatis*	*Malassezia pachydermatis*

disease such as drug eruptions and autoimmune disease should be considered. Contact irritant or hypersensitivity should be considered when signs of otitis become worse after commencement of topical therapy. Contact reactions may be to one of the active ingredients in the topical product such as an antibiotic, antifungal or glucocorticoid, or can be to the vehicle (e.g., propylene glycol).

Examination of each case should include a full physical and dermatologic inspection before examining the pinnae and ear canal. A physical examination may reveal signs, for example of bradycardia in a hypothyroid dog. Accompanying signs of more generalized disease may provide useful clues. Dogs with atopic dermatitis or adverse food reaction may have pedal salivary staining due to foot licking, or recurrent ventral pyoderma. Dogs with endocrine disease may have seborrhea, a poor hair coat or bilaterally symmetric alopecia which typically spares the face and distal extremities. Where keratinization disorders cause otitis, lesions may be more generalized (e.g., diffuse thinning of the coat with prominent follicular casts on hairs in cases of sebaceous adenitis). Dogs that shake their heads or traumatize their pinnae without signs of otitis may be in the early stages of allergy or may have disease that principally affects the pinnae. These diseases include those caused by ectoparasites such as *Sarcoptes scabiei*, *Notoedres cati*, lice and the rabbit flea (*Spilopsyllus cuniculi*), and immune-mediated diseases such as vasculitis and dermatomyositis. The pinna is an excellent area to view primary lesions, which tend to be better preserved at this site due to the difficult accessibility. Pustular lesions on the pinna may be seen with sterile autoimmune disease such as pemphigus foliaceus or, rarely, with pyoderma. Papular eruptions are most commonly seen with ectoparasites, and ulcers with immune-mediated disease such as vasculitis.

Examination of the ear canal may be undertaken with either a hand-held or a video otoscope (Figure 167.2). The latter obviously has the advantage of better illumination and magnification and allows for superior visualization of the canal and tympanic membrane. Assessment of the canal is important to decide which predisposing and perpetuating factors are present. Predisposing factors such as neoplasia, stenosis of the canal, or the presence of a large amount of hair need to be addressed as part of the overall management of the otitis (Figure 167.3).

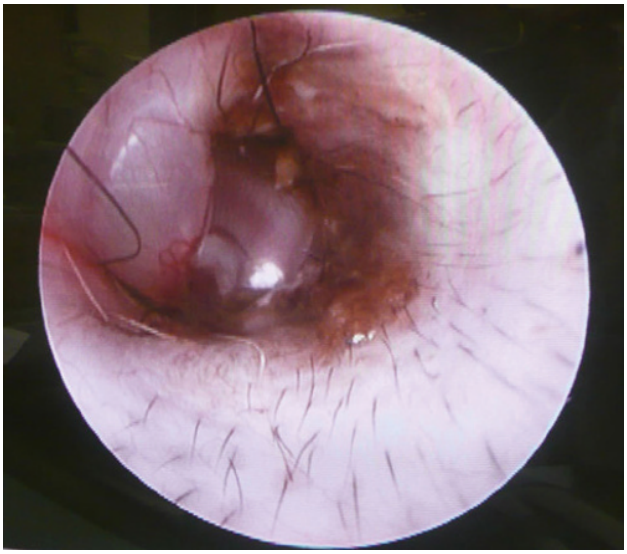


Figure 167.2 Video otoscopic image of the external ear canal and tympanic membrane of a dog.

Identifying and treating perpetuating factors such as chronic changes and otitis media are important to prevent relapse of the otitis. The degree of pathologic change present helps the clinician decide if the otitis can be treated medically or whether surgical intervention is more appropriate. Assessment of the tympanic membrane can help in making a diagnosis of otitis media if the structure is abnormal or ruptured.

Diagnosis

Predisposing and perpetuating factors, and to some degree primary and secondary causes, can be recognized

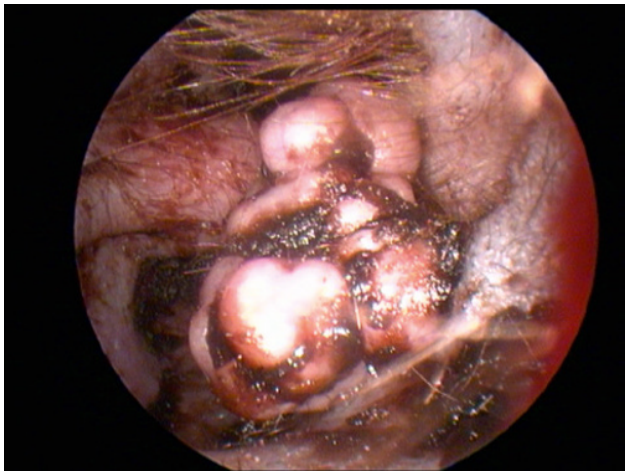


Figure 167.3 Ceruminous gland adenomas in the ear of a dog illustrating a predisposing factor of otitis externa.

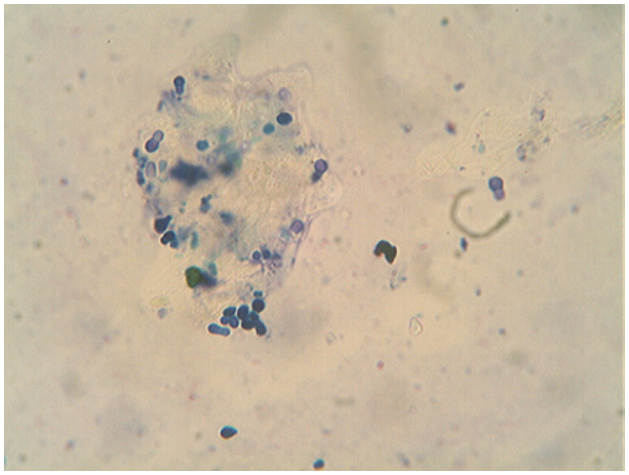


Figure 167.4 Ear cytology stained with Diff-Quik showing *Malassezia* organisms and anucleated squamous epithelial cells.

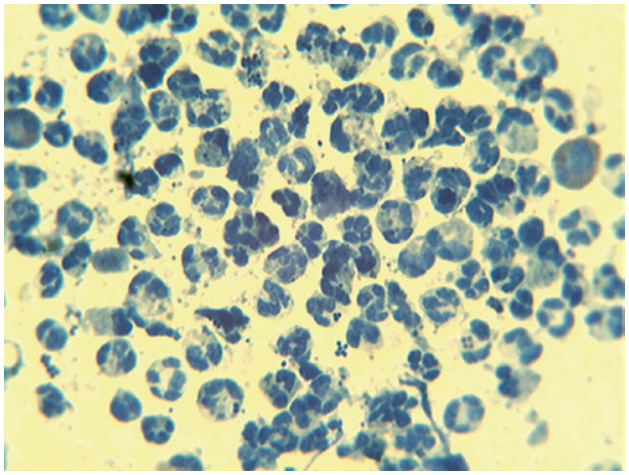


Figure 167.5 Ear cytology stained with Diff-Quik showing degenerate neutrophils and phagocytosed cocci.

by a history and clinical examination. Diagnostic investigations allow a more definitive identification of primary and secondary factors. Where a history suggests a primary cause then appropriate diagnostic tests may include food trials, *in vitro* or *in vivo* allergy tests, ectoparasite assessment, endocrine function tests or skin biopsy. Secondary infection can be identified by cytology of exudate and, where necessary, culture and susceptibility. Samples should be collected, if possible, before cleaning is performed using a shielded cotton swab (sample is taken by inserting the swab down an alcohol-cleaned otoscope cone) from the horizontal canal and rolled onto a clean glass slide. Both unstained (to identify ectoparasites such as *Demodex* spp. and *Otodectes cynotis*) and stained (to identify inflammatory cells, bacteria, and yeast) samples should be examined. Samples to be stained should be heat fixed before staining with a modified Wright's stain such as Diff-Quik (Figures 167.4 and 167.5).

Cytologic findings and interpretation are shown in Table 167.2. Cytology is often all that is needed to institute therapy in otitis externa. However, where rods are found with cocci on cytology (Figure 167.6), where cocci are identified but have failed to respond to rational therapy or where otitis media is suspected, culture and susceptibility is advised as bacterial sensitivity patterns may be unpredictable.

Therapy

Therapy can be divided into two parts; the first is the selection of an appropriate cleaner and the second is dealing with the pathologic process, which may be treating infection and/or reversing pathologic change within the ear canal. Assessment of the otic discharge allows the clinician to select the best cleaning product (Table 167.3).

Where the discharge is thick and waxy (e.g., keratinization disorders, hypothyroidism and *Malassezia* infection) then the cleaner needs to be able to break up the wax (i.e., ceruminolytic activity). Where an inflammatory infiltrate is present and the discharge is more purulent or mucopurulent (e.g., gram-negative infection), then an aqueous-based flush is better.

Examples of agents with good ceruminolytic properties include dioctyl sodium or calcium sulfosuccinate, carbamide peroxide, triethanolamine polypeptide oleate condensate, hexamethyltetracosane, and squalene. Propylene glycol and mineral or vegetable oils are less potent ceruminolytics. Aqueous-based flushing agents include ethylenediamine tetraacetic acid (EDTA)-tris, 0.2% chlorhexidine, and 2% acetic acid. Although the main function of an ear cleaner is to clean, many contain components that have antibacterial or antiyeast activity. Such actives include

Table 167.2 Cytologic findings and interpretation

Finding	Normal ear	Abnormal ear
Cerumen	Low numbers of anucleate corneocytes	Larger numbers of anucleate and nucleated corneocytes
Malassezia	Low numbers adherent to corneocytes	Peanut-shaped organisms >5–10/high power field (hpf) considered significant
Bacteria	Low numbers adherent to corneocytes	Large cocci in pairs, fours or clumps usually *Staphylococci* spp. Smaller cocci in chains usually *Streptococci* spp. Rods cannot be differentiated from each other and may be *Proteus* spp., *Escherichia coli* or *Pseudomonas* spp.
Inflammatory cells	Absent	Neutrophils only in acute disease, neutrophils and macrophages in chronic disease. Neutrophils are seen in all bacterial skin infections, neoplasia, and irritant and allergic dermatitis
Acantholytic cells	Absent	Seen in autoimmune disease (e.g., pemphigus foliaceus)
Neoplastic cells	Absent	Uncommon. Some neoplasms may shed cells into cerumen; fine needle aspirates are more useful
Ectoparasites – *Otodectes cynotis*, *Demodex* spp.	Absent	Eggs, immature stages, and adults can be found in cerumen

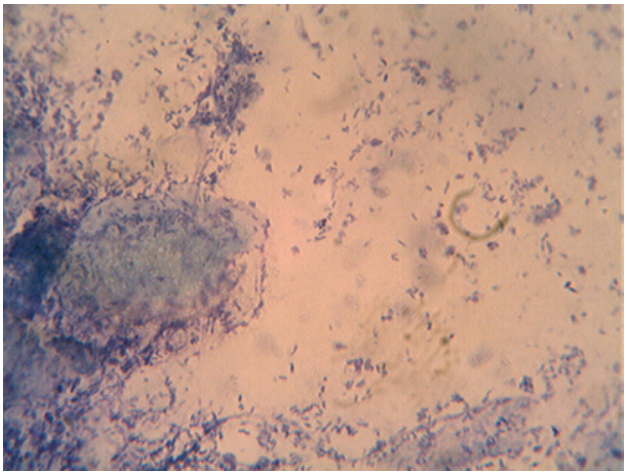


Figure 167.6 Ear cytology stained with Diff-Quik showing numerous rod-shaped bacteria consistent with *Pseudomonas* spp. intermixed with cocci.

EDTA-tris, lactic acid, salicylic acid, isopropyl alcohol, parachlorometaxylenol (PCMX), and microbial adhesion-blocking carbohydrates. EDTA-tris has been shown to have antibacterial potentiating activity and will render bacteria more sensitive to topical antibiotic therapy with aminoglycosides or fluoroquinolones when the ear is presoaked with this product 10 minutes before antibiotic application. The cleaning solution should be used to flood the ear canal and then gently massaged to dissolve debris before an absorbent pad is used to remove excess material.

Antiparasitic agents are found in many different ear preparations. Active ingredients with antiparasitic actions include ivermectin (0.01%), pyrethrins (0.05–0.15%), rotenone (0.12%), piperonyl butoxide (1.5%), milbemycin oxime (0.1%), and thiabendazole (4%). All products have activity against *Otodectes cynotis*. In addition, ivermectin and milbemycin applied topically would be expected to have some activity against *Demodex* spp. Products with generalized effects such as topical selamectin and moxidectin may also be used to treat ear mites. Finally, excellent results have been reported for orally and topically administered, long-acting, systemic parasiticides of the isoxazoline class for the treatment of *O. cynotis* and demodicosis in dogs and cats.

Antibiotic therapy may initially be based on cytology. However, where rods or mixed infection are seen on cytology or where cocci are identified and the case has not responded to previous therapy, culture and susceptibility should be performed. Antibiotics can be considered as first, second or third line for topical therapy of otitis externa and indeed for otitis media (Table 167.4).

Glucocorticoids are useful in the therapy of otitis externa. They reduce swelling, pruritus, inflammation, and glandular secretions. They can also help to open up the ear canal to allow adequate penetration of topical drugs. They may be given systemically or topically (Table 167.5).

The more potent topical steroids, such as mometasone furoate and hydrocortisone aceponate, produce more marked antiinflammatory effects than dexamethasone or betamethasone, which are both more potent than prednisolone.

Antiyeast drugs are rarely needed systemically. The azole antifungals miconazole, clotrimazole, and posaconazole as well as nystatin are available in a range of licensed veterinary ear drops in the United States and Europe.

Table 167.3 Selection of ear cleaner based on the type of discharge present

Type of discharge	Thick and waxy	Moderately waxy/ purulent	Mildly waxy/ purulent	Mucopurulent/ hemorrhagic
Typical findings	Sterile ceruminous otitis	*Malassezia* otitis	Gram-positive otitis	Gram-negative otitis

The waxier the discharge, the greater the ceruminolytic properties of the ear cleaner to emulsify the wax



The more mucopurulent the discharge, the more aqueous the cleaner to break down mucus and flush the ear



Table 167.4 Topical antibiotic therapy for use in otitis externa and media

Order of use	Drug	Indications	Safety in otitis media
First-line drugs	Framycetin	Gram-positive and many gram-negative bacteria	Unsafe
	Neomycin	Gram-positive and some gram-negative bacteria	Unsafe
	Fusidic acid	Gram-positive bacteria	Unsafe
	Florfenicol	Gram positive bacteria	Unsafe
Second-line drugs	Gentamicin (may be used as first line where neomycin unavailable)	Gram-positive and many gram-negative bacteria	Proprietary veterinary products unsafe; aqueous solutions appear safe at 2.0–4.0 mg/mL
	Polymyxin	Excellent Gram-negative activity	Unsafe
	Enrofloxacin Ciprofloxacin Marbofloxacin Orbifloxacin	Fluoroquinolones have excellent Gram-negative and -positive activity. Their use is best reserved for gram-negative infection	Proprietary veterinary products unsafe; aqueous solution mixed with EDTA-tris appears safe. Enrofloxacin used at 0.5–1.0 mg/mL. Marbofloxacin used at 0.1–0.3 mg/mL
	Silver sulfadiazine	Broad spectrum; excellent activity against *Pseudomonas* spp.	Safety of veterinary product unknown; 1% cream mixed with sterile water diluted 1:10 appears safe
Third-line drugs best reserved for severe gram-negative infection on the basis of culture and sensitivity	Amikacin	Resistant gram-negative bacteria	Ototoxic – off-license use of aqueous solution of 30–50 mg/mL
	Tobramycin	Resistant gram-negative bacteria	Ototoxic – off license use of aqueous solution of 8 mg/mL
	Carboxypenicillins	Resistant gram-positive bacteria	Ototoxic – off-license use of aqueous solution of 10 mg/mL

All aqueous solutions constitute off-license use of these drugs.

All therapeutic protocols should include regular follow-up examinations every 7–14 days. Cytology should be performed at each visit and antimicrobial therapy should be continued until a complete clinical and cytologic resolution of the infection has been achieved. Long-term management should include regular ear cleaning with an appropriate product and therapy of the underlying primary cause.

Table 167.5 Systemic glucocorticoid therapy for use in otitis externa and media

Glucocorticoid	Dosage (mg/kg)	Comments
Prednisolone	1.0–2.0 PO q24h	Should be reduced to an alternate-day regime after two weeks then completely tapered
Methylprednisolone	0.8–1.8 PO q24h	
Triamcinolone acetonide	0.1–1.8 PO q24h	
Dexamethasone	0.1–0.2 IV	Given as a single treatment at the time of ear flush; may be repeated at subsequent rechecks after 7–10 days if other glucocorticoids are not being used

PO, by mouth (*per os*).

Otitis Media

Etiology/Pathophysiology

Otitis media is inflammation of the middle ear and is often bacterial in origin. The organisms most commonly isolated are *Staphylococcus pseudintermedius*, *Pseudomonas* spp., *Escherichia coli*, *Proteus* spp., and *Enterococcus faecalis*. Occasionally, *Malassezia pachydermatis* may be involved. In most cases, infectious otitis media is secondary, resulting from a descending infection as an extension of otitis externa, rather than an ascending infection from the oropharynx or a result of hematogenous infection. Other causes of otitis media include primary secretory otitis media (PSOM) principally recognized in the Cavalier King Charles spaniel, foreign bodies, nasopharyngeal polyps seen most commonly in cats and neoplasms such as squamous cell carcinomas and lymphoma.

Secondary otitis media is caused by the drainage of exudate and infectious organisms into the tympanic bulla from the external ear canal. This causes inflammation to the lining epithelium, the mucoperiosteum, which forms a pseudostratified columnar epithelium containing increased numbers of secretory cells and glands. As a result of ongoing inflammation, granulation tissue forms within the bulla. With more chronic disease, this develops into dense connective tissue and, with time, bone spicules may develop within this dense tissue.

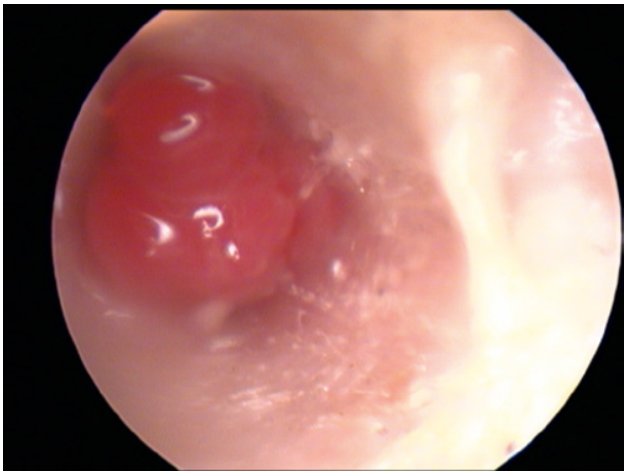


Figure 167.7 Nasopharyngeal polyp in a cat.

Signalment

When otitis media occurs as an extension from otitis externa, it most commonly affects middle-aged or older dogs. Occasionally, younger dogs may be affected. Breeds that are predisposed to otitis externa will also be susceptible to developing otitis media. Nasopharyngeal polyps can be seen in any age of cat, including very young kittens (Figure 167.7).

Primary secretory otitis media can be seen in young to middle-aged Cavalier King Charles spaniels.

History and Clinical Signs

Approximately 50–80% of all dogs with otitis externa of more than six months duration will have otitis media. Owners often report that dogs shake their heads and are reluctant to open their mouths to, for example, carry a ball, yawn, bark or eat hard food. This is generally due to pain in the region of the temporomandibular joint. Owners may complain that their dog's hearing has deteriorated, which may be due to conductive changes in hearing as a result of fluid within the middle ear or cochlear damage if infection has spread to the inner ear. Neurologic signs in the form of ataxia or nystagmus are more suggestive of otitis interna than otitis media. Cranial nerve dysfunction which can be seen with otitis media includes Horner syndrome, especially in cats, facial nerve paralysis and keratoconjunctivitis sicca which can occur due to damage to the parasympathetic innervation of the lacrimal gland.

Diagnosis

The principal steps in diagnosis are otoscopy, myringotomy, and diagnostic imaging. Otoscopy is an insensitive modality for diagnosing otitis media. Where the



Figure 167.8 A swab being passed through a sterile otoscope cone, which guards the swab from discharge and contaminants present in the vertical ear canal during cytologic sampling.

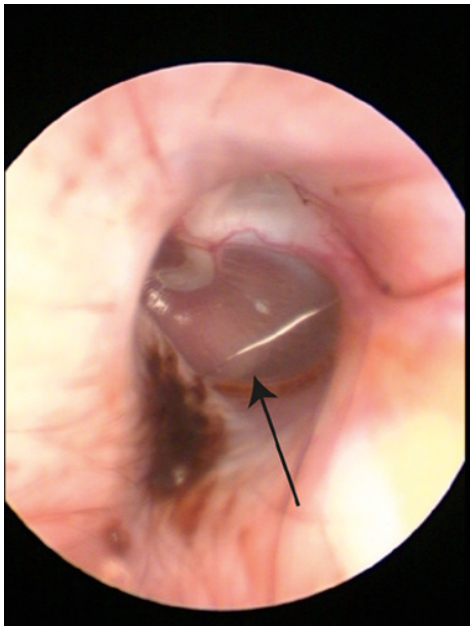


Figure 167.9 Videootoscopic image of a normal tympanic membrane in a dog. Black arrow indicates the recommended site of myringotomy in the caudoventral quadrant of the pars tensa.

tympanic membrane can be visualized and can be seen to be ruptured or intact but abnormal, suggesting previous damage, then a diagnosis of otitis media is possible. If the tympanic membrane is ruptured, samples may be taken from the middle ear. A clean otoscope cone or videootoscope head should be inserted as far into the horizontal canal as possible and a fine catheter or microswab may be inserted through the tube or working channel to "guard" it from discharge in the external canal (Figure 167.8). Material can be gathered onto the swab or suctioned up the catheter to sample the middle ear.

If the tympanic membrane is intact but appears abnormal, it is possible a previous defect in the tympanum has healed in the presence of ongoing otitis media. In these cases, myringotomy should be performed to take samples from the middle ear. Direct visual observation (ideally with a video otoscope) in a carefully cleaned ear canal is important to avoid damage to sensitive structures. The myringotomy should be performed by an experienced clinician using a diode or carbon dioxide (CO_2) laser or manually using a sterile rigid polypropylene catheter cut to an angle of 60°. A small hole made in the pars tensa in the caudoventral quadrant to avoid the pars flaccida and the manubrium of the malleus (Figure 167.9) allows for collection of material from the middle ear, which can be examined cytologically and submitted for culture and sensitivity. Cytology in otitis externa is useful but in otitis media, the presence of mucus from the middle ear can make identification of bacteria difficult. Where cytology reveals signs of an inflammatory infiltrate and infectious organisms, a definitive diagnosis of otitis media can be made. Where cytology is unremarkable, cultures are necessary and are probably best undertaken in all cases.

Advanced imaging is useful in otitis media. Radiography is only diagnostic in chronic disease. The open-mouthed view, which allows for comparison of both sides, and the lateral oblique view provide the most information. Changes on radiography that are consistent with otitis media are increased density of the air-filled bulla, thickening, lysis or irregularity of the tympanic bulla wall, or formation of new bone. Computed tomography (CT) and magnetic resonance imaging (MRI) are more sensitive modalities, picking up subtle changes such as granulation tissue or fluid or mucus within the middle ear.

Therapy

Therapy of otitis media may be divided into several stages:

- flushing the bulla
- infusion of topical medication(s) into the bulla
- reduction of inflammation with glucocorticoids (topical or systemic)
- administration of systemic antibiotics
- reassessment every 7–10 days

Continue therapy until negative cytology and cultures have been achieved and the ear appears clinically normal.

Flushing the bulla is the most important part of treatment. This is best achieved in an anesthetized animal, which should be intubated and the endotracheal cuff fully inflated to avoid the risk of inhalation of any flush solution. An aqueous-based flush helps hydrate the mucous within the bulla and aid removal by suction. Suitable flushes include water, sterile saline, dilute chlorhexidine solution (<0.2%), and EDTA-tris. All have a high degree of middle ear safety. Ceruminolytics are generally not necessary in otitis media due to the nature of the discharge, and only squalene has been shown to be safe in the dog. The cat's middle ear appears to be more sensitive to ototoxic effects and only water, sterile saline, and EDTA-tris are considered safe.

Once the ear has been cleaned, medication can be administered. No medication is licensed for the therapy of otitis media so in each case, a careful assessment should be made of the risks of topical drugs causing signs of ototoxicity versus the benefits in resolving the infection. The safest antibiotics for infusion into the tympanic bulla are aqueous solutions of fluoroquinolones (ciprofloxacin, enrofloxacin, marbofloxacin) and aqueous gentamicin. Other aminoglycosides such as tobramycin and the semisynthetic penicillin ticarcillin have been associated with severe hearing loss when used to treat otitis media. Antifungal drugs that are considered safe are clotrimazole, miconazole, nystatin, and tolnaftate, although the author has seen temporary deafness caused by both clotrimazole and miconazole that resolved when topical medication was withdrawn. Drugs that are infused directly into the bulla are thought to stay trapped within this structure for several days, providing high local levels of the drug.

Therapy with glucocorticoids is important to reduce the inflammation and exudation in middle ear disease and to help reduce the formation of granulation tissue. Many different protocols are available for therapy. The author's preference is to administer intravenous dexamethasone (2 mg/mL) at a dose of 0.1–0.2 mg/kg at the time of the ear flush and then follow with antiinflammatory doses of prednisolone at 1–2 mg/kg daily PO for two weeks. Alternative systemic glucocorticoids are listed in Table 167.5. Aqueous dexamethasone, fluocinolone, and a commercial product containing dimethyl sulfoxide (DMSO) and fluocinolone (Synotic®, Fort Dodge Animal Health) are recognized as having low ototoxic potential and can be infused by catheter into the bulla after flushing.

The use of systemic antibiotics in otitis media is a subject of debate. The levels of systemic antibiotics achieved in the tympanic bulla can never approach the levels achieved by topically administered drugs. However, where topical therapy cannot reach the middle ear due to, for example, stenosis of the external ear canal or where the ear is so severely ulcerated or painful that the dog will not tolerate topical therapy, then systemic medication may be the only option. All oral drugs should be prescribed on the basis of culture and susceptibility. Oral fluoroquinolones are the most appropriate first-line drugs in otitis media; aminoglycosides and ticarcillin-clavulanic acid may be used systemically but only where all other drug options have been explored. Drug doses are found in Table 167.6.

Follow-up appointments are important in otitis media and should be undertaken every 7–10 days. If necessary, the dog should be readmitted to permit further flushing of the tympanic bulla under anesthesia. Topical and systemic therapy may be adjusted on the basis of culture and sensitivity results. Antiinflammatory therapy may be reduced as the disease improves. The author will generally reduce prednisolone to an alternate-day dosage after two weeks and then taper, aiming to withdraw it after a further two weeks. Therapy should be continued until the ear appears clinically, cytologically, and culturally normal. Maintenance therapy should include regular ear cleaning and maintenance of any underlying causes.

Table 167.6 Systemic antibiotic therapy for use in otitis media

Drug	Dosage (mg/kg)	Comments
Difloxacin	5.0–10.0 PO q24h	Higher dose rates constitute off-license usage
Enrofloxacin	5.0–20.0* PO q24h	
Marbofloxacin	2.0–5.0 PO q24h	
Orbifloxacin	5.0–12.5 PO q24h	
Gentamicin	6.0–8.0 SC q24h	Renal function must be assessed (urine analysis and blood samples) before starting and during aminoglycoside therapy
Amikacin	15.0–20.0 SC q24h	
Ticarcillin-clavulanic acid	15.0–25.0 IV q8h	Use can be justified only under exceptional circumstances

* Doses higher than 5.0 mg/kg in cats can cause retinal damage which can lead to blindness.
IV, intravenous; PO, by mouth (*per os*); SC, subcutaneous.

Further Reading

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168

Cutaneous Manifestations of Systemic Disease

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The skin can manifest myriad changes associated with systemic diseases. Some, such as the cutaneous manifestations of hyperadrenocorticism, are so well recognized and characteristic that they provide obvious clues about the underlying etiology. Others are more subtle or rare. In addition to the diseases described in this chapter, the skin can directly exhibit symptoms of bleeding disorders (petechiae, ecchymoses, bruising), icterus, dehydration, and cachexia. Changes in the skin can be a direct result of a multisystemic disorder (e.g., vasculitis affecting multiple organs) or result from disease occurring in another organ (e.g., superficial necrolytic dermatitis associated with liver disease). The skin is an easier site to sample compared to other organs, and skin biopsies (or in some cases cytologic examination or cultures) can be essential to facilitating the diagnosis of the underlying disease.

Although internal diseases are relatively uncommon as a cause of skin disorders, their likelihood increases when certain findings are present. Internal disease is more likely in patients exhibiting unexpected changes in weight, activity level, appetite, thirst, or urine production, and these signs should be investigated as part of the history collection. Patients presenting with skin disease for the first time at an advanced age without a readily identifiable cause also warrant further work-up for internal disease.

Hormonal and Metabolic Disorders Causing Cutaneous Manifestations

Canine and Feline Hypercortisolism

Hypercortisolism (i.e., Cushing disease, Cushing syndrome) is common in dogs and causes both nonspecific and fairly distinct dermatologic changes. The signs are similar whether endogenous or exogenous glucocorticoids are the cause. The most common but nonspecific change occurs in the hair coat, with a lack of luster and density, slower growth, and often a lightening of the color. Hair is progressively lost, resulting in alopecia that spares the head and distal extremities and predominantly affects the trunk, typically in a symmetric pattern. More specific signs include thinning skin and resultant prominent blood vessels, as well as comedones, milia, and calcinosis cutis. Easy bruising, seborrhea, slow wound healing, and striae are also seen. Generalized demodicosis can occur, and iatrogenic or spontaneous hypercortisolism is an important consideration in adult-onset disease. Lesions of superficial bacterial pyoderma are commonly seen in dogs with hypercortisolism.

Naturally occurring and iatrogenic hypercortisolism are rare in cats. Cutaneous signs include alopecia and thin skin. Skin fragility, described below, occurs in over 50% of cases, and may be more common in cats with adrenal neoplasia. A unique finding reported only in iatrogenic hypercortisolism is medial curling of the pinnae.

Calcinosis Cutis

Calcinosis cutis refers to the various forms of calcification of the skin. It most commonly occurs in association with iatrogenic or spontaneous hypercortisolism in dogs. It appears to be more common in large-breed dogs. It is more rarely seen with systemic fungal infections such as blastomycosis, with diabetes mellitus, and with various other diseases. Rarely, calcinosis cutis affecting multiple footpads or the interdigital skin has been seen in dogs and cats in association with chronic renal disease (Figure 168.1). This site is not typically affected in dogs with hypercortisolism, so renal failure should be considered in a patient with calcinosis affecting multiple feet.

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Figure 168.1 Calcinosis cutis affecting multiple feet in a young cat with chronic renal disease.



Figure 168.2 Calcinosis cutis. Firm, coalescing erythematous papules on the lateral thorax of a mature bulldog with iatrogenic hypercortisolism.

Calcinosis cutis often starts as erythematous papules that coalesce into very characteristically firm plaques (Figure 168.2). The lesions can ulcerate and become pruritic. The axilla, groin, and dorsal trunk are commonly affected. The diagnosis is made on the basis of characteristic clinical features and histopathology, and investigation for the underlying cause is warranted in all cases.

The treatment of calcinosis cutis relies on identification and removal of the underlying metabolic problem and if this can be achieved, it is associated with a good prognosis. Correction of hypercortisolism usually allows calcinosis cutis to resolve within several months, but some lesions can undergo osseous metaplasia and persist indefinitely.



Figure 168.3 Feline acquired skin fragility in a geriatric cat. Extensive tearing of the very thin skin following minor trauma.

Feline Skin Fragility Syndrome

Feline acquired skin fragility syndrome is a rare condition characterized by extremely thin skin that tears and bruises easily (Figure 168.3). It is associated with spontaneous or iatrogenic hypercortisolism and seems to be more common with adrenal tumors. It can also result from excessive levels of progestational compounds, either administered therapeutically or secreted from adrenal tumors. The syndrome has also been reported in association with diabetes, cholangiohepatitis, hepatic lipidosis, neoplasia (e.g., pancreatic and intestinal carcinoma), and other diseases.

Cats with acquired skin fragility syndrome may present for spontaneous skin tears following minimal handling or trauma. They have extremely fragile, thin skin that tears very easily during restraint. The skin is not hyperextensible and bleeds minimally upon tearing. The diagnosis is usually made by the very characteristic clinical findings, although histopathology is confirmatory. Affected cats have a poor prognosis.

Canine Hypothyroidism

Hypothyroidism is a common endocrine disorder of dogs. Dermatologic changes occur in 60–80% of cases, but can be subtle. Cutaneous signs of hypothyroidism include progressive alopecia in areas of wear, including the dorsal and distal tail ("rat tail" appearance), ventral and lateral trunk, the upper limbs (typically caudal thighs), and often the dorsal aspect of the muzzle. The pattern of alopecia is somewhat different from the classic bilaterally symmetric alopecia sparing the head in hypercortisolism. Some hypothyroid dogs maintain a

normal hair coat. The loss of guard hairs, leaving behind the finer undercoat, can lead to the appearance of a "puppy coat." The hair coat can also lighten due to longer retention of hair and subsequent bleaching. Recurrent pyoderma and otitis externa are common. Pruritus is not a feature of hypothyroidism but can be seen if secondary pyoderma, *Malassezia* dermatitis, or otitis externa are present. Advanced cases can present with thick, puffy skin (myxedema) due to accumulation of dermal glycosaminoglycans. This is a rare manifestation as most hypothyroid dogs are diagnosed and treated before progressing to this stage.

The diagnosis of hypothyroidism relies on history, examination findings, complete blood count and serum biochemistry findings, thyroid hormone (total T4 and free T4) and thyrotropin (TSH) measurements, and occasionally skin biopsies. The total T4 is often assayed in dogs with dermatologic disease. Because it is lowered by multiple nonthyroidal factors (e.g., drugs and severe nonthyroidal illness), it is easy to mistakenly diagnose hypothyroidism using this measurement alone. Confirmatory testing should be performed before initiating treatment. Although a response to thyroid supplementation is sometimes used as a diagnostic tool, treatment with thyroxine can result in temporary improvement of many dermatologic conditions by stimulating hair growth. This can lead to false confirmation of an incorrect diagnosis of hypothyroidism.

Treatment of hypothyroidism is usually very rewarding and most of the cutaneous abnormalities can be corrected. However, during the initial few weeks of therapy, there can be increased scaling as well as profound hair loss as telogen hairs are replaced due to a coordinated initiation of the new hair cycle.

Sex Hormone Dermatoses

These uncommon dermatoses can be associated with gonadal and adrenal disorders. They most often present with truncal alopecia. Hyperestrogenism can occur in intact male dogs with functional testicular tumors (see section on Neoplastic and Paraneoplastic Disorders Affecting the Skin at the end of this chapter), or in intact female dogs with cystic ovaries or, more rarely, with functional ovarian tumors.

Hyperandrogenism in male dogs is rare. It can be idiopathic or associated with testicular neoplasia. In the idiopathic form, young dogs exhibit hypersexual behavior and sometimes aggression, as well as seborrhea oleosa and truncal hair loss. Hyperandrogenism due to testicular neoplasia results in hyperplasia of the circumanal glands and the tail gland, which appear thickened and universally enlarged. Macular hyperpigmentation can also be seen. The diagnosis of these conditions can be made with endocrine testing and ultrasonography.

Superficial Necrolytic Dermatitis

Superficial necrolytic dermatitis, sometimes called hepatocutaneous syndrome, is most often seen in dogs with a characteristic idiopathic hepatopathy. It can also be seen with anticonvulsant medications and pancreatic tumors. Superficial necrolytic dermatitis has been rarely reported in cats. This condition is described in detail in Chapter 169.

Xanthomas

Xanthomas are rare granulomatous skin lesions that occur in association with an abnormality in lipid metabolism. Most have been associated with diabetes mellitus or with the feeding of high-fat foods. An underlying hereditary defect of lipid metabolism has also been reported. The lesions occur most commonly on the head (particularly the preauricular area or ears), distal limbs, and bony prominences, and consist of small white or yellow papules, nodules, or plaques. Histopathology is needed to make the diagnosis.

The treatment of xanthomas relies on the correction of the underlying metabolic problem and if this can be accomplished, the prognosis is favorable. Xanthomas in cats with idiopathic hypertriglyceridemia can undergo regression with a low-fat diet.

Amyloidosis

Amyloidosis refers to a diverse group of diseases featuring the extracellular deposition of protein fibrils with characteristic staining properties (amyloid). In dogs and cats, most cases of amyloidosis show systemic involvement, affecting the kidneys and less commonly other organs. Skin lesions are seen in some patients. Amyloidosis can also be limited to the skin. In this form, dermal or subcutaneous nodules can be seen anywhere, but most commonly on the ear. Purpuric macules have also been reported. The diagnosis is made by histopathology. Solitary nodules can be excised but no effective treatment is reported for more widespread lesions.

Other hormonal disorders that can sometimes cause cutaneous manifestations include the most common endocrine diseases of the cat. Diabetic cats sometimes develop seborrheic skin disease, thin skin, and alopecia. Hyperthyroid cats can exhibit an increased rate of claw growth, excessive shedding and matting, alopecia due to excessive grooming, and occasionally other changes.

Although pruritus is a well-documented complication of hepatobiliary disease in humans, it is not typically

recognized in companion animals. One case report described pruritus in a puppy with a portosystemic shunt whose pruritus resolved upon correction of the vascular abnormality.

Systemic Infectious Disease Causing Cutaneous Manifestations

Feline Herpesviral Dermatitis

Feline herpesvirus-1 (FHV-1) can cause a characteristic facial dermatitis in cats. The condition is most common in adult cats, and not all cases exhibit the ocular or respiratory signs typical of this viral infection. There can be a recent history of an upper respiratory tract infection in the weeks preceding development of the lesions in some cats. The lesions consist of inflamed and often ulcerated areas near the nares. They most often affect the nasal planum, dorsal aspect of the muzzle, and periocular skin (Figures 168.4 and 168.5). The lesions do not appear pruritic even though eosinophils typically predominate. The clinical appearance and eosinophilic inflammation can lead to an inappropriate diagnosis of an eosinophilic plaque or mosquito bite hypersensitivity, with inappropriate treatment using corticosteroids, which can lead to marked worsening of the disease.

The diagnosis of feline herpesviral dermatitis is made by the fairly striking clinical appearance of the facial form, histopathology, and either immunohistochemistry or polymerase chain reaction (PCR) testing for FHV-1 on biopsy samples. Viral inclusion bodies are difficult to find on histopathology, so this condition should be considered in biopsies consistent with eosinophilic plaques located on the face.



Figure 168.4 Feline herpesviral dermatitis and rhinitis in an adult cat. Small crusts and a loss of the cobblestone architecture of the nasal planum are seen.

Treatment of FHV-1 infection with oral famciclovir is effective for cutaneous, ocular, and respiratory symptoms. It can be more effective than other therapeutic strategies. The drug appears to be well tolerated in cats but there is some uncertainty about the dose and duration of treatment, with recent recommendations reflecting higher doses than had been used previously. In some cats, the skin lesions can become recurrent or chronic.

Feline Leukemia Virus and Feline Immunodeficiency Virus Infection

Feline leukemia virus (FeLV) usually causes skin lesions by its immunosuppressive actions, although it can also induce skin tumors. The cutaneous symptoms are quite nonspecific. Affected cats are susceptible to a number of secondary infections including recurrent abscesses, pyoderma, dermatophytosis, demodicosis, and paronychia. Multiple cutaneous horns of the footpads are sometimes seen in cats infected with FeLV. Giant cell dermatosis is a histologically unique and rare manifestation causing pruritus and crusting of the face and often other areas of skin. Although feline immunodeficiency virus (FIV) is more commonly associated with recurrent or chronic oral disease, some cats also exhibit skin infections. The signs of these two immunosuppressive viral diseases are very similar. The diagnosis is made by serologic testing.

Canine Distemper

Canine distemper virus infection in dogs can be manifested by a combination of respiratory, ocular, gastrointestinal, neurologic, and cutaneous signs that



Figure 168.5 Feline herpesviral dermatitis in an adult cat. Extensive unilateral eosinophil-rich ulceration is present on the face.

appear simultaneously or sequentially. The classic but uncommon cutaneous manifestation of canine distemper is "hard pad disease" – footpad and nasal hyperkeratosis. The footpads are thickened, fissured, and unusually hard. The centers of the footpads can feel surprisingly hard even when they appear minimally affected. Widespread impetigo can also be seen in puppies. The diagnosis is often made on the basis of clinical signs in a dog with an inadequate vaccination history. Histopathology and immunohistochemistry on affected skin can also be useful to confirm the diagnosis.

Systemic Mycoses

Cutaneous lesions consisting of papules, nodules, ulcers, abscesses, and draining tracts are seen in many systemic mycoses. They are seen most commonly in blastomycosis (20–50% of cases) and feline cryptococcosis (40%), and result from hematogenous spread of the fungus to the skin. Sporotrichosis is generally transmitted by cutaneous inoculation of fungal spores, in most cases resulting in cutaneous or cutaneous lymphatic signs. However, cats with sporotrichosis have a high frequency of upper respiratory and lung lesions, suggesting that the inhalatory mode of infection also plays a role in this species, and the hematogenous route is important in the cutaneous dissemination of the disease.

Nasal mycotic rhinitis in dogs (most commonly aspergillosis) is usually associated with profuse mucopurulent nasal discharge and can cause crusting and ulceration of the nasal planum (Figure 168.6). Depigmentation of the nasal planum ventral to the nares is a characteristic finding.



Figure 168.6 Mild nasal mycotic rhinitis in a mature dog with nasal aspergillosis.

The ideal diagnostic method for systemic or localized mycoses is identification of the fungal organism by cytologic and histopathologic examination of affected tissues. Serology is useful as a noninvasive diagnostic test for cryptococcosis and can also be used to monitor response to therapy. A sensitive urine or serum antigen test is currently available for the diagnosis of blastomycosis when organisms are not found on cytology or histopathology. Sampling of the affected tissue for a definitive mycotic rhinitis typically requires rhinoscopy.

Leishmaniasis

Leishmania organisms are protozoa of several species that cause a spectrum of clinical disease in dogs and other mammals, including cats. Leishmaniasis varies in its clinical presentation from focal to generalized cutaneous disease to disseminated internal disease. The severity varies from asymptomatic to fatal. *Leishmania* protozoa are usually vector borne by sandflies, but vertical transmission and direct horizontal transmission are likely important in certain populations of dogs. Leishmaniasis has a worldwide distribution but is endemic in parts of Europe (most commonly in the Mediterranean basin) and South and Central America. It was considered to be of minimal importance in North America until the early 2000s, when *Leishmania* was found in multiple foxhound kennels.

Leishmaniasis in dogs most frequently combines cutaneous and internal disease. The most common sign is a nonpruritic exfoliative dermatitis with alopecia that is generalized but most pronounced on the head (Figure 168.7). A characteristic feature is adherent silvery-white scale. Mucocutaneous ulcerations, alopecia, and erythema can also be seen. Less commonly, nodular skin disease is present.

The diagnosis of leishmaniasis can be made by cytology (from skin, lymph nodes, bone marrow aspirates), histopathology, PCR testing of blood and other tissues, and antibody serology testing.

Lagenidiosis

Lagenidiosis is a rare disease caused by a fungus-like, aquatic, "water mold" oomycete of the genus *Lagenidia*. It occurs most often in dogs living in the southeastern United States and has been reported in cats. The disease is sometimes limited to the skin and local lymph nodes, but often also causes lesions at distant sites, including the great blood vessels, respiratory tract, and mediastinum. The systemic form is universally fatal. The diagnosis is made by histopathology, which is similar to histopathology from tissues originating from dogs with pythiosis or



Figure 168.7 Two-year-old boxer with visceral leishmaniasis caused by *Leishmania chagasi*. The skin lesions are generalized and characterized by erythema and thick scales adhered to the skin surface and hair shafts. *Source:* Courtesy of Dr Romeika Reis Lima.

zygomycosis. More specific tests include serology for anti-*Lagenidium* antibodies, culture, and PCR testing.

The prognosis for dogs with systemic lagenidiosis is grave. For dogs with only cutaneous lesions, aggressive resection can be curative and amputation can be considered for those with distal limb lesions affecting one leg. Radiography of the thorax and ultrasonography of the abdomen is recommended prior to surgery because of the frequency of systemic dissemination. Medical therapy with antifungal drugs is typically ineffective alone but has been described as an adjunct to surgical resection.

Many other infectious diseases can present with cutaneous manifestations. This list includes canine herpesvirus infection, pseudorabies, feline infectious peritonitis, feline calicivirus infection, toxoplasmosis, neosporosis, brucellosis, pythiosis, entomophthoromycosis, and rickettsial and ehrlichial infections in dogs.

Nutritional Disorders Causing Cutaneous Manifestations

Zinc-Responsive Dermatosis

Zinc-responsive dermatosis is an uncommon skin disease in dogs. It includes syndromes caused by nutrient deficiency, nutrient imbalances, and the inability to absorb or utilize zinc. Absolute nutritional zinc deficiency is unlikely in a patient eating a well-balanced diet. Relative deficiencies can be seen in dogs when zinc absorption is impaired by excessive amounts of other nutrients.

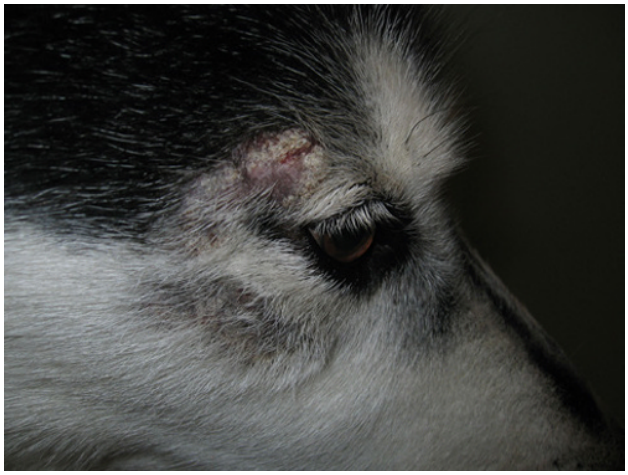


Figure 168.8 Zinc-responsive dermatosis (syndrome I) in an adult Siberian husky. Crusting, erythema, alopecia, and hyperpigmentation of the periocular skin are present.

Syndrome I zinc-responsive dermatosis occurs in dogs eating a well-balanced diet and has been reported most commonly in Siberian huskies and Alaskan malamutes. A more severe form has been reported in a litter of pharaoh hounds. Skin lesions usually begin in early adulthood and consist of early erythema followed by crusting, scaling, lichenification, and alopecia. The distribution is typically around the mouth, chin, eyes, and ears (Figure 168.8). An inability to absorb zinc from the gastrointestinal tract has been shown in some malamutes.

Syndrome II zinc-responsive dermatosis has been reported predominantly in large-breed puppies or young adult dogs eating diets deficient in zinc or diets that interfere with zinc absorption (e.g., excessively high in calcium, other minerals and vitamins, or phytates). Dogs with this syndrome have extensive crusting and fissuring of the footpads and nasal planum, and generalized crusting plaques. Very similar but more severe clinical signs have been seen in generic dog food dermatosis, which was seen in North American in the 1980s but was virtually eliminated with the reformulation of these foods. In this syndrome, a deficiency of multiple nutrients is likely and more severe systemic signs are present.

The diagnosis of zinc-responsive dermatoses is made by clinical signs, dietary history, and histopathologic findings.

The treatment of syndrome I zinc-responsive dermatosis consists of oral zinc supplementation. Most cases respond well within 4–6 weeks, but require ongoing

treatment to maintain remission. Zinc methionine is a commonly used veterinary preparation. The dose of elemental zinc is 2–3 mg/kg per day. The addition of low-dose corticosteroids has also been reported to benefit patients not responding adequately to zinc supplementation. The intravenous administration of zinc sulfate has been described in patients with a poor response. Young dogs with syndrome II zinc-responsive dermatosis show a dramatic response to zinc and dietary correction, but do not require lifelong supplementation.

Feline Pansteatitis

This rare condition has been reported in cats eating diets high in polyunsaturated fatty acids (PUFAs) such as red tuna, without adequate vitamin E consumption. PUFAs increase oxidative stress through free radical production. Affected cats show inflammation and necrosis of subcutaneous and intraabdominal fat resulting in firm, painful nodules. They are often lethargic, anorexic, febrile, and painful with movement and palpation.

The diagnosis is made by histopathology coupled with a suggestive dietary history. Vitamin E supplementation and a dietary change can be used, but the prognosis for severe cases is poor.

Immune-Mediated Systemic Diseases Causing Cutaneous Manifestations

Panniculitis

Panniculitis in dogs and cats can be due to myriad etiologic factors, such as infectious agents, drug reactions, and immune-mediated diseases (systemic lupus erythematosus, polyarthritis, or others). Patients with panniculitis should be evaluated for pancreatic disease, as panniculitis has been associated with pancreatitis and pancreatic tumors. The reader is referred to Chapter 164 for a more detailed discussion of panniculitis.

Systemic Lupus Erythematosus (SLE)

This multisystem autoimmune disease shows highly variable signs affecting various organs. It is rare in dogs and very rare in cats. Circulating autoantibodies directed against a wide variety of tissue antigens are present. The estimated frequency of skin lesions is 20–50% of affected dogs and cats. The lesions can consist of mild alopecic scarring, scaling, and crusting, to widespread ulcers involving the skin and oral mucosa. Lesions of the nasal planum more typically seen with discoid lupus erythematosus may be present. Some patients exhibit lesions in hairless areas exposed to light. In addition to skin disease, other manifestations include polyarthritis, hematologic changes, protein-losing nephropathy, and other signs. German shepherd dogs are predisposed to SLE.

The diagnosis of SLE can be difficult. Criteria for the diagnosis of canine SLE include the presence of a positive antinuclear antibody (ANA) titer as well as a number of other clinical and laboratory findings. The reader is referred to other sections within this book for a more thorough discussion of these criteria. Skin biopsies can be helpful but although the classic changes of SLE are quite suggestive, the histopathologic findings in SLE are variable. Direct immunofluorescence or immunohistochemistry can be used to demonstrate immunoglobulin and complement at the dermoepidermal junction.

The prognosis for dogs with SLE is guarded, but some patients can be controlled effectively for years. The disease is highly variable in its severity, which can also wax and wane. Corticosteroids are used most often, frequently with the addition of steroid-sparing agents.

Vascular Diseases

A variety of diseases affecting the cutaneous blood vessels can result in skin lesions. Vasculitis refers to vascular diseases in which blood vessels appear to be the target of an inflammatory response. Although many cases are idiopathic, vasculitis can be initiated by myriad factors including drugs, rabies vaccination, infectious diseases, and food allergy. Thus, the term *vasculitis* describes a cutaneous reaction pattern rather than an etiologic diagnosis.

Lesions are often found on the pinnal apex. The footpads are also commonly affected with central or marginal ulcers. More widespread lesions can also be seen, consisting of purpura, erythematous plaques, hemorrhagic bullae, and ulcers. The skin is often the only organ affected but in some cases, other organs are concurrently affected. For example, cutaneous and renal vasculopathy of greyhounds is associated with renal disease.

Canine Uveodermatologic Syndrome

This rare syndrome consists of granulomatous uveitis and concurrent depigmenting dermatitis. A genetic basis is present, with akita dogs reported most frequently. The uveitis is usually bilateral and acute in onset, with the skin lesions occurring later in most cases. Depigmentation is seen on the skin of the nasal planum, lips, eyelids, and occasionally elsewhere. The diagnosis can be made tentatively based on the unique combination of clinical signs, and definitely using skin biopsies.

Other systemic diseases with an immune-mediated etiology that cause cutaneous lesions include erythema

multiforme, toxic epidermal necrolysis, cryoglobulinemia and cryofibrinogenemia, graft-versus-host disease, acute eosinophilic dermatitis (Wells-like syndrome), acute neutrophilic dermatitis (Sweet-like syndrome), familial canine dermatomyositis, and hypereosinophilic syndrome.

Neurologic Disorders Causing Cutaneous Manifestations

Canine Chiari-Like Malformation

Canine Chiari-like malformation has been reported most frequently in young Cavalier King Charles spaniels. It can be found in other breeds, and brachycephalic small-breed dogs are predisposed to the condition. Chiari-like malformation is a developmental abnormality leading to hypoplasia of the occipital bone and thus a reduced volume of the caudal fossa, the part of the skull that accommodates the cerebellum and brainstem. The cerebellum variably herniates through the foramen magnum, crowding the spinal cord and altering the flow of cerebral spinal fluid in that region with resultant syrinx formation. It is easily mistaken for a dermatologic condition, as it often causes persistent unilateral or bilateral scratching at the cervical and shoulder regions. A characteristic feature is that some dogs do not actually make contact with the skin when exhibiting the scratching. The presence of pruritus in this area, particularly if it is unilateral and not accompanied by skin lesions, should increase the suspicion of canine Chiari-like malformation. Neck pain is a common feature and is found in most affected dogs on physical examination.

The diagnosis can be made by the very characteristic clinical signs in a predisposed breed, but definitive diagnosis requires magnetic resonance imaging (MRI). The reader is referred to the neurology section for a more comprehensive discussion of Chiari-like malformation.

Sensory Neuropathies

Both inherited and acquired sensory neuropathies can result in cutaneous manifestations. A sensory neuropathy of English pointers, German short-haired pointers, English springer spaniels, and French spaniels results in severe paw licking and chewing progressing to further mutilation of the limbs and autoamputation. This condition has also been reported in one miniature pinscher. Canine ganglioradiculitis is an inflammatory disease of the cranial and spinal ganglia and nerve roots. Affected dogs develop sensory deficits and mutilation/hyperesthesia. Cauda equina syndrome can cause lumbosacral hyperesthesia, pruritus, and/or self-inflicted lesions of the hindlimb(s).

Neoplastic and Paraneoplastic Disorders Affecting the Skin

Male Feminizing Syndrome Secondary to Testicular Neoplasia

Dermatologic manifestations of canine testicular tumors are rarely encountered in parts of the world where neutering is common. Male feminization occurs most often with Sertoli cell tumors, affecting 24–57% of dogs with these tumors. Cryptorchid testes are at greatly increased risk for development of neoplasia. The syndrome is thought to be related to estrogen secretion from the tumor, but other factors may play a role as elevated estrogen levels are not always found. Bilaterally symmetric alopecia beginning in the perineal, inguinal, and flank regions is most common in affected dogs. Seborrhea, comedones, and hyperpigmentation of the skin, particularly in the inguinal and perianal areas, can also be seen in more advanced cases. Gynecomastia, nipple enlargement, and a pendulous prepuce can be present. A characteristic clinical feature is linear preputial dermatosis: a line of erythema with variable hyperpigmentation or comedones extending from the opening of the prepuce along its ventral aspect to the scrotum. Affected male dogs may attract other male dogs.

The tumor may be palpable in the affected testicle, and the nonneoplastic testicle can atrophy. However, testicular palpation is not universally abnormal and is not possible in cryptorchid dogs. Affected dogs can also exhibit myelosuppression. Approximately 20% of these tumors are malignant and roughly 10% will metastasize to the lungs and abdominal lymph nodes.

Although skin histopathology, estrogen levels (particularly estradiol-17-beta), ultrasonography and sometimes general bloodwork can be suggestive, the constellation of characteristic clinical signs, histologic confirmation of testicular neoplasia, and response to castration are diagnostic for the syndrome.

Feline Paraneoplastic Exfoliative Dermatitis

Feline exfoliative dermatitis is a paraneoplastic syndrome seen in old and middle-aged cats with thymomas. Skin lesions usually precede systemic signs such as dyspnea and weight loss. Affected cats show generalized erythema and severe scaling, often beginning on the head and neck but progressing to widespread lesions. The scales can become quite large, sometimes in excess of 1 cm in diameter. Alopecia is a common finding. Some patients also exhibit crusting, and brown keratosebaceous material can be present around the eyes and mouth, in the ear canals, and in the interdigital spaces. Pruritus is absent to mild unless secondary infections are

present. Secondary *Malassezia* dermatitis and bacterial overgrowth can occur.

The pathogenesis of the cutaneous syndrome is not well understood, but is thought to be a cell-mediated immunologic reaction secondary to the underlying thymoma. A mediastinal mass can be detected in most patients by radiography or ultrasonography and fine needle aspirates can be diagnostic. Surgical removal of the thymoma induces regression of the skin lesions. Median overall survival time after surgery in one small study was 1825 days, with a three-year chance of survival of 74%.

Feline Paraneoplastic Alopecia

Feline paraneoplastic alopecia is a highly visually distinct, bilaterally symmetric progressive alopecia in which the skin appears unusually thin and shiny (Figure 168.9).

The majority of affected patients are older cats with pancreatic carcinoma, but the condition has also been reported with biliary carcinoma. The pathogenesis of the cutaneous lesions is poorly understood but is thought to be induced by the cytokine milieu released by the tumor. The alopecia typically begins on the ventral abdomen and thorax, with progression to the head and medial extremities. The hair epilates easily, revealing smooth, shiny, glistening skin that is not fragile. Some affected cats have scaly or fissured footpads that can be painful. The condition is not always pruritic but affected cats may groom excessively, especially if the skin disease is complicated by secondary *Malassezia* dermatitis. The onset is typically quite acute and rapidly progressive. Affected cats are systemically ill and exhibit weight loss.

The clinical appearance is visually striking and distinctive. Histopathology confirms the diagnosis. Routine hematology and serum biochemical profiles are typically not helpful. Ultrasonography can be useful in finding the underlying neoplasm, but often fails to reveal a mass. Unfortunately, this disease carries a poor to grave prognosis as many tumors are not resectable and metastasis is common.



Figure 168.9 Feline paraneoplastic alopecia in an adult cat with pancreatic carcinoma. *Source:* Courtesy of Dr Edward Clark.

Nodular Dermatofibrosis

Nodular dermatofibrosis is a syndrome of multiple cutaneous nodules of collagenous origin occurring in conjunction with renal cystadenocarcinomas or cystadenomas in dogs. This syndrome most commonly occurs in German shepherd dogs and their crosses, and the renal disease is almost always bilateral. The disease is typically diagnosed in middle age. In addition to the renal tumors, intact females can develop uterine leiomyomas. In the German shepherd dog, an autosomal dominant mode of inheritance is suspected. Molecular studies have suggested that nodular dermatofibrosis is not a paraneoplastic syndrome but a genetic disease linked to a mutation in the gene encoding folliculin. It is analogous to Birt–Hogg–Dubé syndrome in humans. Rarely, nodular dermatofibrosis has been found in other breeds in the absence of internal tumors.

Nodules are typically most numerous on the head and limbs, including the feet, but can occur on other areas of the skin, generally in a symmetric fashion. They are firm, localized in the dermis or subcutaneous layer, mobile, and covered by intact epidermis that can sometimes ulcerate, causing lameness. The nodules range in size but can be up to 5 cm in some cases. The disease has a protracted clinical course, with the appearance of renal failure or metastasis occurring months or more often years from the time that the lesions are first noticed. The mean time from first observation of nodular dermatofibrosis to death is about 2.5 years.

The diagnosis of nodular dermatofibrosis is generally made by histopathology of the skin masses combined with abdominal ultrasonography. When skin biopsies are collected, the presence of multiple lesions and the suspicion of this condition should be conveyed to the pathologist.

There are currently no reported effective treatment options and because bilateral renal disease is virtually always present, surgery is not an option. The cutaneous nodules should be monitored and excised if they become ulcerated or infected leading to patient discomfort or if they disturb patient mobility due to their size or location. It is important to relay the fairly slow progression of the disease to owners of affected dogs.

Feline "Lung-Digit" Syndrome

Feline "lung-digit syndrome" describes an unusual pattern of metastasis that is seen with various types of

primary lung tumors, particularly bronchial and bronchoalveolar adenocarcinoma. This syndrome warrants mention because affected cats are most often presented for their skin disease rather than for pulmonary disease. Multiple digits on multiple feet are commonly involved. The most commonly recognized clinical signs on presentation include swelling of the distal digits, ulceration of the skin of the digit or nailfold, purulent discharge, as well as constant extrusion, deviation, or loss of the nail.

The diagnosis is made by radiography of the digits, which reveals osteolysis of the third phalanx, by thoracic radiography, and by digital biopsy. Clinical signs and radiography can provide a high index of suspicion for "lung-digit" syndrome. The prognosis for affected cats is grave, with a median survival time of 67 days after presentation in one study.

Paraneoplastic Pemphigus

Paraneoplastic pemphigus is a very rare blistering disease involving the skin, mucocutaneous junctions, and mucosal surfaces. It has been reported in two dogs, one in association with thymic lymphoma and one with splenic spindle cell sarcoma. Only one case has been reported in a cat, in association with lymphocytic thymoma. Autoantibodies develop as a result of the neoplastic process which targets epithelial adhesion molecules, mainly of the plakin family, leading to loss of cellular cohesion.

Clinically, the disease is severe and very similar to pemphigus vulgaris in which vesicobullous and erosive to ulcerative lesions predominate in the skin and mucosal surfaces. Histologically, it bears some of the same features of pemphigus vulgaris but also features of erythema multiforme and the diagnosis is made on the basis of skin biopsies and investigation for underlying neoplasia.

Other cancers are sometimes associated with skin lesions. Superficial necrolytic dermatitis, although most commonly associated with liver disease, has also been found in dogs with pancreatic glucagonoma, in a cat with a pancreatic tumor, and recently in a cat with primary hepatic neuroendocrine carcinoma. One of the underlying causes for generalized adult-onset demodicosis is neoplasia, particularly indolent lymphoma.

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www.caninechiariinstitute.org/ – this site contains very useful information on canine Chiari-like malformation (accessed July 18, 2019).

169

Superficial Necrolytic Dermatitis

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Etiology/Pathophysiology

Superficial necrolytic dermatitis (SND), also known as hepatocutaneous syndrome and metabolic epidermal necrosis, is an uncommon, generally fatal, crusting and scaling skin disease, which is similar to necrolytic migratory erythema in humans. It has been described in dogs, cats, and black rhinoceroses. For the purposes of this chapter, the remaining discussion will be confined to the disease in dogs.

Superficial necrolytic dermatitis is an external manifestation of an internal disease, most commonly advanced hepatopathy, but it has also been associated with glucagonoma, ingestion of mycotoxins or long-term phenobarbital and phenytoin treatments. There is a recent case report describing SND associated with an insulin- and glucagon-producing pancreatic carcinoma. Diabetes mellitus can be a complication of this disease.

The exact etiopathogenesis of SND is currently unknown. Several studies investigating the serum amino acid profile of dogs with SND have found profound hypoaminoacidemia, indicating that this may participate in the development of skin lesions because amino acids are necessary to maintain cellular integrity in the epidermis. In one study, glutamic acid, phenylalanine, tryptophan, and ornithine were not significantly different but all other amino acids were 60% or less than the mean reference values for normal dogs. In 72% of the dogs studied, either glutamine or arginine was the most diminished plasma amino acid. Deficiencies in cutaneous essential fatty acids, zinc, and biotin have also been suggested to play a role in skin lesion development.

Signalment

Superficial necrolytic dermatitis is a disease of older dogs, with an average age of 10 years. Currently, there are not enough reported cases to enable accurate determination of breed or sex predilection, though one paper reported a predilection towards Shih tzus.

Clinical Signs

Skin lesions are mostly associated with those areas on the body where trauma naturally occurs, including the footpads, muzzle, and mucocutaneous junctions (periocular, perioral, anal and genital regions). It is not uncommon for lesions to also develop on the elbows, hocks, and margins of the pinnae. The development of cutaneous lesions is often the reason for owners to seek veterinary advice. The footpads typically become thickened, crusted, and fissured which often leads to pain and lameness (Figure 169.1). The elbows, hocks, and prepuce may be alopecic, erosive to ulcerated, erythematous, crusty, and scaly (Figure 169.2).

Secondary bacterial and fungal (often yeast) infections occur frequently and aggravate the cutaneous lesions associated with SND.

In cases where there is severe liver disease, dogs may have jaundice of the sclera and/or mucous membranes. In cases associated with diabetes, dogs may be polydipsic and polyuric.

There are many laboratory abnormalities associated with SND, which may vary according to the individual case and underlying disease. Those that have been reported include mild to severe normocytic, normochromic, nonregenerative anemia, microcytosis, hyperglycemia, glucosuria, and possibly ketonuria if the patient has developed diabetes mellitus. Urine amino acids including lysine, proline and 1-methylhistidine are increased. Increases in liver enzymes, hypoalbuminemia, decreases in creatinine and phosphorus, and increases in cholesterol and triglycerides have also been reported. It should be noted that there is no clinical

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Companion website: www.wiley.com/go/bruyette/clinical



Figure 169.1 Shih tzu with superficial necrolytic dermatitis. Pawpads are inflamed and hyperkeratotic.



Figure 169.2 Crusty lesion covering an inflamed and eroded lesion localized to the hock of a dog with superficial necrolytic dermatitis. Note that the lesion extends to the ventral aspect of the metatarsus. *Source:* Courtesy of Sheila Torres.

correlation between the severity of the liver pathology and the severity of the skin lesions.

Diagnosis

Skin biopsies of early lesions display very characteristic histologic changes. The epidermis has moderate to severe parakeratotic hyperkeratosis and acanthosis. There is both intercellular and intracellular edema with keratinocyte vacuolation in the upper half of the epidermis, which results in significant epidermal pallor. There is basilar epidermal hyperplasia. Because of the eosinophilic superficial keratin accumulation coupled with central pallor and basilar hyperplasia which stains deep blue, skin biopsies taken from early lesions display a striking "red" (eosinophilic), "white" (central pallor), and "blue" (basophilic basilar hyperplasia) pattern. Biopsy tissues taken from chronic lesions often lose the central pallor which could result in an erroneous diagnosis of zinc-responsive dermatosis. Epidermal pustulation, cleft formation, necrosis, erosions, and ulcers may also be seen. In the dermis, there may be a mild superficial perivascular lymphoplasmacytic infiltrate, edema with vascular ectasia, and congestion.

Abdominal ultrasound of dogs with hepatic disease and SND reveals a liver with a slightly irregular surface. There are variable sized hyperechoic regions (strands) present diffusely throughout the parenchyma. The strands encompass round to oval hypoechoic areas. The result is a "Swiss cheese" or "honeycomb" appearance to the liver. Biopsies taken from the liver display a vacuolar hepatopathy with parenchymal collapse. Pancreatic tumors may be visualized with ultrasound; however, if not visualized and the liver ultrasound is normal, glucagon levels should be assayed to rule out a glucagonoma.

Therapy

Treatment for dogs with SND is usually short-lived and largely unrewarding. Most cases are fatal, with life expectancy ranging from 1.7 to 6.4 months. One reported case survived for 32 months before being euthanized.

Treatment should initially be directed at stabilizing dogs with diabetes. Surgical resection can be beneficial in cases associated with glucagonomas but it is important to keep in mind that glucagonomas typically metastasize rapidly, so the improvement post surgery may be temporary. In one reported case, metastasis precluded surgery, and the dog was treated with subcutaneous octreotide (2 µg/kg twice daily), a somatostatin analog that inhibits glucagon release. Skin lesions and systemic signs improved within five days. The dosage was increased to nearly 3 µg/kg twice daily and all clinical signs improved further within 10 days. Anorexia was the main side-effect. The dose (1–3.4 µg/kg) and frequency of administration (2–3 times daily) of the octreotide injections were adjusted to maintain disease control with minimal side-effects. The dog was later euthanized due to progressive metastatic disease. In another case report, adipose tissue-derived mesenchymal stem cells were infused in addition to intravenous amino acids, 46 times over a 30 month period. Survival time was increased to 32 months after diagnosis.

Many dogs with liver disease have been treated with amino acids, either intravenously or orally. Amino acid solutions which have been used include Aminosyn® 10% solution (Abbott Laboratories), Procalamine® (B. Braun Medical Inc.) and Travasol® 8.5% amino acid injection (Baxter Healthcare) though no particular product has

been especially more beneficial than any other. Because of the hyperosmolarity of the solutions, they should be administered via a central venous catheter over an extended period of time (6–12h) and are repeated every 1–2 weeks until improvement is noted. The infusions are then repeated as necessary to help control relapses. Various doses have been suggested including 25 mL/kg or 500 mL per dog. Some dermatologists advocate administering the infusions three days in a row followed by once- to twice-weekly treatments thereafter and repeating as signs relapse. Clinical improvement may be noted within 5–10 days. If there is minimal to no response after four or more infusions, the therapy is unlikely to be of benefit to the patient. One dog was reported to survive for 24 months but was also treated with intravenous lipid infusions (Intralipid®, Baxter Healthcare) at 1.4 g/kg every 6.5 weeks. In that dog, it was proposed that the addition of the lipids was responsible for the extended survival time.

Oral supplementation with egg whites (cooked), zinc (e.g., zinc methionine 2 mg/kg PO q24h), powdered amino acid commercial supplements, and essential fatty acids has been used and may be of some benefit though all efficacy so far has been anecdotal.

Many dogs are treated with corticosteroids but this practice should be discouraged. The beneficial effects and improvement of clinical signs are short-lived and the corticosteroid may increase the patient's risk for developing diabetes mellitus. Secondary bacterial and/or fungal infections should be treated with appropriate antibiotics or antimycotics.

Prognosis

The prognosis is grave, with most dogs dying or being euthanized within a few months after the beginning of clinical signs.

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170

Miscellaneous Skin Diseases

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Sebaceous Adenitis

Etiology/Pathophysiology

Sebaceous adenitis (SA), also referred to as granulomatous SA, is an uncommon dermatosis that occurs in dogs and rarely in cats. The cause and pathogenesis of SA currently remain unknown, but several etiologic speculations exist, including an immune-mediated disorder targeting the sebaceous gland, a primary keratinization disorder that obstructs the sebaceous gland duct leading to inflammation and ultimately glandular destruction, a developmental, genetically inherited defect resulting in an inflammatory reaction directed against the sebaceous gland and, lastly, aberrant lipid metabolism and/or storage that eventually leads to sebaceous gland destruction.

Despite our lack of understanding of the pathomechanism, the endresult is inflammation and obliteration of the sebaceous glands, which normally produce and cover the skin with a protective layer of sebum. Sebum is instrumental in maintaining epidermal moisture and hydration and also has antimicrobial properties. Thus, a predisposition to secondary bacterial and/or *Malassezia* overgrowth or infection develops. Otitis may also occur. In addition, the inflammation that targets the sebaceous glands ultimately affects the hair follicles, which leads to abnormal changes in the quality of the hair coat, and eventually hair loss.

A genetic predisposition to develop the disease is known in some breeds. In standard poodles and akitas, the disease is inherited as an autosomal recessive trait. The mode of inheritance in the Havanese is currently being investigated.

Signalment

Most commonly, SA tends to afflict young adult to middle-aged dogs, but dogs of any age may be affected. The disease appears to be slightly more common in males. Sebaceous adenitis has been reported in over 50 breeds of dogs although specific breeds have been overrepresented including standard poodles, vizslas, akitas, springer spaniels, German shepherd dogs and their crossbreeds, Samoyeds, and Havanese. Possible increased frequency exists in chow chows, dachshunds, beagles, Lhasa apsos, miniature pinschers, and retrievers.

History and Clinical Signs

The cutaneous changes of SA generally include varying degrees of alopecia, hyperkeratosis, and excessive scaling, with follicular casts (i.e., scales surround a single hair or group of hairs) being a consistent feature. However, the clinical presentation is somewhat dependent on hair coat type and breed. In general, short-coated breeds seem to differ clinically from long-coated breeds. In short-coated breeds such as viszlas and dachshunds, the disease is manifested by symmetric to asymmetric, "moth-eaten," annular to coalescing and serpiginous to rarely diffuse areas of alopecia with fine, white scaling affecting the head, pinnae, neck, and trunk. Follicular casts are subtle and hairs are easily epilated. Pruritus is typically absent. In long-coated breeds, such as the standard poodle, the lesion distribution and lack of pruritus are similar to those of short-coated breeds, but diffuse alopecia is more common and obvious follicular casting is present. The hairs are often dull and brittle and may lose their typical architecture (i.e., the classic curly hair coat of the poodle becomes wavy or straight). The hair may also become lighter or darker in color. Groups of hairs surrounded by scales (i.e., follicular casts) are easily epilated (Figure 170.1).

Commonly, the lesions initially affect the head, pinnae, and neck and progress caudally to the dorsal and lateral

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Figure 170.1 Examples of follicular casts from an adult black standard poodle. Groups of hairs are ensheathed at their base by keratosebaceous debris.



Figure 170.2 Dorsum of an adult male castrated standard poodle with a notably darker, wavy to straight hair coat in those areas afflicted by SA. Scales and follicular casts are also present.

aspects of the trunk (Figure 170.2). In chronic cases, the lesions may extend to the legs and tail. Secondary bacterial folliculitis and *Malassezia* dermatitis are common. As excessive scale accumulates in the ear canal and aural orifice, otitis externa may occur. In some cases, otitis and excessive otic scale may be the sole manifestation of SA, as is commonly observed in the Havanese. This has also been reported in the vizsla, although the pinnal lesions were erosive to ulcerative (Figure 170.3).

When secondary infections are present, pruritus tends to intensify. Sebaceous adenitis in the akita may manifest in a more severe form with accompanying systemic signs such as fever, lethargy, and inappetence, which may result

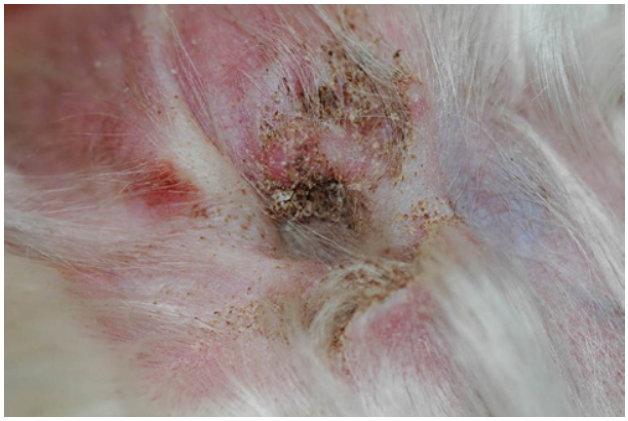


Figure 170.3 A 4-year-old male castrated Havanese with marked, fine white scaling associated with the medial and lateral aspects of the pinnae extending into the aural orifice and external ear canal.

in weight loss. Cutaneous signs are also more severe. Follicular casts and partial to generalized alopecia are present, but akitas also tend to develop diffuse erythema, greasy, generalized keratosebaceous scaling, and significant superficial and occasionally deep pyoderma.

In cats, few case reports exist describing the clinical manifestations of SA. Generalized adherent scaling and hypotrichosis has been described along with distinctive dark brown periocular scales/crusts.

Diagnosis

Initially, a tentative diagnosis of SA can be made based upon the signalment, history, and physical examination findings. Differential diagnoses include demodicosis, dermatophytosis, superficial bacterial folliculitis, keratinization disorders such as primary idiopathic seborrhea, ichthyosis, and vitamin A-responsive dermatosis, follicular dysplasia, zinc-responsive dermatosis, endocrinopathies, such as hypothyroidism, and hair cycle arrest (i.e., alopecia X). Autoimmune/immune-mediated differentials to consider include alopecia areata and pseudopelade. Surface cytology and deep skin scrapes should be performed in every case to evaluate for superficial bacterial folliculitis and *Malassezia* dermatitis, and to rule out demodicosis. A dermatophyte culture should be performed if clinically applicable. If an underlying endocrinopathy is suspected, appropriate screening tests, such as a complete blood count (CBC), serum chemistry profile, and urinalysis (UA), as well as thyroid function testing should be performed.

Biopsy and histopathology are needed in order to confirm the diagnosis of sebaceous adenitis. Multiple punch biopsies (3–5) should be procured from lesions of varying appearance and chronicity to improve confirmation of the diagnosis. It is important to include very early

lesions in order to identify the inflammatory reaction targeting the sebaceous glands. These lesions will likely be missed if only chronic, alopecic lesions are sampled. The histopathologic changes will vary depending upon the stage of the lesion sampled and include granulomatous to pyogranulomatous dermal inflammation targeting the sebaceous glands, to complete absence of sebaceous glands along with perifollicular fibrosis and varying degrees of follicular keratosis.

Therapy

As the pathomechanism of SA appears to be due to a combination of an immune-mediated inflammatory disease and a keratinization disorder, treatments have been aimed at controlling these two aspects and involve a combination of systemic and topical therapies to reduce further sebaceous gland inflammation and destruction, prevent secondary skin and otic infections, remove excessive scale, promote moisturization and protection of the skin, and improve the quality of the hair coat.

In mild cases of SA, topical therapy along with high doses of oral essential fatty acids (which can be used in all cases as an adjunctive therapy) can be effective. The suggested dose of omega-3 fatty acid supplementation is 180 mg eicosapentaenoic acid and 120 mg of docosahexanoic acid per 10 lb of body weight per day combined with omega-6 fatty acid supplementation. In general, topical therapy involves an initial bath using a keratolytic and keratoplastic shampoo, followed by an emollient rinse or oil treatment, and concluded with a final bath aimed at removing any residual oil and scale. In the interim, as often as daily to as infrequently as once-weekly treatments consisting of sprays and rinses, spot-on formulations, conditioners, and mousses with emollient, humectant, antimicrobial, and barrier repair functions are utilized.

Shampoos, such as those containing sulfur and salicylic acid, should be selected. These shampoos are commonly formulated with antimicrobials such as benzoyl peroxide (Oxiderm + PS®, Ceva Animal Health, Lenexa, KS, USA; DermaBenSs®, Dechra, Overland Park, KS, USA) or chlorhexidine (MPA Seba-Hex®, Vetoquinol, Forth Worth, TX, USA). Products containing benzoyl peroxide also act as excellent degreasers. The shampoo should be lathered well and allowed contact with the skin for 10 minutes while gently massaging followed by a fresh, lukewarm water rinse.

A variety of oil-based treatment regimens have been suggested to further assist in loosening and removing scales, follicular casts and crusts, and to replenish the skin barrier. These include a 50:50 mixture of water and baby oil or bath oil, such as Eucerin® skin calming dry skin body wash (Beiersdorf AG, Hamburg, Germany) or Alpha Keri® bath oil (Novartis Consumer Health, Parsippany, NJ, USA), or a mixture of 50–75% propylene glycol in water. The oil or propylene glycol mixture is allowed a contact time of 1–2 hours. Once soaking is complete, another bath is performed with the previous shampoo. Alternatively, a liquid dish-washing detergent can be used such as Dawn dish soap (Proctor and Gamble, Cincinnati, OH, USA), but may be too drying for some dogs. Frequency will depend on the severity of the disease, but it tends to be more frequent (1–3 per week) in the beginning and reduced as the patient improves (every 1–4 weeks). Between the bathing/oil treatment regimens, sprays such as DermAllay® oatmeal spray conditioner (Dechra) and Douxo® seborrhea micro-emulsion spray (Ceva) can be utilized for their moisturizing and humectant properties. Mousse formulations, such as Douxo seborrhea mousse (Ceva), provide another convenient means of restoring the skin barrier. When maintenance antimicrobial therapy is needed, Douxo chlorhexidine PS micro-emulsion spray or chlorhexidine climbazole mousse (Ceva) can be used once to twice daily to twice weekly for maintenance. For more refractory cases, daily application of 50–75% propylene glycol can be beneficial. Topical spot-on treatments, such as Dermoscent® Essential 6 spot-on (Bayer, Shawnee Mission, KS, USA) which contains omega-3/omega-6 fatty acids and essential oils, are easy to apply and can be efficacious. Initially, it is applied as directed once weekly for eight weeks and then decreased to once every two weeks. Another alternative is Douxo seborrhea spot-on (Ceva) which contains phytosphingosine, a natural component of the epidermis that plays a key role in barrier function. Oil soaks may eventually be replaced by these products if an acceptable response is noted. Finally, extra virgin olive oil and coconut oil have been anecdotally reported to be effective moisturizers. These products are inexpensive and also have mild antimicrobial properties.

In more severe cases of SA, systemic treatments should be utilized in conjunction with topical therapy and essential fatty acid supplementation. Among the systemic treatments, vitamin A, synthetic retinoids, a combination of a tetracycline antibiotic and niacinamide, and ciclosporin have been used for the management of SA with variable success. Retinoids have antiproliferative, antiinflammatory, and immunomodulatory effects and generally require 4–8 weeks before response is seen, although maximal response may not be appreciated until 3–4 months of therapy are achieved. Oral vitamin A (retinol) can be tried for milder cases of SA and appears to be a safe and efficacious form of adjunctive therapy for some dogs. Doses range from 400 to 1000 IU/kg PO daily. For more severe or refractory cases, synthetic retinoids such as isotretinoin or acitretin (1 mg/kg PO q12–24h) should be considered for a trial period of at least 4–8 weeks. If a positive response is

noted, the lowest effective dosage and frequency of administration should be used as maintenance therapy (i.e., 0.5–1.0 mg/kg PO q12–24h). These drugs are expensive and can be difficult to obtain as they are strictly regulated. Side-effects include keratoconjunctivitis sicca (KCS), polyuria and polydipsia due to xerostomia, vomiting, and diarrhea. Laboratory abnormalities can include elevation of liver enzymes, hypercholesterolemia, and hypertriglyceridemia.

All retinoids are potent teratogens. Monitoring should include pretreatment measurement of tear production via a Schirmer tear test (STT) and a serum biochemical profile at minimum. The authors typically repeat the STT and serum chemistry profile in 1–2 months and if no abnormalities are noted, then once to twice a year.

The use of tetracycline, doxycycline or minocycline and niacinamide may be beneficial for the treatment of SA, especially in short-coated breeds, given the antiinflammatory and immunomodulatory actions that can be gained when these drugs are utilized in combination. It generally requires 4–8 weeks before response to this therapy is seen, although maximal effect may not be appreciated until 3–4 months of therapy are achieved. Side-effects include vomiting, diarrhea, and decreased appetite. Hepatotoxicity is also possible, albeit rare. Tetracycline and niacinamide are dosed at 250 mg for dogs <10 kg and 500 mg for dogs >10 kg q8h. When doxycycline is utilized in place of tetracycline, a dosage of 5–10 mg/kg PO q12h is suggested and minocycline can be dosed at 5–12.5 mg/kg PO q12h. The dosage of niacinamide remains at 250 mg for dogs <10 kg and 500 mg for dogs >10 kg q8h. If a positive response is noted, the lowest effective dosage and frequency of administration should be used as maintenance therapy.

Ciclosporin is currently the preferred treatment for SA, especially in severe cases or those that have not responded acceptably to topical therapy and/or other systemic treatments. Ciclosporin is a calcineurin inhibitor with a number of immune-modulatory functions. Perhaps most important in the case of SA is its ability to impair T lymphocyte function. Ciclosporin has also been shown to increase the numbers of sebaceous glands. Ciclosporin (Atopica®, Elanco US, Greenfield, IN, USA) can be administered at an initial dosage of 5 mg/kg PO q24h. Ciclosporin has an extended lag time of 4–6 weeks before clinical response may be seen. If a positive response is noted, the lowest effective dosage and frequency of administration should be used as maintenance therapy. Side-effects include vomiting, diarrhea, anorexia, gingival hyperplasia, papillomatosis, secondary infections including opportunistic urinary tract infections, hirsutism, and involuntary shaking. More serious side-effects include nephropathy, hepatopathy, bone marrow suppression, and lymphoplasmacytoid dermatosis although these effects appear to be extremely rare with daily doses of approximately 5 mg/kg/day. The authors typically recommend a baseline CBC, serum chemistry profile, UA, and urine culture. These tests are repeated every six months to yearly to monitor for possible side-effects.

In general, response to corticosteroids is poor. They can be tried as a last resort if there has been no response to other therapeutic options or in cases where those options are cost prohibitive. A starting dosage of 1 mg/kg/day PO can be used and gradually reduced to the lowest dosage and frequency possible. There may be a more favorable response in cases where the histopathology findings reveal severe inflammation.

It is important to recognize and treat secondary infections, as they can greatly contribute to the patient's morbidity. The reader is referred to Chapters 158, 166 and 167 in this section regarding the diagnosis and treatment of pyodermas, *Malassezia* dermatitis, and otitis.

Prognosis

The prognosis of SA ultimately depends upon the severity and chronicity of the disease and the degree and recurrence of secondary infections. The response to therapy is quite variable from one patient to the next. The disease in the akita can be particularly refractory. There is no cure for SA and it has a chronic, often progressive nature which requires lifelong therapy. In and of itself, SA is not a lethal disease but a clinically and cosmetically acceptable response is not always obtained and/or may be too expensive or labor intensive for the owner. For these reasons, euthanasia may ultimately be chosen.

Eosinophilic Dermatitis

Etiology/Pathophysiology

Eosinophilic dermatitis, also known as eosinophilic dermatitis with edema and eosinophilic cellulitis, is an uncommon syndrome that has been described in dogs and has been compared to Wells syndrome in humans. The disease is presumably multifactorial with myriad possible triggers including allergic and parasitic diseases, arthropod bites, immune-mediated disease, stress, and drugs, which culminates in an allergic hypersensitivity and/or immune-mediated reaction. In one study, more than 50% of the dogs developed eosinophilic dermatitis following treatment for vomiting and diarrhea. In a more recent study that focused solely on the development of eosinophilic dermatitis in dogs with signs of gastrointestinal disease, particularly vomiting, diarrhea and

hematochezia, it was found that pancreatitis, inflammatory bowel disease, and adverse food reaction were the most common triggers, although the cause of the gastrointestinal signs could not be documented for all dogs. In some dogs, an adverse drug reaction was considered as a possible trigger.

Signalment

Labrador retrievers and their crosses appear to be overrepresented, but the disease can occur in any breed. Age and sex predilections have not been identified.

History and Clinical Signs

Eosinophilic dermatitis is a visually distinctive disease. Lesions develop acutely and are characterized by arciform and serpiginous erythematous macules and plaques with edema (Figure 170.4). The macules often have a targetoid appearance although diffuse erythroderma may be present. The ventral abdomen and thorax are commonly affected, as are the pinnae and face (Figure 170.5). Edema may be generalized, affecting the face and limbs. Often, patients are moderately to severely pruritic. Lymphadenopathy may be present.

Diagnosis

The diagnosis of eosinophilic dermatitis is based upon its distinct clinical presentation and disease course along with biopsy and histopathology. Differential diagnoses include erythema multiforme, vasculitis, and sterile neutrophilic dermatosis. Multiple biopsies should be procured early on from several different-appearing lesions. Edematous areas, if present, should also be sampled. Histopathologic findings are variable and include mild to severe perivascular to diffuse eosinophilic dermatitis with varying amounts of edema, which is often protein rich in severe cases. Flame figures (degranulating eosinophils associated with collagen fibers) may be noted along with variable degrees of vascular damage. CBC and serum chemistry abnormalities are not common. Occasionally, peripheral eosinophilia and basophilia may be documented. In cases associated with gastrointestinal disease, hypoalbuminemia is a common finding.



Figure 170.4 Abdomen of an adult male castrated Labrador retriever with serpiginous erythematous macules and edematous plaques.

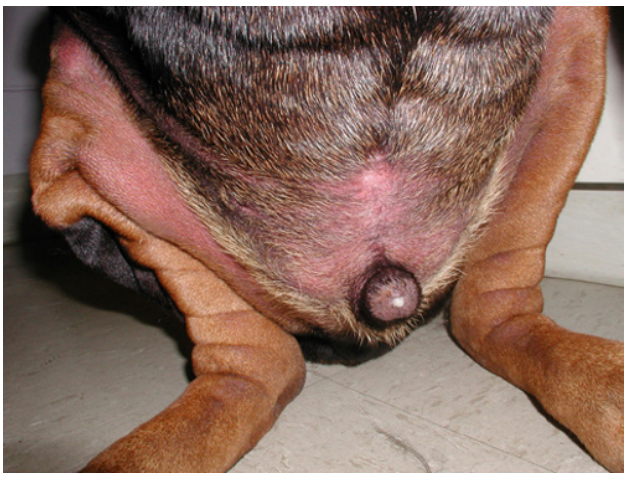


Figure 170.5 Diffuse erythroderma and edema present on the ventral abdomen and pelvic limbs of a 3-year-old female spayed dachshund.

Therapy

Appropriate drug withdrawal is paramount when a cutaneous adverse drug reaction is suspected. In addition, patients respond favorably to antihistamines and/or corticosteroids. Diphenhydramine or hydroxyzine may be administered at a dosage of 2 mg/kg PO q8–12h. In a recent study, cetirizine was the most commonly prescribed antihistamine with doses of 0.6–1.1 mg/kg PO q24h. Cetirizine has several antieosinophilic effects that may make it particularly effective for treating eosinophilic dermatitis. Reported starting dosages of prednisone include a range of 0.6–2.8 mg/kg/day. In milder forms of the disease, therapy may not be required with lesional self-resolution occurring within a few weeks. Topical glucocorticoid therapy with hydrocortisone, betamethasone, or triamcinolone may also be considered. However, the treatment duration should not extend beyond two weeks given the risk of localized cutaneous atrophy and other complications that may occur from prolonged topical steroid application.

Prognosis

Eosinophilic dermatitis usually carries a favorable prognosis. Disease resolution tends to be swift, especially when underlying triggers are identified and removed

(i.e., drugs). Typically, treatment duration varies from one to four weeks, and only rarely will there be recurrences or a waxing and waning course.

Sterile Neutrophilic Dermatosis

Etiology/Pathophysiology

Sterile neutrophilic dermatosis is a rare disease which closely resembles acute febrile neutrophilic dermatosis (Sweet syndrome) in humans. The few documented cases in the veterinary literature all involve dogs. In people, the disease is typified by pyrexia and a neutrophilic leukocytosis along with painful papular to nodular skin lesions that consist predominantly of a diffuse infiltration of mature neutrophils within the dermis on histopathology. Extracutaneous sites of neutrophilic inflammation and concurrent disease processes have also been identified in humans, including respiratory and gastrointestinal tract infections, inflammatory bowel disease, arthritis, and neoplasia, although many cases are idiopathic. Disease development has also been associated with various drugs.

In dogs, the clinicopathologic abnormalities mirror those observed in humans. Concurrent neutrophilic inflammation has been reported to affect the lungs, heart, esophagus, and various joints. Adverse drug reactions appear to be an important cause of the disease in dogs. Several case reports have been associated with the administration of carprofen. Firocoxib has also been implicated in an additional case report. The pathogenesis is not completely understood, but is thought to involve an immune-mediated process.

History and Clinical Signs

There are currently no known breed, gender, or age predilections given the paucity of reported cases. Similar to the disease in humans, extracutaneous signs are commonly associated with the cutaneous manifestations, but not obligatory. Pyrexia is a key feature, although it is not always documented. Other reported clinical abnormalities include anorexia, lethargy, weakness, lameness, and lymphadenomegaly. A mature neutrophilia may be present. Other laboratory abnormalities may be present and are reflective of the various underlying disease processes.

Cutaneous lesions include the acute development of erythematous macules and papules as well as pustules and plaques. Ulcerations of the oral cavity and the body have been reported. The ventral aspect of the abdomen, axillae, and groin are preferentially involved, although the lesions may occur anywhere. Edema may be present and can extend ventrally to involve the legs. Pruritus is usually absent.

Diagnosis

The diagnosis of sterile neutrophilic dermatosis is based upon recognition of the sudden onset of systemic signs that precede or occur simultaneously with the cutaneous lesions in conjunction with the presence of a neutrophilic leukocytosis and compatible histopathologic findings. Differential diagnoses include infectious dermatitides, superficial pyoderma, pemphigus foliaceus, sterile pustular erythroderma of miniature schnauzers, eosinophilic dermatitis and edema, erythema multiforme, and cutaneous adverse drug reactions. The diagnostic workup should include skin cytology, CBC, serum chemistry profile, and UA. Titers for tick-borne diseases should also be considered, depending upon geographic locale and potential for exposure. Thoracic radiographs and abdominal ultrasound are also indicated to evaluate for underlying diseases. Multiple skin biopsies should be procurred and tissue cultures submitted. Histopathologic findings that are supportive of sterile neutrophilic dermatosis include dermal edema with a moderate to severe perivascular to diffuse neutrophilic infiltrate.

Therapy

Treatment of this disease includes the discontinuation of potentially offending drugs, along with supportive care and immunosuppressive doses of corticosteroids. A positive response may be evident within 48 hours and remission has been documented to occur within a week in some cases. In other cases, therapy may be slowly tapered over the course of four weeks. In severe cases, intravenous or subcutaneous administration of dexamethasone followed by a tapering course of prednisone may be considered.

Prognosis

Sterile neutrophilic dermatosis has a fair to good prognosis depending upon the underlying etiology. It stands to reason that in cases where the underlying disease is severe and untreatable, the prognosis may be grave.

Ichthyosis

Etiology/Pathophysiology

Canine ichthyosis is a rare hereditary cornification disorder recognized in various breeds such as Norfolk terriers, Jack Russell terriers, golden retrievers, and American bulldogs. The disease in dogs has been typically classified as either epidermolytic or nonepidermolytic based on histopathologic findings. With the exception of Norfolk terriers and a Labrador cross, all

other breeds reported to date have had the nonepidermolytic form.

The disease is caused by the abnormal expression of protein or lipid molecules that form the stratum corneum structure. Genetic studies have identified different mutations of these molecules according to the breed investigated as follows:

- Norfolk terriers – a splice-site mutation in keratin 10 (*KRT10*)
- golden retrievers – a mutation in the *PNPLA1* gene that participates in lipid organization and metabolism in the outer epidermis
- American bulldogs– a mutation in the *NIPAL-4* gene resulting in decreased expression of the protein icthyin
- Jack Russell terriers – a loss-of-function mutation in transglutaminase 1 (*TGM1*) which mediates calcium-dependent cross-linking of proteins that form the cornified envelope.

A congenital ichthyosiform disease associated with keratoconjunctivitis sicca has been described in Cavalier King Charles spaniels but a candidate gene has not been identified to date.

More recently, a new variant of congenital ichthyosis was described in 14 Great Dane puppies based on clinical, histopathologic, and transmission electron microscopy findings. Pedigree analysis of 13 of the 14 puppies revealed that all dogs were related. The disease in these puppies most resembles the congenital, autosomal recessive, nonepidermolytic, lamellar ichthyosis described in the golden retriever. However, unique histologic differences were observed which have yet to be reported in ichthyotic dogs. Of note, enlarged sebaceous glands that were also composed of numerous degenerative sebocytes containing an alcianophilic, lipid-rich material within the cytoplasm were documented. This same material was also identified within dilated hair follicle lumina.

An autosomal recessive mode of inheritance has been reported for all breeds where a pedigree analysis could be performed thus far.

Signalment

As for most hereditary disorders, the clinical signs are typically recognized early in life. The disease presents at birth in Jack Russell terriers, Norfolk terriers, and Cavalier King Charles spaniels. It is reported to manifest before weaning in American bulldogs and has a variable age of onset in golden retrievers (3 weeks to 3 years).

History and Clinical Signs

The disease phenotype can vary according to the breed and this may be partially the result of different genetic mutations.

Golden Retriever

Affected dogs present with small to large, attached to loose, white to gray scales localized primarily on the neck, trunk, rump, and ventrum (Figure 170.6). A characteristic early sign is a dark, sandpaper-like appearance of the ventral glabrous skin (Figure 170.7). Pruritus is typically not present but, may occur if secondary infections develop. Clinical signs may wax and wane with periods of remission and exacerbation.

Norfolk Terrier

At birth, the disease is characterized by formation of superficial bullae and erosions after mild mechanical



Figure 170.6 One-year-old golden retriever with ichthyosis. Large, loose to adhered, white to gray scales localized to the lateral trunk.



Figure 170.7 Eight-month-old golden retriever with ichthyosis. The ventral abdomen is covered with adhered gray scales, giving a hyperpigmented appearance. The skin has a sandpaper-like texture when gently palpated.

trauma. In adulthood, the skin fragility persists but areas of dark gray hyperkeratosis and hyperpigmentation will develop and are worse in the intertriginous regions. Pruritus has not been described and footpads, claws, teeth. and hairs were reported to be normal.

Jack Russell Terrier

Affected dogs are born with thick, large, adherent, white to dark scales in areas with sparse hair coat and loosely adherent scales in other parts of the body. Footpads are reported to be moderately hyperkeratotic and the nails soft. Secondary bacterial and *Malassezia* infections may be a complicating problem.

American Bulldog

Shortly after birth, puppies present with a disheveled hair coat and erythema associated with tightly adherent tan scales localized to the hairless skin (axilla, abdomen, groin) which acquires a wrinkled appearance. In adulthood, the hairless areas develop a reddish-brown discoloration. Large, loosely adherent, white to tan scales are present throughout the body (Figure 170.8). Foodpad hyperkeratosis is a rare finding in adult dogs. Affected dogs are very prone to developing *Malassezia* overgrowth which can be severe and result in pruritus (Figure 170.9).

The clinical appearance of American bulldog ichthyosis is frequently misdiagnosed as atopic dermatitis which can indeed co-exist in some dogs.

Cavalier King Charles Spaniel

Puppies are born with a rough and curly hair coat and as they become older, the glabrous skin becomes hyperpigmented and hyperkeratotic, particularly around the nipples and inguinal region. Scales, footpad hyperkeratosis and abnormal nails, that may slough, develop at about 6 months of age or older (Figure 170.10). Keratoconjunctivitis sicca is noted as the puppies open their eyes and can be mild to severe.



Figure 170.8 Two-year-old American bulldog with ichthyosis. Loosely adhered scales localized throughout the trunk.

Great Dane

Clinically, Great Dane puppies present with generalized fine, dry, white to yellow scaling along with a greasy, leathery appearance to the axillary and inguinal regions. Marked skin wrinkling is present on the head, muzzle and distal limbs.

Other Breeds

Ichthyosis has been anecdotally reported in West Highland white terriers and English springer spaniels. An epidermolytic form was described in a Labrador cross based on histopathologic findings. More recently,



Figure 170.9 Same dog shown in Figure 170.8. *Malassezia* overgrowth present on the flank and ventral abdomen resulting in a brownish discoloration of the skin and hair coat.



Figure 170.10 One-year-old Cavalier King Charles spaniel with ichthyosiform disease showing severe footpad hyperkeratosis.

ichthyosis was documented in a goldendoodle dog based on histopathologic findings and genetic testing, which identified the *PNPLA1* mutation found in golden retrievers, indicating that the disease was likely inherited from its golden retriever predecessors.

Diagnosis

The diagnosis historically has been based on the characteristic history, clinical signs, and histopathologic findings. When performed, skin biopsies should be submitted to a pathologist with experience in dermatology. A commercially available genetic test is now offered through Optigen (www.optigen.com/) and is easily performed using a venous blood sample and has become the authors' primary means of confirming a diagnosis of ichthyosis in breeds where testing is an option. Electron microscopy and genetic studies are needed to characterize the molecular abnormality and mode of transmission.

Therapy

The treatment goals should be to prevent/treat secondary infections and reduce the excessive scaling, hyperkeratosis, and inflammation by restoring the stratum corneum barrier. This may be achieved by various topical therapies which should be tailored to the patient's needs. Shampoos with keratolytic and keratoplastic properties such as sulfur and salicylic acid, followed by a good moisturizer, can be used 2–3 times weekly. Products containing lipids such as phytosphingosine (Douxo seborrhea spot-on or spray), or fatty acids and essential oils (Dermoscent Essential 6 spot-on) can be used after bathing. Combinations of oral omega-3 and omega-6 fatty acids can be used as adjunctive therapy. Secondary infections should be treated appropriately with topical and/or systemic antifungals or antibiotics as required for each individual patient.

Prognosis

Clients have to understand that ichthyosis is a noncurable condition and the prognosis to achieve disease control is generally fair. Veterinarians should become familiar with the different clinical presentations and breed-related disease severity and educate clients on what to expect.

Eosinophilic Granuloma Complex

Etiology/Pathophysiology

Feline eosinophilic granuloma complex is a group of lesions that affect the skin, mucocutaneous junctions, and oral cavity. They can develop in cats with adverse food reaction, atopic dermatitis, flea bite allergy or mosquito bite hypersensitivity, suggesting an immunologic dysregulation. The role of bacteria in lesion development is still questionable but certain lesions have improved significantly or resolved with antibiotic therapy. Many cases remain idiopathic and some cats may be genetically predisposed to develop this condition. Cats can have a single lesion, multiples of the same type or a combination of different ones. Lesions may be refractory to treatment, resolve with or without treatment and not return, or be recurrent.

Signalment

There is no breed, sex or age predilection but linear granuloma lesions typically develop in cats less than 2 years of age.

History and Clinical Signs

Lesions associated with the complex include eosinophilic granuloma, eosinophilic plaque, and indolent ulcer.

Eosinophilic Granuloma

This is the only true granulomatous lesion of the complex and has various clinical presentations such as nodules, papules or linear plaques. They can be single or multiple and develop anywhere on the body, including the lips (pouting lip), chin (fat chin), oral cavity, footpads, pinnae, caudal aspect of thighs or other areas (Figure 170.11).



Figure 170.11 A cat with eosinophilic granuloma localized to the feet. The digits of the right hind foot are swollen and erythematous. The footpad of the third digit is also swollen and has a focal area of erosion to ulceration.

Lesions are often erythematous and those localized in the oral cavity and footpads are more likely to erode or ulcerate and have pale foci of necrosis. Pruritus is variable and circulating eosinophilia may be present.

Eosinophilic Plaque

Plaque lesions are typically multiple and coalescing, eroded to ulcerated and more often localized to the ventral abdomen and medial thighs (Figure 170.12). Pruritus is typically present and cats with eosinophilic plaques often have an underlying allergic disease. Peripheral lymphadenopathy and circulating eosinophilia may be present.

Indolent Ulcer

This is also known as eosinophilic ulcer or rodent ulcer. It is characterized by a well-demarcated ulcer which has an elevated border and a center that is pinkish to yellowish. The lesion is typically localized to the upper lip and can be very extensive and span the philtrum or be adjacent to the upper canine tooth (Figure 170.13). Pruritus is not present.

Diagnosis

Typically, diagnosis is based on the history and clinical appearance of the lesions. A biopsy will confirm the diagnosis and should be performed when lesions develop in older cats to exclude neoplasia, are refractory to treatment or have an unusual presentation. Cytology is important to determine the presence of bacterial infection. The presence of intracellular cocci indicates an infection but extracellular rods suggest oral contamination. Eosinophils may not be found on cytologic samples.



Figure 170.12 Five-year-old domestic longhair cat with eosinophilic plaques. Coalescing erythematous plaques with an eroded and moist surface are localized to the caudal-ventral abdomen and inner thigh.



Figure 170.13 One-year-old cat with an eosinophilic ulcer. This cat also has eosinophilic granuloma lesions localized to the oral cavity.

Therapy

Identifying and controlling the underlying disease is an important part of the treatment regimen as it may prevent recurrences. Most cases respond well to oral glucocorticoid therapy such as prednisolone (2.2–4.0 mg/kg), methylprednisolone (2.0–3.0 mg/kg), triamcinolone (0.2–0.3 mg/kg) or dexamethasone (0.3–0.6 mg/kg), all administered daily until remission and then every other (prednisolone and methylprednisolone) or every third day (triamcinolone and dexamethasone) as maintenance. Injection of methylprednisolone acetate should only be considered if the cat cannot receive oral therapy. The recommended dose is 4.0–5.0 mg/kg subcutaneously (SC) or intramuscularly (IM) given every 2–4 weeks until remission. Cats are more prone to develop diabetes mellitus with long-acting, injectable glucocorticoids. Ciclosporin at 5.0–7.5 mg/kg/day can be used in refractory cases or cases that cannot tolerate glucocorticoid therapy. The lowest possible maintenance dosage should be tried. Chlorambucil at 0.1–0.2 mg/kg/day until remission and then tapered to every other day can be used in recalcitrant cases. A small number of cats have responded to interferon-alpha at 300–1000 units/day PO or SC for 30 days.

Radiotherapy, cryosurgery, surgical excision, and laser therapy are options for single lesions refractory to medical therapy. Eosinophilic ulcers are most likely to benefit from these treatment modalities but recurrences are common.

Prognosis

Most lesions respond well to treatment but some are quite refractory. In addition, recurrences are common and a triggering cause for lesion development is often not determined.

Symmetric Lupoid Onychitis (Symmetric Lupoid Onychodystrophy)

Etiology/Pathophysiology

The cause of symmetric lupoid onychitis (SLO) is currently unknown but the predisposition of some breeds to develop the disease suggests that genetics plays a role. Moreover, the risk of developing SLO in the Gordon setter has been associated with the dog leukocyte antigen (DLA) class II alleles.

Signalment

Most dogs develop the disease between 2 and 6 years of age but it can occur at any age. Gordon setters, English setters, and German shepherd dogs appear to be predisposed but SLO has been recognized in various breeds. There is no sex predilection.

History and Clinical Signs

Onychomadesis (sloughing of claws), onycholysis (separation of claw structure distally and progressing proximally), and paronychia (inflammation of claw folds), causing the dog to lick the paws, along with lameness, are typically the initial clinical presentation (Figure 170.14).

It may start in one or more claws of a single paw but within weeks, it spreads to involve most, if not every, claw of all four paws. Regrown nails are short, misshapen, dry, and brittle (Figure 170.15). Secondary infection associated with purulent exudate is common. The disease only affects the paws.

Diagnosis

The diagnosis is generally based on the history and characteristic clinical presentation but a claw biopsy (onychectomy and submission of the entire third phalanx) may be needed to rule out other causes of nail disorders and confirm the histopathologic changes expected with SLO. Cytology of exudate is necessary to determine the presence of bacterial infection and culture and susceptibility should be considered based on the cytologic findings and the dog's history of antibiotic therapy.



Figure 170.14 Seven-year-old Labrador retriever with symmetric lupoid onychitis. The claw of the fifth digit is showing onycholysis (i.e., separation of the claw structure).



Figure 170.15 Four-year-old mixed-breed dog with symmetric lupoid onychitis. Claws are misshapen, short, and brittle.

Therapy

No single treatment is universally effective in SLO. High doses of omega-6/omega-3 essential fatty acids combined with a tetracycline antibiotic (e.g., doxycycline at 5.0–10.0 mg/kg q12h) and niacinamide (250 mg for dogs <10 kg and 500 mg for dogs >10 kg q8h) are commonly used as the initial therapy. Pentoxifylline at 15–20 mg/kg q12h to q8h can be added to the treatment regimen. More

severe cases may require other immunomodulatory drugs such as oral prednisolone (1.0–2.0 mg/kg/day), azathioprine (2.2 mg/kg/day) or ciclosporin (5 mg/kg/day). Remission should be expected in two weeks with the prednisolone and 4–6 weeks with the ciclosporin and azathioprine; therefore, taper the dose to avoid undesirable side-effects or discontinue treatment if no improvement. Amputation of the third phalanx should be considered in cases that are refractory to medical therapy.

An expected response to therapy translates to cessation of onycholysis and onychomadesis and resolution of pain. In these cases, affected claws will regrow but will have an abnormal structure. It may take months before any significant improvement can be noted.

Prognosis

Prognosis is poor for cure and fair for disease control. Owners have to understand that claws will appear abnormal despite satisfactory improvement of the claw disorder.

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Section 13

Diseases of Bone and Joint

171

Skeletal Development and Homeostasis

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Skeletal Development and Growth

Skeletal Development

The first evidence of the developing axial and appendicular skeleton is seen during the embryonic period (day 19–35 after fertilization) when mesenchymal cells condense in the areas of the future bones. The mesenchymal model transforms into a cartilage model (the anlage), which then enlarges and transforms into mature bone both pre- and postnatally. The enlargement of the cartilaginous bones occurs by formation of new cartilage in diaphyseal and epiphyseal growth centers and growth plates. The newly formed cartilaginous bones transform into mature bone via the processes of endochondral and intramembranous ossification (see later). Joints cavities between the developing bones are formed by the processes of segmentation and cavitation. The formation of the joint surfaces (see later) and intraarticular structures follows thereafter.

Most of the longitudinal growth of long bones is contributed by the growth plates (approximately 75–80%) and epiphyseal growth centers (approximately 20–25%), with a minor contribution by the diaphyseal growth center. In dogs, most bone length growth occurs when the animal is between 12 and 26 weeks of age. This period is characterized by the most rapid rate of bone length growth and endochondral ossification, both in epiphyseal growth centers and growth plates, that a dog will experience during its entire lifetime. In addition, growth and mineralization of many epiphyseal growth centers commence and cease at predetermined times. At the end of this period, cartilage only persists between the epiphysis and the metaphysis (growth plate) and at the articular surface covering the epiphyses. Growth plate-associated longitudinal growth continues thereafter at a much slower rate until the process stops completely and the cartilaginous growth plates are replaced by bone (growth plate fusion). Just as with the epiphyses, the growth cessation and "fusion" of growth plates occur at predetermined times (Table 171.1). The rate of skeletal development and the final bone size vary widely among canine and feline breeds.

Intramembranous and Endochondral Ossification

Bone is formed through two fundamentally distinct mechanisms: endochondral ossification (EO) and intramembranous ossification (IO). The key feature of EO is that it involves the sequential resorption of hyaline cartilage that is replaced with bone. Under physiologic conditions, EO takes place in diaphyseal and epiphyseal growth centers, growth plates and – at a very slow rate – at articular surfaces. Endochondral ossification also occurs under pathologic conditions and as a repair process. Examples are secondary fracture healing, osteophyte formation, synovial osteochondromatosis, and heterotopic bone formation.

Intramembranous ossification occurs through condensation and differentiation of mesenchymal tissues, without the requirement for an intermediate cartilage form. During the embryonic period, it plays a role in the development of flat bones (e.g., desmocranium). Later during development, IO takes place in basic multicellular units (BMU or osteon) in Haversian canals, and on endosteal, periosteal, and trabecular surfaces. It provides an important mechanism for appositional bone growth at the periosteal (outer) surface of bone, resulting in diaphyseal circumferential growth (i.e., widening) of bones over time. Intramembranous ossification occurs under pathologic conditions and/or as repair process seen, for example, in panosteitis, hypertrophic osteoarthopathy, and primary fracture healing.

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Table 171.1 Epiphyseal growth center appearance and growth plate fusion of selected bones in immature dogs

Anatomic site		Age when ossification center appears	Age when fusion occurs
Humerus	Diaphysis	Birth	
	Proximal epiphysis	1–2 wk	10–13 mo
	Distal epiphysis		6–8 mo to shaft
	Medial condyle	2–3 wk	6 wk to lateral condyle
	Lateral condyle	2–3 wk	
	Medial epicondyle	6–8 wk	6 mo to condyle
Radius	Diaphysis	Birth	
	Proximal epiphysis	3–5 wk	6–11 mo
	Distal epiphysis	2–4 wk	8–12 mo
Ulna	Diaphysis	Birth	
	Olecranon	8 wk	6–10 mo
	Distal epiphysis	8 wk	8–12 mo
Femur	Diaphysis	Birth	
	Proximal epiphysis (head)	2 wk	7–11 mo
	Trochanter major	8 wk	6–10 mo
	Trochanter minor	8 wk	8–13 mo
	Distal epiphysis		8–11 mo to shaft
	Trochlea	2 wk	3 mo condyle to trochlea
	Medial condyle	3 wk	
	Lateral condyle	3 wk	
Tibia	Diaphysis	Birth	
	Medial condyle	3 wk	6 wk to lateral
	Lateral condyle	3 wk	6–12 mo to shaft
	Tuberosity	8 wk	6–8 mo to condyle 6–12 mo to shaft
	Distal epiphysis	3 wk	8–11 mo
	Medial malleolus	3 mo	5 mo
Fibula	Diaphysis	Birth	
	Proximal epiphysis	9 wk	8–12 mo
	Distal epiphysis	2–7 wk	7–11 mo
Tarsus	Talus	Birth–1 wk	
	Fibular	Birth–1 wk	

Source: Modified from Owens JM. *Radiographic Interpretation for the Small Animal Clinician*. St Louis, MO: Ralston Purina Company, 1982, and Ticer JW. *Radiographic Technique in Small Animal Practice*. Philadelphia, PA: Saunders, 1975.

Growth-Plate Associated Growth

Growth plates facilitate bone length growth by the formation of new cartilage. The volume increase of cartilage in a growth plate is a function of chondrocyte proliferation, chondrocyte enlargement, and matrix formation. Because growth in width of a growth plate is constrained, the newly formed cartilage pushes the epiphysis away from the metaphysis, thus elongating the bone. At about the same time – albeit with a different circadian rhythm – growth plate cartilage is converted into bone at the junction of the growth plate and the metaphysis via EO. Because the rate of bone length growth and the rate of advancement of the EO mineralization from the metaphysis are approximately the same, the thickness of a growth plate will not vary much from day to day.

The growth plate is located between the epiphysis and metaphysis, and may be divided into a resting zone, a proliferative zone, a hypertrophic zone, and a mineralization zone.

Changes in the morphology of the chondrocytes and the volume and composition of their surrounding matrix in the different zones of the growth plate represent the temporal alterations taking place through a chondrocyte's life-span. Chondrocytes in the resting zone are primarily stem cells, that divide at a slow rate, and daughter cells. The daughter cells initially assume a flat morphology and divide, slowly enlarge, and synthesize a type 2 collagen and proteoglycan rich matrix; they are organized in so-called clones, chondrons or columns. Cells in this stage of the lifecycle are located in the proliferative zone. Then, chondrocytes suddenly and rapidly increase their cell volume by active swelling, while continuing the synthesis of matrix. Chondrocytes in this stage of their life cycle are spheroidal and relatively large and are located in the hypertrophic zone. Shortly thereafter, chondrocytes achieve their final size and shape and convert their surrounding matrix into one that is permissive of mineralization. This cell type is located in the zone of mineralization on the metaphyseal side of the growth plate. Chondrocytes abutting the metaphyseal vasculature die abruptly, presumably via the process of apoptosis. The life-span of chondrocytes varies and is mostly dependent on the growth plate location, the animal's age, breed, and species.

The regulation of chondrocytic proliferation and hypertrophy, the main determinants of bone length growth, is complex and facilitated by various growth factors, transcription factors, extracellular matrix proteins, and cell–matrix interactions. The traditional understanding is that growth hormone while acting on stem cells promotes the formation of insulin-like growth factor-1 (IGF-1)-responsive daughter cells. Then, through autocrine and paracrine systems, IGF-1 stimulates clonal expansion of chondrocytes (dual effector theory). The change from a proliferative chondrocyte phenotype to a hypertrophic chondrocyte phenotype is mainly controlled by a local feedback loop involving parathyroid hormone-related peptide (PTHrP), Indian hedgehog (IHH), and transforming growth factor-beta (TGF-beta). However, other regulators also may be involved. More recently, transcription factors, extracellular matrix proteins, and cell–matrix interactions functioning as regulators of chondrocytic proliferation and differentiation have been identified. Research in this area is largely driven by these regulators' role in the etiology and pathogenesis of skeletal dysplasias. Discussion of these regulatory mechanisms and canine and feline skeletal dysplasias is beyond the scope of this chapter.

Essential to EO in the growth plate is the sequential resorption of growth plate cartilage and its replacement by metaphyseal bone. Chondrocytes with increased membrane activity of alkaline phosphatase, in the zone of mineralization, undergo their terminal differentiation. They synthesize type X collagen and the surrounding matrix now includes chondrocalcin, osteonectin, and osteopontin. Chondrocytes juxtaposed to the metaphyseal vasculature (terminal hypertrophic chondrocytes) die abruptly by apoptosis and their space is invaded and taken over by metaphyseal blood vessels, a process facilitated by metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF) produced by hypertropic chondrocytes. Osteoprogenitor cells migrate via the newly formed metaphyseal vessels, differentiate into osteoblasts, and form woven bone on the calcified cartilage matrix of the longitudinal septa. The so-called primary spongiosa thus formed consists of a lattice of calcified cartilage and woven bone. The move from hyaline cartilage to bone is completed with the replacement of primary spongiosa by secondary spongiosa, a lamellar bone. The regulation of the conversion of cartilage to woven bone is complex, but it appears that genetic, nutritional, metabolic and mechanical factors all play a role. Defects of growth plate EO are often seen with skeletal dysplasias and metabolic bone diseases.

Epiphysis-Associated Growth

The epiphysis of developing bone consists of a mineralized center surrounded by hyaline cartilage. The cartilage on the end of immature bones, the articular-epiphyseal complex (AEC), consists of two functionally different layers: a relatively thin outer layer and a relatively thick inner part.

The outer layer is specialized immature articular cartilage, is avascular, and does not participate in epiphyseal EO. Following maturation, the articular cartilage will consist of a superficial zone, a transitional or middle zone, a radial or deep zone and a zone of calcifying cartilage. Completion of the maturation process of the articular surface is indicated by the presence of the tide mark, a microscopically visible line(s) separating the uncalcified radial zone from the zone of calcifying cartilage. The inner layer of the AEC is functionally similar to the growth plate and is responsible for epiphyseal enlargement by new cartilage formation and mineralization of the newly formed cartilage.

The cartilage on the metaphyseal side of the mineralized center of the epiphysis also consists of two layers. Adjacent to the mineralized epiphysis is true epiphyseal cartilage, while the cartilage on the metaphyseal side represents growth plate cartilage. Morphologically, there are two main differences between epiphyseal and growth

plate cartilage. First, the chondroepiphysis is visually disorganized and does not have the ordered zonal and columnar arrangement of the growth plate. Furthermore, in contrast to the proliferative, hypertrophic and mineralization zones in the growth plate, the chondroepiphysis has a rich blood supply. Chondroepiphyseal blood vessels originate from the perichondrium and are located in so-called cartilage canals. Under physiologic conditions, these cartilage canals play a role in the nourishment of epiphyseal chondrocytes, in the formation and maintenance of the epiphyseal ossification center and in providing mesenchymal stem cells. It has been suggested that damage to cartilage canal vessels may result in osteochondrosis. Cartilage canal vessels are distinct from vessels on the metaphyseal side of the growth plate.

Just as with growth plate-associated growth, enlargement of the epiphysis-associated growth is a function of chondrocytic proliferation, chondrocytic enlargement, matrix formation, and duration of chondrogenic activity in the chondroepiphysis. Chondrocyte proliferation mostly takes place on the epiphyseal periphery, whereas EO occurs towards the center, where chondrocytes are larger and surrounded by more matrix. Cartilage canals regress through the process of chondrification as the ossification front from the center of the epiphysis reaches newly formed epiphyseal cartilage. Towards the end of the growth period, blood vessels from the epiphyseal bone marrow anastomose with cartilage canal vessels. When epiphyseal growth and ossification are completed, a thin layer of avascular articular cartilage and an avascular growth plate remain. The regulation of epiphyseal enlargement and endochondral ossification is not well understood and certainly not as well studied as the regulation of the growth plate. However, most likely there will be strong similarities with the regulation of the growth plate.

Bone Morphology

Composition of Bone

Bone is a composite material consisting of a fiber-reinforced matrix (similar to reinforced concrete, or Kevlar body armor). The fibers and the matrix in which they are embedded are manufactured by bone-forming cells (osteoblasts) and are susceptible to breakdown by bone-resorbing cells (osteoclasts).

Bone Matrix

Bone is initially deposited as nonmineralized matrix (osteoid), the major components of which are a proteoglycan-rich ground substance with embedded fibers of type 1 collagen. A number of important noncollagenous proteins are also found in bone, including osteocalcin (also known as bone Gla protein), osteopontin, and osteonectin. The importance of type 1 collagen is most clearly evidenced by the profound clinical signs seen in patients with congential defects in collagen 1 synthesis (osteogenesis imperfecta, also known as "brittle bone disease"). Abnormalities in either the quality or quantity of type 1 collagen result in dramatic alterations in the material and mechanical properties of bone by compromising the fiber reinforcement of osteoid. As a result, the bone is embrittled and prone to fracture.

The next stage after formation of the osteoid is deposition of mineral, in the form of hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$). The process of matrix mineralization remains incompletely understood but is thought to involve selective mineral deposition within matrix vesicles released by osteoblasts. Once they reach a certain size, the needle-like hydroxyapatite (HA) crystals are released from the matrix vesicles into the extracellular space, where they serve as templates for ongoing deposition of mineral within the collagen fibrils. The tissue-nonspecific isoform of alkaline phosphatase is believed to play a role in controlling the release of HA crystals from the matrix vesicle, as well as in the progression of mineralization in the extracellular matrix.

Cells of Bone

Osteoblasts are the cells that synthesize new bone. They are derived from mesenchymal precursor cells (variously referred to as mesenchymal stem cells or marrow-derived stem cells) and exist either as flat resting cells or as more metabolically active cuboidal cells. In both cases, osteoblasts remain intimately attached the bone surface. Over time, as additional osteoid is deposited and then mineralized, osteoblasts become encased in bone, forming osteocytes. These cells are known to be critical determinants of cell–cell and matrix–cell signaling within bone, playing an active role in transducing mechanical stimuli (strain) into bone cell activity. Signaling is facilitated by the presence of long cellular extensions (filopodia) on osteocytes; the filopodia run through small channels (canaliculi) within the bone. The extended surface area of the filopodia allows the osteocytes to sense changes in the composition of the extracellular fluid within the canaliculi, while their connectivity allows for efficient signaling between cell bodies.

Osteoclasts are the cells that resorb bone. In contrast with the mesenchymal origins of osteoblasts, osteoclasts derive from hematopoietic cells via the recruitment, activation, and fusion of mononuclear cell precursors. Hallmarks of the osteoclast include a multinucleate cell with a highly invaginated basal membrane (the so-called "ruffled border") apposing the bone surface, expression of the enzymes tartrate-resistant acid phosphatase and

cathepsin K, and the formation of a "sealing zone" through which cells attach to bone.

The process of osteoclastic bone resorption involves local acidification by means of a vacuolar ATPase. Under acid conditions, calcium and phosphorus are liberated from the bone matrix. At the same time, cathepsin K degrades the type 1 collagen, as well as other noncollagenous proteins within the bone matrix.

In cancellous bone, bone resorption occurs at the bone surface; in cortical bone, osteoclasts may act either directly on an exposed bone surface (e.g., on the endosteum or periosteum) or within the interstitium of bone, by resorbing bone within the longitudinally oriented Haversian canals, in a process known as intracortical remodeling.

Structure of Bone

The canine skeleton consists of approximately 319 bones that can be classified as follows.

- Long bones (e.g., femur, humerus)
- Cuboidal bones (e.g., carpus, tarsus)
- Flat bones (e.g., skull, rib)
- Irregular bones (e.g., vertebrae, pelvis)
- Sesamoid bones (e.g., fabellae)

Macrostructure of Bone

The shape of an individual bone is genetically determined but can be altered by changes in mechanical loading, blood supply, trauma, etc. For long bones, three anatomically distinct regions are recognized.

- Diaphysis – the shaft of the long bone, composed of cortical bone surrounding the medullary cavity.
- Epiphysis – the end of a long bone that is initially separated from the rest of the bone by the presence of a growth plate (physis).
- Metaphysis – the region between the epiphysis and the diaphysis.

Bone is present in one of two forms, cortical or cancellous. Cortical bone is very dense (it is also known as compact bone) and is mainly found as an envelope for the flat bones and in the diaphyseal regions of long bones. Cancellous bone is less dense and exists as a three-dimensional network of interconnecting struts (trabeculae), primarily within the metaphyseal and epiphyseal regions of the long bones, as well as in the irregular bones. Cancellous bone has a significantly higher surface area (per unit volume) for cellular activity than cortical bone and, as a result, is more metabolically active. The regions of the skeleton in which there are increased amounts of cancellous bone tend to be the high turnover sites; in humans, these are the sites that are most sensitive to hormonal change and most likely to develop osteoporosis (proximal femur, spine, distal radius).

Microstructure of Bone

Bone is organized as either lamellar bone or woven bone. Woven bone is an immature form of bone and is only seen in the skeletally mature animal at sites of fracture healing, bone growth, and skeletal diseases such as neoplasia or panosteitis. When present in the adult skeleton, it is rapidly remodeled into lamellar bone. Woven bone is more cellular than lamellar bone and its collagen fibers are aligned at random; as a result, woven bone is isotropic (i.e., mechanical properties do not depend on specimen orientation).

Lamellar bone is found throughout the mature skeleton in both cortical and cancellous bone, irrespective of whether the bone was formed by intramembranous or endochondral ossification. The collagen fibers in lamellar bone are oriented in parallel with one another and, as a result, lamellar bone displays anisotropy when tested mechanically.

This means that the mechanical properties depend on the direction of loading – similar to plywood, which is easily cut in one plane ("with the grain") but hard to cut at right angles ("across the grain").

Under polarized light microscopy, lamellar bone appears to have a regular sheet-like structure rather than the irregular structure of woven bone. In cancellous bone, the sheets of lamellar bone are oriented parallel to the surface of individual trabeculae. In cortical bone, lamellar bone is usually arranged in osteons, consisting of a central vascular channel surrounded by multiple concentric layers of lamellar bone; the osteons that comprise the osteonal complex are bounded externally by circumferential lamellae and separated one from another by interstitial lamellae.

The arrangement of bone within osteons provides the cortical bone with strength and some limited flexibility in bending and torsion.

Vascular Supply to Bone

In the long bone, there are three separate but related circulatory systems.

- The *nutrient artery* enters the long bone through the nutrient foramen in the diaphysis. Once within the medullary canal, the nutrient artery divides into ascending and descending medullary arteries that are the primary blood supply to diaphyseal cortical bone. Blood flow is centrifugal.
- The *metaphyseal vessels* arise from geniculate arteries that form the blood supply to periarticular tissues.

These vessels penetrate the cortex at the level of the metaphysis. In addition, smaller proximal and distal metaphyseal arteries derive from the ascending and descending medullary arteries. The metaphyseal arteries are the primary blood supply to cancellous bone.

- The *periosteal capillaries* supply the outer one-third of the cortex. These capillaries are derived from adjacent soft tissues (muscles, fascia) that insert on the bone (e.g., at the linea aspera on the femur). This blood supply is centripetal in nature.

There is considerable overlap and interplay between the circulatory systems in bone, perhaps most evident when bone is injured. If the medullary system is compromised, for example as a consequence of fracture or intramedullary reaming, the periosteal blood supply will increase in an attempt to revascularize the diaphysis. External fixation devices and bone plates affect both the endosteal supply and the periosteal supply. The design of modern bone plates, with limited contact with the periosteal surface, represents an effort to try to reduce the negative impact of plating on periosteal blood supply. Preservation of an effective blood supply is a basic principle of surgery since it is a critical determinant of tissue healing and subsequent function. Disturbances in blood supply play a role in the pathophysiology of several important orthopedic conditions, including ischemic necrosis, osteomyelitis, delayed union, and nonunion of fractures.

Bone Physiology

Bone Modeling and Bone Remodeling

Bone remains a dynamic structure throughout life. This is critical for both the maintenance of skeletal strength and the continued role of bone as a mineral reservoir. Mineral sequestered within the bone matrix can be mobilized rapidly in response to calcitropic hormones such as parathyroid hormone, vitamin D3, and calcitonin that respond to, and modulate, circulating calcium concentration.

Bone modeling is the process through which changes in bone shape occur. In modeling, bone formation and bone resorption can occur at different surfaces, resulting in shape changes. For example, radial growth of a long bone is achieved through new bone deposition at the periosteal surface. If there was not concurrent removal of bone from the endosteal surface, the net result would be a bone with a very thick cortex and a very narrow medullary canal. Removal of bone from the endosteum leads to expansion of the medullary canal and preservation of a space for trabecular bone (important for both structural support and bone turnover) and bone marrow (important for hematopoiesis).

Bone remodeling, the process in which bone is first removed and then replaced, is executed by the coupled activities of bone-resorbing osteoclasts and bone-forming osteoblasts. Bone remodeling is temporally and spatially coupled, and proceeds through defined stages of activation ⇒ resorption ⇒ formation. Bone remodeling activity proceeds as a surface phenomenon on bone trabeculae within cancellous bone, or on the endosteal or periosteal surfaces of cortical bone. However, cortical bone remodeling also occurs through osteonal (Haversian) remodeling that is carried out by a complex and unique structure, the basic multicellular unit (BMU), that consists of a cutting cone of osteoclasts in front and a closing cone of osteoblasts at the rear. The BMU moves through bone over a period of several months, removing damaged or unnecessary bone and replacing it as dictated by local mechanical and/or biologic stimuli. The removal of damaged bone is critical to the replacement of bone that has been microfractured, for example as a result of chronic overload (as may be seen in elite human, canine or equine athletes in training).

In the healthy adult animal, bone formation and resorption (i.e., overall remodeling) are balanced. However, imbalances in remodeling occur with aging. The most important example of remodeling imbalance is seen in postmenopausal osteoporosis in women, in which loss of estrogen results in a relative increase in bone resorption, reduced bone mass, and an increased risk of "fragility" fracture.

What Controls Bone Remodeling?

The last 15 years have seen an explosion in what is known about osteoclast biology, driven in large part by the quest for greater understanding of disease states caused by dysregulated osteoclast activity. The major clinical and research emphasis has been on postmenopausal osteoporosis in women. Although the role of estrogen deficiency has long been recognized, we now know that local paracrine factors play a critical role in driving the excessive bone resorption that characterizes this disease. At a cellular and molecular level, the control of bone resorption depends on the availability of osteoclastic precursor cells, local levels of macrophage colony-stimulating factors (M-CSF) and the activities of the receptor activator of NF-kappa B (RANK), its ligand (RANK ligand, or RANKL) and its decoy receptor, osteoprotegerin (OPG). These interactions are illustrated in Figure 171.1. RANK is expressed as a surface receptor on mononuclear osteoclast precursors; binding of RANKL to the receptor results in cell–cell fusion to form the

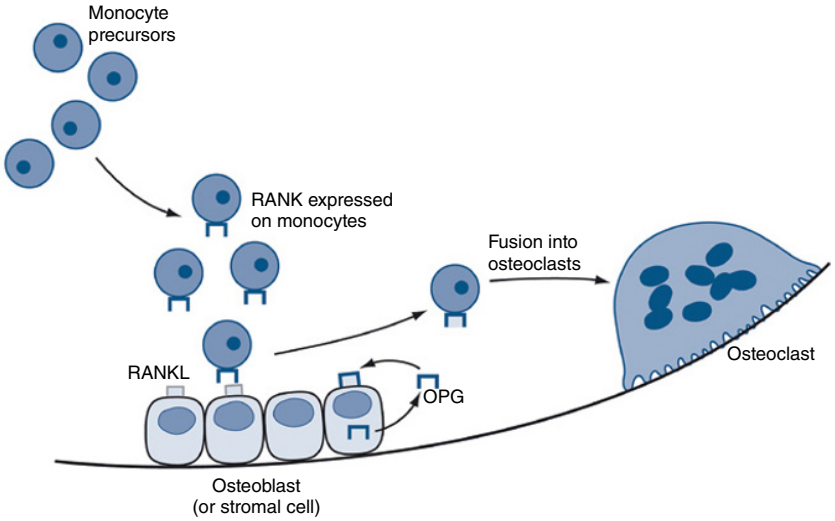


Figure 171.1 Molecular control of osteoclast differentiation. Monocytes stimulated by M-CSF and RANKL fuse to form multinucleate osteoclasts. Interruption of the RANK-RANKL axis offers a therapeutic approach to disease characterized by increased osteoclastic activity. *Source:* Reproduced with permission from Allen MJ. Cellular and molecular biology. In: Damron T, ed. *Oncology and Basic Science (Orthopaedic Surgery Essentials)*. Baltimore, MD: Lippincott, Williams and Wilkins, 2007.

multinucleate osteoclast. Increases in the ratio of RANKL to OPG favor net bone loss, while decreases favor net bone accrual.

A number of drug therapies have now been developed for modulating osteoclastic activity. The most widely used antiresorptive agents are bisphosphonates such as pamidronate, clodronate, alendronate, and zoledronate. These compounds, which bind to mineral within the bone matrix, are released when mineral is resorbed by osteoclastic activity. Direct exposure of the osteoclast to high levels of these drugs leads to osteoclast apoptosis and a decrease in bone resorptive activity. Although initially introduced for osteoporosis, bisphosphonates are now widely used in the management of patients with other forms of pathologic bone resorption, including hypercalcemia of malignancy (e.g., with anal sac adenocarcinoma), primary bone cancer (e.g., osteosarcoma, feline oral squamous cell carcinoma) or secondary bone metastases (e.g., from mammary or prostatic carcinoma).

An alternative approach to controlling osteoclastic activity involves targeting the RANK-RANKL pathway by administration of exogenous OPG or RANK-Fc antibodies that serve as competitive antagonists for the RANK receptor.

Decreases in normal bone resorptive activity are also not without consequence. The most extreme example of this can be seen in patients with osteopetrosis, a congenital disease in which there is failure of osteoclast formation or functionality. The classic clinical features of bone fragility, osteoarthritis, and marrow failure can all be explained by failures of osteoclastic resorption, including an inability to remodel and expand the medullary canal (and an absence of space for hematopoiesis), failure to remodel cortical and trabecular bone (leading to increased bone mineral density) and failure to resorb and replace damaged bone (leading to bone fragility secondary to bone fatigue failure).

Since net bone mass is sensitive to changes in both formation and resorption, attention has also been paid to the role of anabolic factors that modulate skeletal activity. In the context of long bone growth, it has been shown that growth hormone is capable of enhancing longitudinal bone growth in the immature skeleton. In the adult animal, preclinical studies have confirmed the anabolic potential of both exogenous parathyroid hormone (PTH) and bone morphogenetic proteins (BMPs). Intermittent (daily) treatment with recombinant or synthetic forms of human PTH is effective in enhancing overall bone mass and accelerating bone repair after fracture. Bone morphogenetic proteins, including BMP-2 and BMP-7, have been studied extensively in dogs and BMP-2 is now available commercially as a potential treatment to accelerate or enhance fracture healing.

Effects of Mechanical Loading on Bone

Julius Wolff (1836–1902) was a German surgeon who first identified the relationship between mechanical forces and bone structure. He likened the arrangement of trabecular bone in the neck of the femur to the arrangement of supports in a crane, with the trabeculae being oriented to best resist the forces to which the femoral neck was being exposed. Although originally published in German in 1892, Wolff's law can be summarized thus: "Bone changes its structure according to the mechanical loads to which it is exposed."

Once the adult skeleton has formed, it continues to adapt to the prevailing mechanical environment. Graphic evidence of the importance of mechanical loading in driving the change in bone shape and bone mass (bone modeling) comes from professional tennis players

(who develop significant increases in bone mass in their dominant forearm) or astronauts (who lose significant bone mass after even a few weeks in the microgravity of space). Practical examples of modeling in the context of veterinary orthopedics include the remodeling of fracture callus, functional adaptation of the metacarpal, metatarsal and central tarsal bones of racing greyhounds, bone loss following limb disuse, the development of stress fractures secondary to accelerated bone remodeling in racing thoroughbreds, and "stress shielding" around orthopedic implants.

Bone Pathophysiology

Bone Response to Injury

The basic biology of bone's response to trauma has been a subject of intense investigation over the years, particularly within the context of understanding what happens after bone fractures. The fundamental response of bone to trauma is similar to that seen in other tissues, and includes cellular recruitment, differentiation, and formation of an appropriate replacement tissue. In the context of normal bone healing after fracture, three overlapping stages are recognized: the inflammatory stage, the repair phase, and the remodeling phase.

Inflammatory Phase

Significant trauma, such as fracture, inevitably result in disruptions to the medullary blood supply, leading to extravasation of blood and the formation of a clot between and around the ends of the fractured bone. Damage to the periosteum also results in formation of clot around the external surface of the bone. Although mechanically incompetent, the clot acts as a rich source of growth factors for angiogenesis and subsequent fracture healing. This last point is of critical significance when contemplating surgery for a fracture – excessive manipulation of the soft tissue clot results in loss of many of the cells (and signaling molecules) that are ultimately required for successful healing. An "open but do not touch" approach allows the surgeon to assess the fracture and to apply fixation methods that do not interfere with (but instead harness) the body's innate healing response. This is the concept of biologic osteosynthesis.

Repair Phase

Macrophages that are brought in through the newly forming capillary bed serve to remove tissue debris and initiate the conversion of the clot into first granulation tissue and then callus. Callus formation starts with the deposition of collagen (initially types 1, 2, and 3) by fibroblasts. At the same time, mesenchymal cells that were brought into the area during the inflammatory response differentiate into chondrocytes and deposit a cartilage framework that is subsequently mineralized. It should be noted that the progressive transition from clot ⇒ granulation tissue ⇒ soft callus ⇒ hard callus recapitulates the process of endochondral bone formation that occurs during normal bone formation.

Remodeling Phase

The final stage of fracture healing involves the gradual incorporation of the relatively disorganized hard callus into the skeleton. This is the longest phase of fracture healing. Remodeling of the callus is governed by Wolff's law and, ultimately, the process of bone remodeling results in a structure that is best able to resist the mechanical forces to which it is subjected.

Thermal Injury to Bone

Bone is damaged by temperatures exceeding 47 °C for more than one minute. The most common scenarios for thermal injury to bone occur during orthopedic surgery and are related to the use of power tools to cut and shape bone, or the bone cement that is used to secure total joint replacement implants.

Power tools such as saws, drills, and reamers are used every day in orthopedic surgery. In the operating room, every effort is made to reduce the risk of thermal injury. This involves the use of sharp drills or saw blades (old, dull blades or drill bits will mill bone and generate heat); low-speed cutting and drilling whenever possible; short rather than sustained bursts of drilling or sawing; and copious saline lavage, which serves both to cool the tissue and to remove bone debris that can otherwise clog up blades and drill flutes.

The standard bone cement used in orthopedic surgery is acrylic cement based on polymethylmethacrylate (as used in Plexiglas). Bone cement is used to secure joint replacement implants into bone. Cement is typically injected in a liquid state but then hardens through a chemical process of polymerization that is exothermic. Since bone cement is usually placed immediately adjacent to cortical or trabecular bone, there is potential for heat injury to the constituent bone cells, as well as to the vascular supply to the endosteum. Data from preclinical animal models indicate that this thermal injury is typically reversible. However, care should be taken to use the minimum volume of cement necessary and to ensure protection of adjacent neurovascular structures.

Vascular Injury to Bone

Vascular trauma to bone may occur secondary to a fracture or as an unwanted consequence of surgical

interventions. Traumatic disruptions during fracture typically involve significant injury to the blood supply on both endosteal and periosteal surfaces. Vascular injury secondary to surgical procedures may affect the entire bone (if, for example, a nutrient vessel is cut by accident) or it may preferentially affect one region (for example, damage to the outer surface of the bone or to the adjacent soft tissues has a greater effect of periosteal blood supply, while introduction of an intramedullary pin or bone cement into the medullary cavity will selectively damage the endosteal blood supply). Application of a plate to the surface of the bone also may damage the periosteal supply.

In most cases, regional changes in blood flow will be able to restore effective vascularity to the bone. For example, loss of periosteal blood supply results in an increase in centrifugal blood flow through the cortex, while endosteal damage results in increased centripetal blood flow from the periosteal vascular network.

Periosteal Trauma

Periosteal trauma occurs either as a consequence of fracture, secondary to surgical manipulation of the bone, or as a consequence of bone pathologies such as infection or neoplasia. Data from preclinical animal models have shown that traumatic loss of periosteum has the potential to result in overall bone loss and an increased risk of fragility in the affected bone. At least two factors appear to be involved in this response. First, loss of periosteal bone-forming cells will lead to a decreased ability to make new bone at the periosteal surface. Second, loss of the vascular supply to the periosteum results in transient derangements in bone blood flow. In healthy animals, the extent of periosteal trauma would have to be significant to cause a whole-bone effect. However, if the bone is otherwise compromised by disease, periosteal damage may result in further bone loss and an increased risk of catastrophic bone failure.

Reactive New Bone Formation

Reactive new bone is a relatively common radiographic finding and a not uncommon confounding factor in bone biopsies taken from sites of bone pathology. While the underlying process of forming new bone represents a biologically conserved and logical response to bone trauma, the response is not specific to any one initiating cause, making it extremely hard for radiologists or bone pathologists to ascribe a specific underlying disease entity as the cause of the new bone formation. Some information may be gleaned from the location of the new bone, with both endosteal and periosteal surfaces being potential sources of reactive new bone formation.

At the periosteal surface, fracture, infection, and neoplasia are the most common causes of a reactive periosteal new bone formation ("periosteal response"). The role of periosteal callus in fracture healing will be discussed shortly. In the context of bone infection and neoplasia, situations in which the periosteum can be underrun by inflammatory or neoplastic infiltrates, the typical response is for new bone formation. The mechanisms responsible for this are not well understood but likely relate to the ability of periosteum to react to increased local mechanical deformation by depositing new bone. There are significant numbers of nociceptors at the periosteal surface, and periosteal involvement in neoplasia and infection tends to be extremely painful. Radiographically, the observation of focal to local periosteal new bone is highly suggestive of aggressive bone conditions such as neoplasia or osteomyelitis.

With neoplasia, disruption and lifting of the periosteum proceed too rapidly for the bone to mineralize in the normal layered fashion, and the net result is that only the edge of the lifted periosteum ossifies. Radiographically, the mineralized flap of periosteum is described as Codman's triangle.

At the endosteal surface, reactive new bone formation is seen predominantly in fracture healing and also as a component of canine panosteitis, which will be discussed later.

Pathologic Bone Resorption

Excessive and dysregulated activation of bone resorption is a hallmark of several important developmental, inflammatory, infectious and neoplastic disorders in animals, including periodontal disease, osteomyelitis, multiple myeloma, and aseptic or septic loosening of total joint replacement implants. A complete description of the pathobiology of these conditions is outside the scope of this short discussion, but it is important to note that the fundamental biologic mechanisms through which bone is removed are the same as are seen in normal (physiologic) bone remodeling. The major differences lie in the nature of the inciting cause; for implant-related bone resorption (osteolysis), it is the inflammatory response to metallic and polymeric debris liberated from the surfaces of the implant that stimulates the inflammatory cascade. In metastatic tumors that target bone, proinflammatory cytokines released from the tumor appear to modulate the osteoclastic response immediately adjacent to the tumor deposits.

Irrespective of the inciting cause, strategies for managing pathologic bone resorption focus on eliminating the underlying inciting cause with appropriate medical therapy (antibiotics, chemotherapy) or surgical intervention (to remove a loose or infected implant). The use of oral

or injectable bisphosphonates also represents a logical approach to suppressing ongoing bone loss in these patients.

Bone Healing after Fracture

The goal of fracture fixation is to restore structure and function to the skeleton. Fracture healing is influenced by a wide array of factors, including the animal's age, location and type of fracture, stability of the fragments, extent of soft tissue and vascular compromise, and presence or absence of necrotic and/or infected tissues. Mechanical stability is known to be of paramount importance in determining the nature, time course, and efficiency of the fracture healing response. Under stable conditions, the fracture will unite via direct (primary) bone healing, in which new bone forms a direct bridge across the fracture plane. Under unstable conditions, a soft tissue callus first forms and it is this callus that is then progressively mineralized in a process known as indirect (secondary) fracture healing.

Role of Mechanical Factors in Fracture Healing

Fractures that are anatomically reconstructed and maintained under stable conditions through the use of internal fixation heal without significant callus. However, even under conditions of ideal bone fragment alignment, it is common to find microscopic discontinuities between the ends of the fragments. The extent of the gap dictates the nature of the reparative response that will predominate. In very small gaps, woven bone forms and continuity is restored between the ends of the bone. If the gap is larger than ~1 mm, the gap will fill in with soft callus. As long as the fracture site remains stable, the callus will successfully mineralize and remodel. In fact, controlled amounts of micromotion have been shown to accelerate bone repair, a finding that has been used to great benefit in distraction osteogenesis, a procedure in which controlled axial distraction of a small bone fragment is used to stimulate and maintain new bone formation. Over time, the regenerated bone formed in this way is capable of filling in a significant defect in the original bone. Distraction osteogenesis can be useful in the management of both large bone defects (e.g., secondary to trauma or neoplasia) and the correction of angular limb deformities.

In the presence of mechanical instability, either with comminuted fractures or with fractures that are unstable despite attempts at fixation, fracture healing is characterized by the formation of abundant callus that unites the bone fragments. The biologic processes that underlie the formation of callus have been described previously. The mechanical properties of the callus similarly evolve as the callus matures from a fibrous connective tissue, through a cartilaginous intermediate and finally to bone. The total area (volume) of the callus depends on (i) the degree of displacement of the fragments and (ii) the extent of mechanical instability at the site of fracture. Once the mechanical properties of the callus are sufficient to minimize interfragmentary strain (2% is often cited as the threshold for new bone formation), primary bone repair can occur and the callus will be remodeled to restore the medullary cavity and cortical profile. It should be noted that the presence of external callus leads to a rapid increase in the mechanical integrity of the bone, so that bone that heals with abundant callus is able to withstand physiologic forces within a relatively short period of time after fracture.

Other Factors that Influence Bone Healing

Certainly, any factor that compromises the ability of callus to form or to differentiate would be expected to delay or prevent fracture healing. In addition to mechanical instability due to incomplete reduction or stabilization, other factors that can lead to delayed or nonunion after fracture include vascular compromise, premature or excessive weight bearing after surgery (hence the importance of controlling activity levels after surgery), infection, radiation therapy, systemic illness, or concurrent treatment with prolonged courses of drugs such as corticosteroids. In humans, smoking is a critically important determinant of wound healing in general and a major risk factor for complications following fracture repair. The potential negative effects of nonsteroidal antiinflammatory drugs (NSAIDs) on bone healing have been the subject of significant research efforts in humans but data in animals are less clear, and there does not appear to be any objective evidence that short-term treatment with NSAIDs has a significant effect on bone healing after trauma or surgery.

Complications with Fracture Healing – Delayed Union, Malunion, and Nonunion

Although the majority of straightforward fractures will go on to heal (unite) without complication, a subset of patients will experience problems with healing. The primary causes of suboptimal fracture healing have been described in the preceding sections, and include incomplete reduction of the fracture, uncontrolled or excessive weight bearing, vascular compromise, infection, and concurrent medical disease or therapy. Three general categories of abnormal fracture healing have been recognized: delayed union, malunion, and nonunion. The diagnosis of disturbed fracture healing is made on

the basis of careful physical examination and radiographic findings.

Delayed union is probably the most challenging to diagnose definitively since it represents healing that occurs at a slower rate than would be expected for a given fracture. As mentioned earlier, the rate and completeness of healing are sensitive to a range of variables, and as a result there can be significant variations in how fast a given fracture heals. Most delayed unions can be managed conservatively, without the need for additional surgical intervention.

Malunions are fractures that have gone on to clinical union but with abnormalities in the alignment of the fragments. In the middiaphysis, this may manifest as rotational abnormalities or angulation between the proximal and distal ends of the bone. At the articular surface, healing without complete restoration of the articular surface would be considered a malunion. The consequences of malunion depend on both severity and location; minor angular malalignment may be clinically asymptomatic, while discontinuities or irregularities in the articular surface can predispose to the development of posttraumatic osteoarthritis.

Nonunion represents the most extreme disturbance in normal fracture healing. The extent and nature of the healing response can be quite variable, but nonunions can broadly be classified into viable nonunions, in which the tissues are still capable of biologic activity, and nonviable nonunions that are devoid of biologic activity. The management of these fractures can be complex and lies outside the scope of this discussion, but often involves aggressive surgical intervention. In select cases, there may also be a role for local (e.g., BMP) or systemic (e.g., PTH) anabolic drug therapies to boost new bone formation.

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172

Metabolic Bone Diseases

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Metabolic bone diseases include osteoporosis, rickets and osteomalacia, fibrous osteodystrophy (secondary hyperparathyroidism), and scurvy (vitamin C deficiency). Fibrous osteodystrophy is an important skeletal disease of young dogs and cats. On the other hand, rickets and osteomalacia are relatively rare. While osteoporosis is the most common metabolic bone disease of humans, it is seldom diagnosed in small animals, possibly due to the lack of sensitive techniques to reliably diagnose the disease. Dogs and cats have the hepatic microsomal enzyme L-gulonolactone oxidase and can synthesize vitamin C (ascorbic acid), therefore scurvy does not occur in these species. The metabolic bone diseases covered in this chapter include fibrous osteodystrophy, rickets and osteomalacia, with a brief discussion of osteoporosis.

Calcium and Phosphorus Physiology

In order to truly understand the pathophysiology of the metabolic bone diseases, good knowledge of normal calcium and phosphorus metabolism is required. Therefore a brief description of calcium and phosphorus homeostasis will be included here.

The hormones vitamin D, parathyroid hormone (PTH), calcitonin, and fibroblast growth factor 23 (FGF23) are essential for controlling plasma calcium and phosphorus concentrations. These hormones facilitate calcium and phosphorus transportation in three main organs: the kidney, intestine, and bone.

Calcium transport is predominantly under the control of PTH and 1,25-dihydroxyvitamin D ($1,25(OH)_2D_3$). Parathyroid hormone is a small peptide secreted by the parathyroid gland when the calcium-sensing receptors on chief cells detect low plasma calcium concentrations. PTH binds to the PTH receptor 1 in renal tubules, resulting in activation of adenylate cyclase and phospholipase C cell pathways, ultimately leading to opening of calcium channels (such as transient receptor vanilloid potential 5, TRPV5), and increased resorption of calcium from the renal filtrate. Increased plasma phosphorus concentrations may also lead to increased PTH secretion by an unknown mechanism. Increased PTH leads to increased breakdown of phosphate channels (Na^+-P_i ATPase pump, NPT2), resulting in decreased resorption of phosphorus from the renal filtrate.

The actions of PTH on bone are dual and antagonistic. Secretion of PTH in response to low plasma ionized calcium leads to increased expression of receptor activator of NF-kB ligand (RANKL) by osteoblasts. When RANKL binds to the RANK receptor on osteoclast precursors, it leads to differentiation and maturation of these cells into mature osteoclasts. At the same time, PTH leads to decreased expression of osteoprotegerin (OPG/OCIF), a decoy receptor that prevents binding of RANKL to RANK. Increased production of osteoclasts ultimately results in increased osteoclastic bone resorption and release of calcium and phosphorus from bone matrix into blood. The anabolic actions of PTH are used in the treatment of osteoporosis in humans. Intermittent low-dose treatment with PTH analogs results in increased differentiation and production of osteoblasts, and therefore increased bone formation.

Low plasma calcium concentration and PTH activate the 1-alpha-hydroxylase enzyme in the kidney, resulting in increased production of $1,25(OH)_2D_3$. Active vitamin D ($1,25(OH)_2D_3$) binds to the vitamin D receptor in the nucleus of intestinal epithelial cells and renal tubular epithelial cells, leading to increased production of vitamin D-responsive proteins, such as calcium channels (TRPV5, 6 and Na^+/Ca^{2+} exchanger), phosphate channels (NPT2a, 2b, 2c), and calcium-binding proteins (calbindin-D_{9k} and D_{28k}). Increased production of these proteins results in increased absorption of calcium and

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phosphorus from the renal tubules and intestinal tract. Active vitamin D also has a negative feedback effect on its own production. In the parathyroid gland, $1,25(OH)_2D_3$ directly inhibits PTH production and increases the sensitivity of the calcium-sensing receptors to calcium, thereby acting to control PTH secretion.

Like PTH, vitamin D may also have dual and antagonistic effects in bone. When plasma blood calcium concentrations decline, $1,25(OH)_2D_3$ leads to increased bone resorption by upregulating RANKL production and inhibiting OPG production, likely in association with PTH. In addition, $1,25(OH)_2D_3$ upregulates inhibitors of bone mineralization. However, $1,25(OH)_2D_3$ can be produced locally in bone, by chondrocytes, osteoblasts, osteocytes and osteoclasts, where it leads to increased bone formation and mineralization.

Calcitonin is the antagonistic hormone to vitamin D and PTH and is released in response to increased plasma ionized calcium concentrations. It inhibits osteoclast motility and leads to retraction of osteoclasts from bone, resulting in decreased bone resorption and therefore decreased release of calcium and phosphorus into the blood.

Traditionally, it was thought that the control of plasma phosphorus concentrations was indirect, as a result of the tighter control of calcium. However, a suite of compounds, known as phosphatonins, are critically involved in phosphorus control, the most important of which is FGF23. Increased plasma phosphorus concentrations and increased $1,25(OH)_2D_3$ may both independently increase FGF23 production by osteocytes in bone. The main target organ for FGF23 action is the kidney. FGF23, together with its co-factor klotho, downregulates the NPT2a and 2c phosphorus channels in the kidney, leading to decreased resorption of phosphorus from the renal tubules. FGF23 also acts on the parathyroid gland to decrease secretion of PTH. FGF23 in combination with the decrease in PTH leads to inhibition of the renal 1-alpha-hydroxylase enzyme decreasing production of active vitamin D. At the same time, there is activation of the enzyme (24-hydroxylase) that breaks down active vitamin D, ultimately resulting in decreased $1,25(OH)_2D_3$.

Fibrous Osteodystrophy

Fibrous osteodystrophy (FOD) is a skeletal disease characterized by the replacement of bone with a combination of fibrous tissue and poorly mineralized woven bone. While the focus of this section is on nutritional hyperparathyroidism, primary and renal hyperparathyroidism may cause similar skeletal lesions.

Etiology/Pathophysiology

Fibrous osteodystrophy is the skeletal consequence of hyperparathyroidism or a chronic increase in PTH. There are four main causes of hyperparathyroidism.

- *Primary hyperparathyroidism* – due to a functional tumor of the parathyroid gland, resulting in autonomous secretion of PTH. The increased PTH leads to hypercalcemia and mineralization of soft tissues, and in long-standing cases clinical FOD. This will be discussed in the endocrine section. A probable hereditary primary hyperparathyroidism has been reported in a litter of German shepherd puppies.
- *Renal hyperparathyroidism* – due to chronic kidney disease. While renal hyperparathyroidism is common in animals with chronic kidney disease, clinical signs due to skeletal changes are usually minimal in adult animals. Nonetheless, recent studies have shown that dogs and cats with chronic kidney disease have decreased bone mineral density and increased bone porosity. Young rapidly growing animals with familial renal disease may develop severe skeletal lesions.
- *Nutritional hyperparathyroidism* – due to a decreased calcium to phosphorus ratio in the diet. This is a common condition of young rapidly growing cats and dogs fed poorly balanced diets post weaning.
- *Pseudohyperparathyroidism or hypercalcaemia of malignancy* – due to a tumor that produces calcitropic hormones. Parathyroid hormone-related peptide (PTHrp) is the best characterized of these calcitropic hormones and has the same effect as PTH. Tumors that most commonly produce PTHrp are lymphoma and apocrine gland adenocarcinoma of anal sac origin. Occasionally, other carcinomas, malignant melanoma, and other tumors may produce other factors that cause hypercalcaemia, such as $1,25(OH)_2D_3$, prostaglandins, and various cytokines (TGF-beta, IL-1-beta). Skeletal changes are mild and difficult to detect; clinical signs are the result of hypercalcemia.

Signalment

Nutritional hyperparathyroidism is typically a disease of rapidly growing young animals after weaning. A case of nutritional hyperparathyroidism in an adult dog has been reported; the Rottweiler was on a home-made diet due to the diagnosis a year previously of lymphocytic-plasmacytic enterocolitis and lymphangiectasia.

History and Clinical Signs

Nutritional FOD occurs when the diet contains excessive phosphorus or deficient calcium. In actual practice, most commonly it is due to a combination of decreased

calcium and increased phosphorus in the diet. The most frequent cause of nutritional FOD is an all-meat diet. The ideal Ca:P ratio of a diet is 1:1. Meat and liver have calcium to phosphorus ratios of 1:20 and 1:50 respectively, and a diet based solely on these components can lead to clinical signs of FOD within four weeks.

Animals with nutritional hyperparathyroidism most commonly present with an ill-defined lameness, disinclination to move, and a failure to thrive. Some animals may have angular limb deformities. In more severe cases, pathologic fractures may occur with only mild trauma. Resorption of alveolar bone in the mandible and maxilla may lead to loosening of teeth. A few animals may develop vertebral compression fractures, which in some cases may lead to neurologic signs. While another term for fibrous osteodystrophy is rubber jaw, this is usually only seen in severe prolonged cases, and is more common in young animals with familial renal disease and renal secondary hyperparathyroidism, rather than nutritional hyperparathyroidism.

Diagnosis

Biochemistry

Animals with nutritional fibrous osteodystrophy have low to low-normal plasma total and ionized calcium concentrations. The calcium deficiency in the diet stimulates PTH release, which subsequently leads to osteoclastic resorption of calcium from bone, thereby maintaining plasma calcium concentration to the detriment of bone mineral content. If the dietary deficiency of calcium is severe or the amount of calcium released from the bones is inadequate then the dog or cat will have hypocalcemia.

The increased PTH concentration leads to increased excretion of phosphorus from the kidney, and so results in an increase in the fractional excretion of phosphorus. Depending on the balance of dietary intake to renal excretion, plasma phosphorus concentrations may be low, normal or increased.

Serum alkaline phosphatase concentrations are increased due to increased bone remodeling but, along with the phosphorus concentration, need to be interpreted with caution as both may be increased in younger animals due to growth.

Plasma intact PTH concentration will be increased but there are a number of cautions to be considered when interpreting plasma PTH concentrations. The first is collection of the sample. PTH is highly susceptible to proteolysis, so serum or plasma should be separated from red cells immediately (samples should be at room temperature for less than two hours) and tested directly, refrigerated for no more than 24 hours or stored frozen at −20 °C. Samples should be shipped chilled/frozen. Serum separator tubes should not be used as they lead to decreased PTH concentrations. In addition, visible hemolysis of the sample interferes with the assay.

Second, there are several different assays available for measuring PTH, including radioimmunoassays (RIA/ERMA) and enzyme immunoassays (EIA/ELISA). In addition, assays are available for whole PTH (W-PTH), intact PTH, N-terminal fragment of PTH, and C-terminal fragment of PTH. PTH undergoes proteolysis in the liver, blood, and other organs, forming N-terminal and C-terminal fragments. The N-terminal PTH fragment cannot bind to the PTH receptor and so does not elicit the classic response to PTH; it is in fact thought to inhibit PTH action. N-terminal PTH fragments are increased in chronic renal failure.

The W-PTH assay is a third-generation PTH assay that is specific for whole 1-84 PTH, while the I-PTH is a second-generation assay that, in addition to measuring 1-84 PTH, also measures large N-terminal PTH fragments. Human two-site RIA/IRMAs for I-PTH have been validated in both cats and dogs, as has a combined W-PTH/I-PTH assay. Human EIAs may not cross-react with canine or feline PTH. Canine-specific I-PTH ELISA assays are also available. Reference ranges are assay specific and ideally should not be extrapolated from other types/brands of assay.

The third important point is that ionized calcium, total calcium, and phosphorus concentrations should be measured on the same sample as PTH. These analytes are essential for the interpretation of the plasma PTH concentration.

Radiography

The predominant change seen on radiography is generalized osteopenia of all bones. It may be most obvious in those bones with a greater proportion of cancellous bone which is more readily resorbed, such as the vertebrae. The mandible may show a marked reduction in bone density, particularly the alveolar bone around the teeth (Figure 172.1). There may be evidence of pathologic fractures (see Figure 172.1), such as compression fractures in the vertebrae and infractions in the long bones. In more severe cases, there may be complete fracture of the long bones. The growth plates are normal in animals with fibrous osteodystrophy, but there may be increased radiopacity in the primary spongiosa directly beneath the growth plate (see Figure 172.1). The cortices appear thinner and more porous. The limbs may show angular deformities, and lordosis of the spine can be present.

New technology such as dual-energy X-ray absorptiometry (DEXA/DXA) and computed tomography (CT) give a more accurate assessment of bone mineral density than plain radiographs. Bone mineral density must be decreased by more than 30% before it is detected on



Figure 172.1 Radiograph from 12-week-old greyhound puppy with fibrous osteodystrophy. (a) Tibia/fibula showing osteopenia, with normal growth plate width, sclerosis of the metaphysis beneath the physis, and a folding fracture. (b) Mandible showing loss of alveolar bone surrounding the teeth. *Source:* Courtesy of K.G. Thompson.

plain radiographs. DEXA and CT may be useful for monitoring the success of treatment. In one study, bone mineral density, as measured by both DEXA and CT, showed substantial improvement once the diet had been corrected.

Therapy

Animals with nutritional FOD should be fed a commercial balanced diet with the recommended 1:1 ratio of Ca:P. Affected animals may also benefit from receiving additional calcium, enough to raise the total Ca:P ratio of the diet to 2:1. The additional calcium may be in lactate, carbonate or gluconate forms and should be continued for two months, after which time the animal can be maintained on a commercial balanced diet. Animals with microfractures or infractions may require pain relief. An important component of treatment is confining affected animals for the first 3–4 weeks of treatment in order to decrease the risk of further pathologic fractures.

Prognosis

With correction of the diet, and provided catastrophic fracture does not occur, the prognosis for a return to normality is excellent. With time and the normal remodeling process, the poor-quality woven bone and fibrous tissue laid down will be replaced with well-mineralized trabeculae and the bones will return to normal strength.

Rickets and Osteomalacia

Rickets is a disease of young animals and is due to a failure of mineralization of osteoid and cartilage at the provisional zone of calcification in the growth plate. Osteomalacia is essentially the same condition but in adult animals. Since adult animals do not have growth plates, in osteomalacia only new osteoid laid down during the normal remodeling process is poorly mineralized. Both conditions are rare in dogs and cats.

Etiology/Pathophysiology

Rickets and osteomalacia are due to either dietary vitamin D deficiency or phosphorus deficiency. Phosphorus deficiency is very rare in dogs and cats, and as described in the FOD section, phosphorus excess is far more common.

Dogs and cats are unusual in mammalian species in that they do not appear to produce vitamin D in the skin under the influence of ultraviolet light. In most animals, ultraviolet B light results in the conversion of 7-dehydrocholesterol, in keratinocytes and the dermis, to previtamin D3 which then undergoes thermal isomerization to vitamin D3. However, cats and dogs have been shown to have only 10% of the 7-dehydrocholesterol in their skin that rats do, and cat skin contains a 7-dehydrocholesterol-delta^{7}-reductase which breaks down 7-dehydrocholesterol. Therefore, irradiation of cat and dog skin with ultraviolet light does not cause an increase in plasma vitamin D concentration. Cats and dogs are, for that reason, reliant on their diet for their vitamin D requirements. However, there are few reports of naturally occurring rickets in dogs and cats in the literature, likely due to the widespread feeding of commercial pet food. In addition, the most common inappropriate diet fed to puppies and kittens is meat and offal, which contain high levels of phosphorus and adequate vitamin D.

Vitamin D deficiency leads to decreased absorption of calcium and phosphorus from the intestine and decreased reabsorption of calcium and phosphorus from the kidney, leading to hypocalcemia and hypophosphatemia. Animals that have rickets due to vitamin D deficiency will often have concurrent FOD due to hypocalcemia. Decreased plasma ionized calcium concentration leads to increased PTH secretion and therefore increased osteoclastic resorption of bone and FOD.

In humans, rickets and osteomalacia are described in patients with gastrointestinal malabsorption disorders, due to failure to absorb fat-soluble vitamins such as vitamin D, and reduced absorption of calcium. Rickets has been described in a 17-week-old male border collie with extrahepatic biliary atresia.

Aluminium toxicity from chronic antacid administration or long-term total parenteral nutrition may also cause rickets and osteomalacia in humans.

Osteomalacia may occur in combination with FOD in dogs and cats with chronic kidney disase. Hyperphosphatemia results in increased plasma FGF23 concentrations, leading to inhibition of the renal 1-alpha-hydroxylase enzyme, causing decreased production of $1,25(OH)_2D_3$. This combination of osteomalacia and FOD is often termed renal osteodystrophy. As mentioned earlier, while bone changes do occur in adult animals with chronic kidney disease, the changes seldom result in clinical signs.

Vitamin D also has an important role in the immune system, and has been associated with many different diseases in both humans and animals. Low serum 25OHD concentrations in dogs have been associated with immune-mediated disorders, various types of cancer, acute pancreatitis, progression of leishmania, chronic enteropathy, chronic valvular heart disease, and poor outcome in congestive heart failure, while in cats, low serum 25OHD has been associated with inflammatory bowel disease, intestinal small cell lymphoma, and mycobacteriosis. However, care should be taken not to overinterpret the role of vitamin D in these diseases. Correlation is not causation, and randomized clinical trials are required to determine the significance of vitamin D in the pathogenesis of different diseases and whether changes in serum 25OHD are primary or occur secondary to the disease.

Signalment

Rickets occurs in young animals and cases of rickets in the literature have been reported in 10–14-week-old puppies and kittens. Nutritional rickets has been reported most commonly in greyhound litters, presumably because these animals are more likely to be fed unusual diets.

Rickets is extremely rare in cats, and naturally occurring nutritional rickets has not been reported in the literature. However, rickets has been induced experimentally in both cats and dogs fed vitamin D-deficient diets.

History and Clinical Signs

As with nutritional FOD, animals with rickets usually have a history of an unusual postweaning ration. In two of the reported cases of rickets in the literature, puppies were fed a diet of milk and meat. Such a diet would likely meet the calcium and phosphorus requirements for the animals, but not vitamin D, as the vitamin D concentration of milk is low.

A case of rickets has occurred in a 10-week-old Shetland sheepdog on a commercial renal failure diet. Such diets are designed to be low in phosphorus and protein in order to alleviate some of the clinical and biochemical changes associated with the disease. However, the level of phosphorus in the diet fed to this young dog was inadequate for a growing animal, leading to phosphorus deficiency and rickets. Similarly, osteomalacia has been reported in an adult dog with food allergies fed an unbalanced elimination ration.

Affected animals present with lameness, reluctance to walk, and a failure to grow and gain weight. Animals may have angular limb deformities, particularly affecting the forelimbs. Rickets most commonly affects rapidly growing physes, such as the distal radius, proximal tibia, distal femur, and proximal humerus. The metaphyses of long bones, particularly the distal radius, may be swollen. Animals may have swollen costochondral junctions, known as the rachitic rosary. Affected animals may have pathologic fractures, and delayed eruption of teeth and enamel hypoplasia may also be seen. In animals with severe hypocalcemia, seizures may be the presenting clinical sign.

Osteomalacia is reported rarely in dogs, and this may partly be due to the subtlety of the clinical signs. The most common clinical sign of osteomalacia in humans is bone pain, and in older dogs this may easily be mistaken as reluctance to move due to chronic degenerative joint disease and not investigated further.

Diagnosis

Biochemistry

Animals with rickets due to vitamin D deficiency will have decreased or low normal serum calcium concentration, hypophosphatemia, increased serum alkaline phosphatase activity, and increased plasma PTH concentration. Serum vitamin D concentrations depend on the inciting cause of the rickets. In vitamin D deficiency rickets, usually both serum 25OHD and $1,25(OH)_2D_3$ concentrations are decreased. However, confusingly in some cases, the increase in PTH as a result of hypocalcemia leads to increased activity of the renal 1-alpha-hydroxylase and normal to increased serum $1,25(OH)_2D_3$ concentrations. Despite this, low serum 25OHD indicates there is insufficient vitamin D being obtained from the diet.

In phosphorus deficiency rickets, animals have severe hypophosphatemia but serum calcium and 25OHD

concentrations are normal. Serum $1,25(OH)_2D_3$ concentrations may be normal to increased.

Radiography

The key radiographic change seen in animals with rickets is widening and increased lucency of the long bones physes (Figure 172.2). A 10-point radiographic scoring method for rickets based on the severity of radiographic changes in the wrists and knees, to produce a score indicating the severity of nutritional rickets, has been developed for human patients. The key features of this scoring system include widening of the growth plate, irregularity of the physeal–metaphyseal interface, and concavity or cupping of the metaphysis. Other radiographic changes may include swollen costochondral junctions, infractions and other pathologic fractures, delayed appearance of ossification centers, curving of long bones, metaphyseal sclerosis, and generalized osteopenia. Stress fractures and decreased bone density are seen radiographically in osteomalacia. In humans, the presence of Looser zones is considered consistent with osteomalacia; these are radiolucent areas surrounded by a zone of sclerosis in the cortex.



Figure 172.2 Radiographs of the carpus from a 5-month-old Pomeranian with hereditary vitamin D-resistant rickets. There is substantial widening of the radial and ulnar physes, irregularity of the physeal–metaphyseal interface and cupping of the metaphyses. The metaphyseal-epiphyseal bone of the radius and ulna is flared. *Source:* Reproduced with permission from LeVine DN, Zhou Y, Ghiloni R, *et al*. Hereditary 1,25 dihydroxyvitamin D-resistant rickets in a Pomeranian dog caused by a novel mutation in the vitamin D receptor gene. *J Vet Intern Med* 2009; **23**: 1278–83.

Radiography can only give a qualitative indication of bone mineral density (BMD). DEXA or quantitative CT is required for a quantitative measurement of BMD. These techniques are also more sensitive in detecting mild to moderate decreases in BMD, and would be useful for monitoring response to treatment.

Therapy

Animals with nutritional rickets should be placed on a commercial balanced diet with the recommended 1:1 Ca:P ratio and adequate levels of vitamin D. This may be supplemented with additional calcium, phosphorus, and vitamin D as required. Care must be taken with vitamin D administration, as vitamin D is toxic at high doses, leading to widespread soft tissue mineralization, so regular monitoring of serum calcium and phosphorus concentrations is recommended. A recent study found that treatment with 25OHD increased serum 25OHD faster than cholecalciferol (vitamin D) treatment, although sample numbers were small and a safe dosage was not determined. Other vitamin D metabolite options include dihydrotachysterol, calcitriol ($1,25(OH)_2D_3$), and alfacalcidol.

Vitamin D_2 or ergocalciferol may be used but large doses are required initially, and its long half-life means that if an animal becomes hypercalcemic it takes up to four weeks for the effects of ergocholecalciferol to wane. Therefore, it is not considered an ideal treatment for rickets in dogs and cats.

Dogs and cats with rickets will benefit from 3–4 weeks of confinement in order to prevent further stress and microfractures. Pain relief for those with microfractures may be helpful.

Prognosis

The prognosis for dogs and cats with nutritional rickets for return to normality is good, providing catastrophic fracture does not occur and the predisposing reason (such as malabsorption, total parenteral nutrition) is removed. Once the poorly mineralized bone laid down during the period of dietary deficiency is replaced during remodeling, the bones will return to normal strength.

Inherited Rickets

Inherited forms of rickets resulting from inborn errors in metabolism have been diagnosed in both cats and dogs. There is confusion in the literature with regard to articles on inherited rickets; a number of reported cases are more consistent with a diagnosis of nutritional FOD than inherited rickets. Care should be taken in making a

diagnosis of inherited rickets, and the diagnosis should be confirmed with genetic testing.

There are three main groups of inherited rickets.

Vitamin D-Dependent Rickets Type I

An autosomal recessive disorder caused by a mutation in the *CYP27B1* (1-alpha-hydroxylase) gene that catalyzes the conversion of 25OHD to $1,25(OH)_2D_3$. Affected animals have clinical signs of rickets, hypocalcemia, hypophosphatemia, very high serum 25OHD concentrations, and low serum $1,25(OH)_2D_3$ concentrations. One unconfirmed case has been reported in a St Bernard dog, and a number of cases reported in cats; however, only two have reported causative mutations in the *CYP27B1* gene. Long-term treatment with $1,25(OH)_2D_3$ (calcitriol) is successful.

Hereditary Vitamin D-Resistant Rickets (Vitamin D-Dependent Rickets Type II)

An autosomal recessive disorder caused by a mutation in the vitamin D receptor (*VDR*) gene. In order to produce its calcemic effects, $1,25(OH)_2D_3$ must bind to the VDR-retinoid X receptor which then binds to vitamin D response elements in the promoter region of the vitamin D-responsive gene. Animals with mutations in the VDR are severely hypocalcemic and hypophosphatemic and have serum $1,25(OH)_2D_3$ concentrations 5–20 times greater than normal. Approximately 70–80% of human cases also have partial to total alopecia that may be obvious at birth or develop over the first few months of life. Confirmed cases have been diagnosed in a Pomeranian dog (see Figure 172.2) and a cat. A small number of human patients have been successfully treated with large doses of $1,25(OH)_2D_3$, but for most patients vitamin D treatment is not successful. Long-term intravenous calcium infusion has been the most successful treatment option for patients that did not respond to high doses of $1,25(OH)_2D_3$.

Hypophosphatemic Rickets

This form may have X-linked, autosomal dominant or autosomal recessive inheritance. Mutations have been found in the *FGF23*, dentin matrix protein 1 (*DMP1*), and ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*) genes. Whichever gene is affected, the pathogenesis behind the disease involves increased plasma FGF23 concentration resulting in renal wasting of phosphate and severe hypophosphatemia, normal serum calcium concentration, and low to low-normal serum $1,25(OH)_2D_3$ concentration. This form of rickets has not been described as yet in dogs or cats, but the description of one case in a cat from the 1990s appears clinically similar to an inherited phosphate wasting disorder.

Tumor-induced osteomalacia (TIO) is a disease with a similar phenotype to inherited forms of hypophosphatemic rickets and occurs due to paraneoplastic production of FGF23 by a tumor. TIO occurs in humans with tumors known as phosphaturic mesenchymal tumor, mixed connective tissue variant (PMT-MCT), which have many similarities to soft tissue sarcomas of dogs. One study found that three of 49 soft tissue sarcomas from dogs had high relative expression of FGF23, although no animals had clinical signs consistent with osteomalacia.

Osteoporosis

Osteoporosis is the result of an imbalance between bone resorption and bone formation. In contrast to fibrous osteodystrophy and rickets, the quality of the bone that is formed is normal; there is just less of it. Although the studies done on ovariectomized dogs have generally been poorly controlled for diet, age and other variables, it seems that unless dietary calcium is restricted, neutered dogs do not develop the postmenopausal osteoporosis that occurs in women. Potential causes of osteoporosis in dogs and cats include the following.

- *Senile osteoporosis* – general decline in bone mineral content with age, as osteoclastic resorption slowly outstrips bone formation during normal bone remodeling. Generally, this decline is not clinically significant.
- *Disuse osteoporosis* – lack of weight bearing due to immobilization or paralysis results in rapid loss of BMD in the immobilized limb and increased BMD in the contralateral limb. This effect is reversible once weight bearing resumes, particularly in young animals.
- *Inflammatory bowel disease and malabsorption* – likely due to a combination of reduced absorption of vitamin D and calcium, with increased inflammatory cytokines such as IL-6 leading to increased osteoclastic bone resorption.
- *Corticosteroid-induced* – glucocorticoids decrease calcium absorption from the intestinal tract, increase calcium excretion from the kidney, decrease osteoblast activity and increase bone resorption, all of which may lead to osteoporosis. A study in beagles with hyperadrenocorticism found that bone trabecular volume was decreased by 25% due to decreased bone formation.
- *Hyperthyroidism* – increased thyroid hormone concentrations lead to increased osteoblastic bone formation and increased osteoclastic bone resorption; however, the rate of bone resorption is greater than bone formation, resulting in osteoporosis. Pharmacologic doses of thyroxine administered to

dogs led to increased bone remodeling. While markers of bone formation (alkaline phosphatase and osteocalcin) may be increased in cats with hyperthyroidism, definitive data on the effect of thyrotoxicosis on bone are lacking.

- *Drugs* – in humans, ciclosporin and phenobarbital have been associated with osteoporosis.

Osteoporosis is rarely diagnosed in cats and dogs, in part possibly due to not considering it as a differential diagnosis for lameness or bone pain, and the insensitivity of radiography for its diagnosis. The future use of improved diagnostic testing such as DEXA and CT may reveal that osteoporosis is more common in these species than is currently thought.

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173

Osteoarthritis in Small Animals

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Osteoarthritis (OA, syn. osteoarthrosis, degenerative joint disease, DJD) is a syndrome that affects synovial or diarthrodial joints and may manifest its presence by causing pain in association with degeneration of articular cartilage (loss of extracellular cell matrix and chondrocytes, inflammatory response of synovium, and critical changes in proteoglycan ratios within matrix and synovial fluid) and changes in periarticular soft tissues. Since typically a low-grade inflammatory process is associated with the development and maintenance of the degenerative process of articular cartilage, the underlying subchondral bone response (e.g., sclerosis), intra- and periarticular response (e.g., synovial hypertrophy, periarticular fibrosis), the term *osteoarthritis* describes the disease process of the diarthrodial joint better than the older term *degenerative joint disease*. Typically, OA is an insidiously progressive, degenerative condition that targets high-motion synovial joints. Osteoarthritis can occur in two forms: primary and secondary, with secondary OA being the more common form presenting clinically in veterinary medicine.

Etiology/Pathophysiology

Primary OA is considered a "wear and tear" phenomenon of joint degeneration occurring in older patients. Although primary OA may be more common in cats than previously appreciated, it appears to be rare in dogs compared to clinical presentations for secondary OA issues. Causes of this form of OA in humans have been linked to obesity, the hormone leptin, and the development of OA. The target or targeted effected tissues that initiate the development of primary OA are unknown but could involve the initial degeneration of the subchondral bone resulting in secondary degeneration of articular cartilage, primary degeneration of articular cartilage, the synovium, or another tissue or combination of degeneration of tissues yet to be determined.

Secondary OA is due to an underlying or secondary cause for the development of the disease. Joint instability, direct joint trauma, infection, toxins, immune-mediated disease, and developmental/congenital disease are some of the known etiologies for the development of secondary OA and others may include infectious (e.g., septic arthritis) or noninfectious (e.g., immune mediated, trauma, developmental/congenital) environment development within the joint. The hyaline cartilage matrix (type 2 collagen, proteoglycan molecules and chondrocytes) is directly damaged which results in chondrocyte death. Synoviocytes are then stimulated to produce myriad cytokins and inflammatory mediators (e.g., interleukins, inducible encosinoids, nitrous oxide, tumor necrosis factor-alpha, etc.). These synoviocyte-based products then in turn stimulate surviving chondrocytes to produce many of the same cytokines and inflammatory mediators which result in the production of chondrocyte-based matrix metalloproteinases which catalytically digest more cartilage matrix (increased aggrecans content of matrix and synovial fluid drawing more water into matrix and synovium) and reduces the matrix's ability to biomechanically manage normal load and shear forces at the cartilage surface (resulting in more matrix loss and debris as well as fracturing of the supporting subchondral bone deep to the cartilage matrix). In addition, the chondrocyte-based cytokines and inflammatory mediators directly result in chondrocyte apoptosis. The cartilage matrix is now in a continuous metabolic state of catabolism which will drive the progression of osteoarthritis in the affected joint (Figure 173.1).

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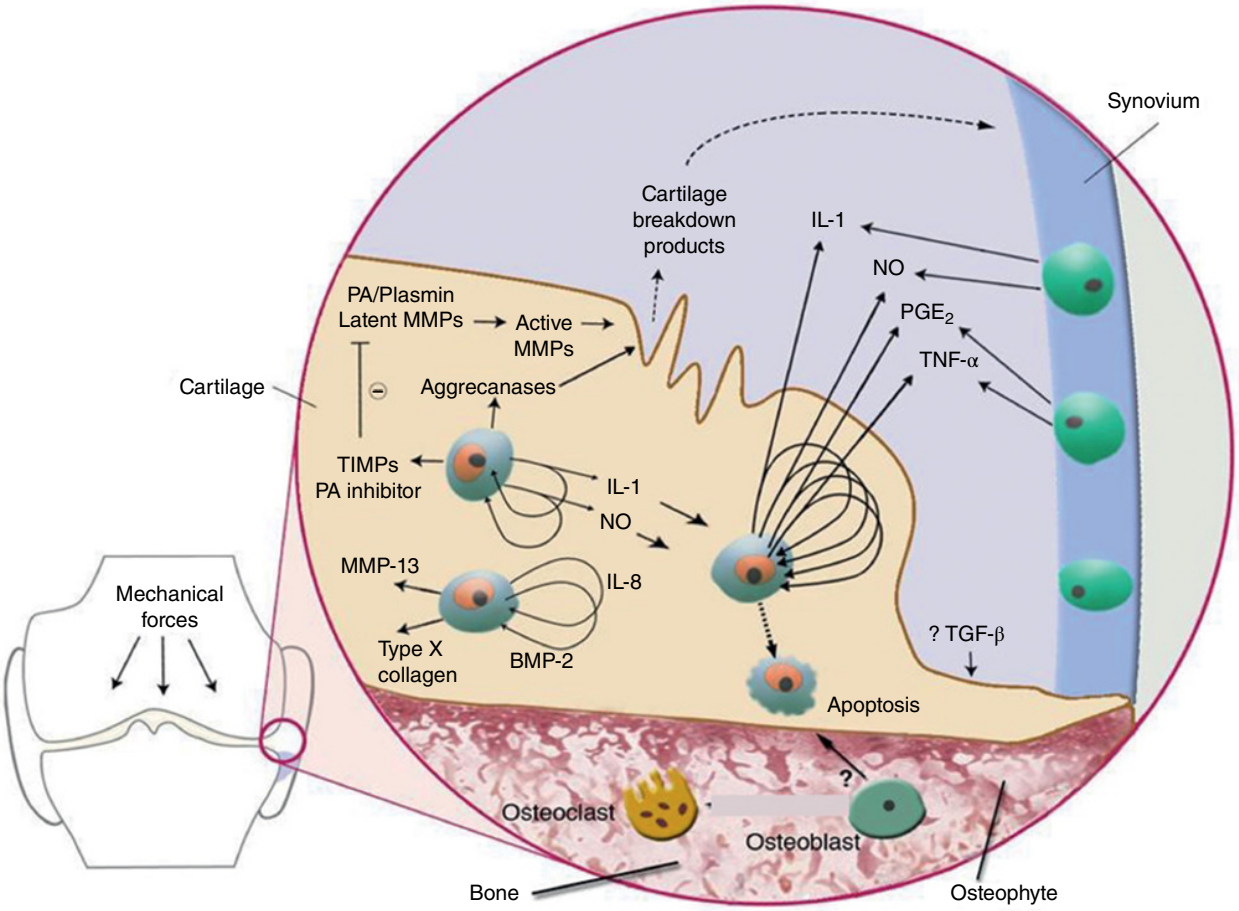


Figure 173.1 Molecular pathogenesis of osteoarthritis. Development and propagation of osteoarthritis with disruption of the cartilage matrix, stimulation of synoviocytes to produce inflammatory mediators and cytokines, stimulation of chondrocytes to produce inflammatory meditators, cytokines, and enzymes (matrix metalloproteinases) that result in apoptosis and matrix loss, all perpetuating the progression of osteoarthritis. IL-1, interleukin-1; IL-8, interleukin-8; MMP, matrix metalloproteinase; NO, nitrous oxide; PA, plasminogen activator; PGE_2, prostaglandin E_2; TGF, transforming growth factor; TIMP, tissue inhibitor of metalloproteinase; TNF-alpha, tumor necrosis factor-alpha. *Source:* (www.med.nyu.edu). Reproduced with permission of Steven Abramson, MD.

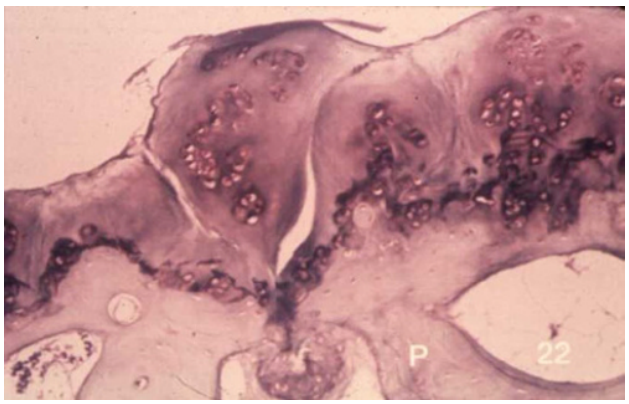


Figure 173.2 Photomicrograph of osteoarthritis. Osteoarthritis cartilages: note the presence of fibrillation, fissuring, cloning chondrocytes, loss of staining due to loss of proteoglycans in the matrix, and fracture of subchondral bone. *Source:* Image courtesy of Dr Steven Arnoczky.

Micro- and macroscopic changes within the synovial joint may result in the clinical signs of lameness due to joint pain (synovitis, microfractures of subchondral bone, osteophytes, and joint effusion/distension) (Figure 173.2).

Epidemiology

The radiographic incidence of OA in referral hospital-based cats is estimated at 26–82% depending on age (older cats, greater incidence). In dogs, OA has been estimated to clinically affect 20% of the dog population in the United States.

Signalment

Primary OA typically occurs in older males or female cats with a higher incidence with older age. As previously

stated, primary OA appears to be relatively uncommon in dogs but would also be hypothesized to occur in older dogs.

Secondary OA can occur in any breed or sex of dog at any age. Certain juvenile skeletal developmental diseases (e.g., elbow dysplasia, hip dysplasia, osteochondritis dissecans. etc.) that result in secondary OA have the propensity to clinical affect dogs between the ages of 5 and 11 months. Skeletally mature dogs of either sex (>1 year of age) may on occasion present with clinical signs of OA due to juvenile skeletal developmental diseases. Many of the juvenile skeletal developmental diseases that affect joints are breed specific or may be breed nonspecific.

Osteoarthritis secondary to etiologies other than juvenile skeletal developmental diseases can occur with any sex and any age of dogs. Cranial cruciate ligament rupture continues to be a common cause of OA in mature dogs. With the exception of hip dysplasia, secondary OA is usually recognized in cats of any sex, breed, or age following joint trauma such as articular fractures.

History and Clinical Signs

The clinical history of most canine OA patients will commonly be a noted lameness of the affected limb following activity. Typically, the lameness will worsen with progressive activity. Hip dysplasia patients have a different gait history from other causes of OA which centers on the appearance of stiffness to rise and then sudden halting of activity (e.g., "sitting down") rather than increasing lameness. Owners may also note a classic "bunny hopping" gait in a hip dysplasia patient when running. With any form of OA, owners may also note pain on flexion, extension, and/or with other manipulation of the affected joint.

The clinical history of most feline OA patients will center on behavior/activity changes; more fractious or more subdued with owner or other animal interactions and less active than noted previously (sitting/crouching for long periods of time).

The clinical signs associated with OA vary from patient to patient and may range from subclinical to a severe functional disability. The following clinical findings are typical of patients with OA.

Gait Assessment

- Reduced weight bearing of affected limb
- Shorten stride length of contralateral normal limb
- Audible clicking or "clunking" during gait
- Pelvic swings enhanced to the contralateral side of the affected pelvic limb
- Head dorsiflexed on affected thoracic limb side
- Narrowed pelvic limb stance

Physical Exam Findings

- Asymmetric or symmetric muscle atrophy
- Asymmetric or symmetric joint thickening/joint effusion/heat
- External rotation of pelvic limb or thoracic limb
- Decreased joint range of motion (flexion and/or extension)
- Crepitus during joint motion
- Pain/discomfort on one or more aspects of joint manipulation (flexion, extension, abduction, adduction, internal or external rotation)

Diagnosis

Diagnostics are initially directed towards orthogonal view radiographs of the affected joint and should include the contralateral joint for comparative assessment. Radiographic features indicative of OA include osteophytes, effusion, subchondral bone sclerosis with or without lucencies or erosive patterns (Figure 173.3).

Other nonimaging modalities can be used for more detailed joint evaluation, including computed tomography (CT) and magnetic resonance (MR) imaging . These modalities may be beneficial if radiographic findings are minimal or equivocal for radiographic features to support a diagnosis of OA.

Arthrocentesis with synovial fluid cytology and fluid analysis may be beneficial to confirm the diagnosis of OA or to rule out other forms of joint disease, including immune-mediated arthropathies, septic arthritis, or neoplasia. Typical secondary OA cytologic findings in dogs are 1000–5000 nucleated cells/mm^3, 88–100% mononuclear cells, and 0–12% neutrophils. Viscosity may be normal to low.

If indicated (and rarely required beyond radiographic diagnostics), minimally invasive diagnostics in dogs can also be performed with arthroscopy. Direct macroscopic visualization of the articular cartilage for evidence of fibrillation, erosions, the presence of osteophytes, and examination of the synovium for hypertrophy and inflammation can provide a definitive diagnosis of OA in a patient (Figure 173.4). Usually, arthroscopy can provide the etiology for the secondary OA as well (e.g. ostochondritis dissecans (OCD), fragmented medial coronoid disease, medical compartment disease of the elbow, cranial cruciate ligament disease, etc.).

Therapy

Management strategies for clinical OA patients are focused on the fact that OA progression cannot be halted or reversed. Fundamentally, no one treatment will be all-encompassing for all patients with OA. An individualized

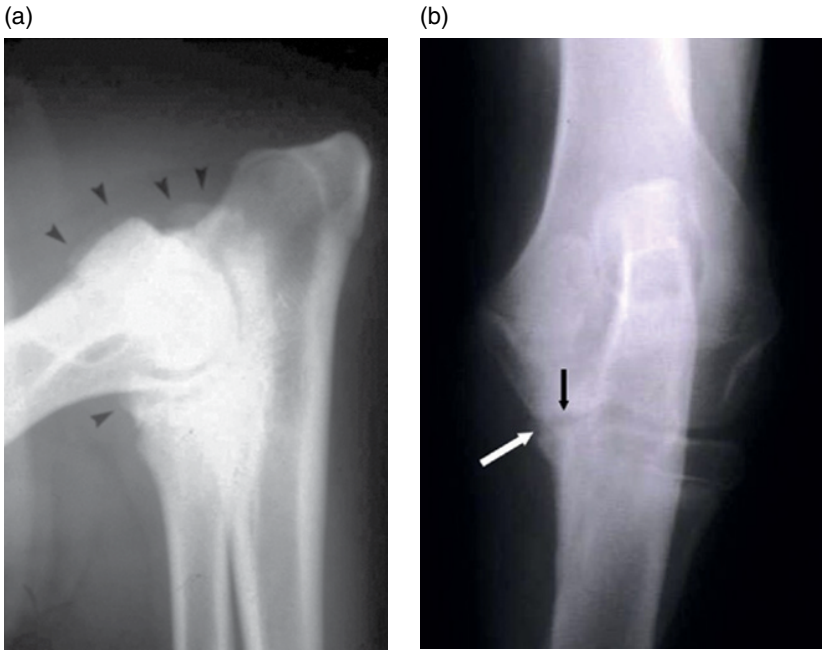


Figure 173.3 (a) Radiographic appearance of osteoarthritis. Two-year-old female-spayed Labrador retriever with chronic elbow dysplasia (mediolateral projection of the left elbow). Note osteophyte development (*black arrowheads*) and marked subchondral bone sclerosis of the ulna. (b) Eleven-month-old male-castrated Labrador retriever with elbow dysplasia due to an OCD lesion of the medial side of the humeral condyle. Note osteophyte development on the medial side of the coronoid process of the ulna (*white arrow*) and the subchondral bone lucency on the medial side of the humeral condyle (*black arrow*).

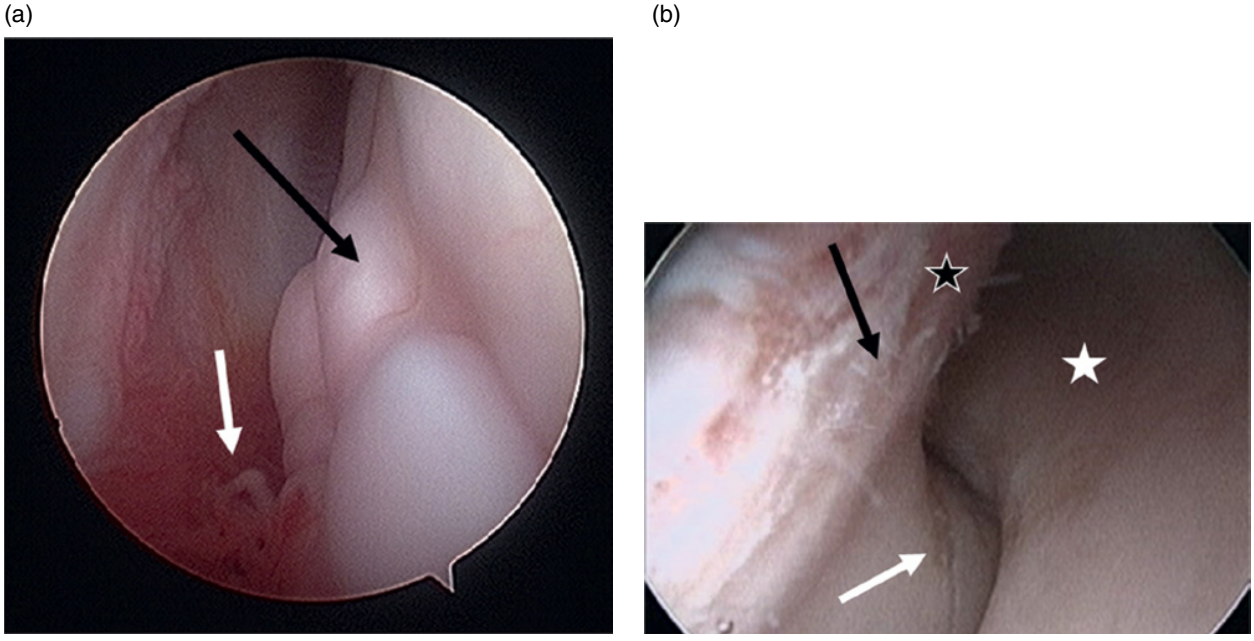


Figure 173.4 (a) Arthroscopic appearance of osteoarthritis. Four-year-old female-spayed Rottweiler with cranial cruciate ligament rupture of the right stifle. Note osteophyte development on the lateral aspect of the trochlear ridge of the right femur (*black arrows*) and synovitis (*white arrow*). (b) Twelve-month-old female-spayed Labrador retriever with elbow dysplasia. Note articular cartilage fibrillation (*black arrow*), erosions (*white arrow*), and ebernation (*black star*) on the humeral condyle and ebernation on the anconeal process of the ulna (*white star*).

approach must be taken to successfully treat OA patients. Current treatment strategies used to treat OA patients are multimodal medical management, surgery or, more commonly, the integration of both treatment modalities.

A multimodal management "pyramid" with three major components – weight control, exercise modification, and pharmaceuticals/nonpharmaceuticals – must be considered when nonsurgically managing a patient with OA (Figure 173.5). Exclusion of one or more of these components from a treatment protocol will result in an overall poorer clinical response from the patient.

Weight Control

Obesity is a major risk factor for the development of OA in people and weight loss can reduce the symptomatic

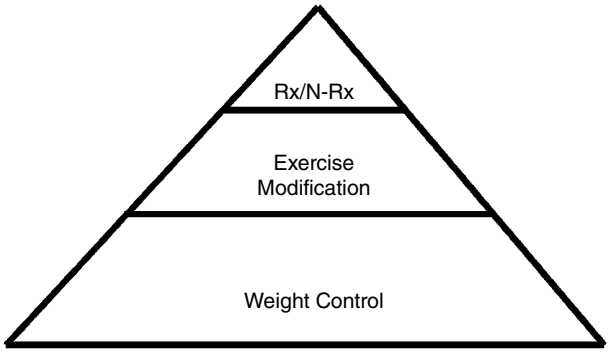


Figure 173.5 Multimodal approach to treating osteoarthritis. Three basic components of the multimodal strategy for the management of the clinical signs of osteoarthritis. The size of the area of each component within the pyramid reflects the importance of that component for successful management of the patient.

effects of OA. Recently, research shows the same is true for other animals. A clinical study investigating the effects of obesity in dogs with hip dysplasia concluded that overweight dogs that achieved an 11–18% body weight reduction were significantly less lame compared to their preweight reduction lameness scores.

Weight control can be one of the most challenging aspects of the medical management of OA in dogs for several reasons.

- A patient that is clinically inhibited by moving an OA joint(s) will not be able to utilize consumed or stored body energy efficiently and will instead increase body stores of energy (fat) when given a constant caloric intake.
- Dogs with underlying endocrine disease (e.g., hyperadrenocorticism, hypothyroidism) will have the metabolic propensity to maintain body fat stores even in the face of a reducing diet.
- Dogs in a multipet household (e.g., other dogs and cats) are more prone to consume greater volumes of food than dogs in single-pet households.
- An inaccurate estimation of the animal's ideal body weight.
- An inaccurate estimation of the animal's energy requirements.
- The owner's lack of willingness to be proactive in trying to reduce their pet's body weight.

Any one or a combination of the above factors will maintain the obese patient indefinitely.

Prior to starting a weight-reducing program, a complete physical exam should be performed. The clinical history (attempted weight reduction in the past with poor results, lethargy, "heat seeking," polyuria/polydipsia, etc.) and physical exam findings (pendulous abdomen, symmetric alopecia, recurrent dermatopathy, etc.) may warrant a complete minimum database (complete blood count [CBC], serum chemistry profile, urinalysis [UA]) to rule out metabolic disease or endocrinopathies.

Weight reduction can be obtained in healthy patients by four methods.

- Reducing current caloric intakes, using reductions by 33–50% of the "normal" volume of the regular diet.
- Calculating caloric content of regular diet and caloric needs based on basal metabolic rates.
- Using specially formulated commercial diets with recommended intake volumes per the manufacturer.
- Pharmacologic management (e.g., dilotapide).

Appropriate caloric restriction should result in the loss of 1–2% of body weight per week.

All weight reduction/control programs must include an exercise element to ensure constant weight loss and eventual body weight maintenance. To encourage activity in the debilitated OA patient, regular pharmacologic treatment may be required for a short period until the patient becomes more ambulatory and physiologically acclimated to the new level of physical activity.

Exercise and Activity Modification

Exercise is very important in people for maintaining strength, stamina, and joint range of motion; there is also less dependency on medication when OA patients are allowed to exercise. It is assumed that the same is true in other animals as well and this is supported by a study in hamsters. Therefore, an important aspect in the management of OA in animals should be controlled exercise. Depending on the animal's activity history, it may be necessary to modify a patient's regular level and type of activity.

It may seem intuitive that an OA animal should not be allowed to have hard-impact, prolonged exercise activity, but controlled clinical studies have not been performed to evaluate this recommendation. However, from clinical experience, practitioners are used to hearing the usual owner's report of greater clinical signs in OA patients after hard, prolonged activity. It is known from kinetic and kinematic gait analysis that dogs with OA will modify their gait to reduce the load of weight bearing and motion of the affected joint. It is therefore safe to assume that prolonged "overactivity" should result in greater modification of gait due to exacerbation of the discomfort associated with an OA joint. Some recommendations for the duration of certain activities in dogs have been made but recommendations for activity duration can also be based on common sense and owner observations of their pet's apparent gait response/comfort level to an activity period.

Just as important as duration of activity is the type of activity undertaken in the animal's daily lifestyle.

Low-impact activities (e.g., walking, cycling) have positive effects on human OA patients. In veterinary medicine, low-impact activities (walking, swimming) have been traditionally favored over hard-impact aerobic activities (jumping, hard starting/running, vigorous climbing/running on irregular terrain) which can overstress degenerative joints. High-impact activities may overstress OA joints and increase the inflammatory condition of OA. Low-impact activities are thought to reduce loads on an OA joint and result in less discomfort for the patient in maintaining good muscle strength/mass and joint function. Walking under controlled conditions (leash restraint) and/or swimming can be recommended to the owner with further instructions to eventually attempt to have the patient increase the duration of these activities gradually so long as the animal appears to remain comfortable in doing so. To strengthen the active stabilizers (muscles and tendons) and to improve the range of motion of joints in OA patients, several physical rehabilitation modalities such as passive and active range of motion exercises, message, deep ultrasound heat applications, and laser therapy can be administered by certified small animal physical rehabilitation technicians and specialists. In many OA cases, the adjunct use of physical rehabilitation can help improve patient comfort and function with very good to excellent clinical results.

Pharmacologic/Nonpharmacologic OA Agents

The primary goal in the pharmacologic management of OA is to relieve the patient of discomfort associated with joint movement. Ideally, this would involve oral or injectable agents with analgesic, antiinflammatory, and potential chondromodulating properties (disease-modifying OA agents, DMOA). Such agents would ideally biochemically block the inducible cyclooxegenase-2 (COX-2) and lipoxygenase pathways. Several FDA-approved "COX-selective" nonsteroidal antiinflammatory drugs (NSAIDs) have been developed for this purpose (e.g., carprofen, meloxicam, firocoxib, etc.). Robenaxocib is currently the only approved NSAID for cats in the United States. Grapiprant, a newer class of prostaglandin receptor antagonist; a non-COX pathway inhibitor for the treatment of the clinical signs of OA, has been developed with the intent to reduce the potential of adverse events of GI. renal, and liver disease seen in the small percentages of patients administered select and non-select COX-2 inhibitors. Grapiprant is specific to the blockage of Prostaglandin E2 receptor 4 (EP4); a primary mediator of OA-based pain and inflammation. Although touted as a "non-NSAID" anti-inflammatory and analgesic drug, OA patients administered grapiprant can have the risk to develop adverse events that include GI disease (emesis, diarrhea, and anorexia), and subclinical hyperalkaline phosphatemia and hypoproteinemia.

All COX-selective (and nonselective) NSAIDs have toxicity potential. Hepatic toxicosis due to NSAID administration has been reported; however, all NSAIDs have a toxicity potential especially if a patient has underlying hepatic or renal disease, or thrombocytopathy. Several *in vivo* studies using chondrocyte cell cultures or cartilage explants have reported a decrease in proteoglycan synthesis in those tissues incubated with selected NSAIDs. It would appear to be a wiser clinical practice to administer NSAIDs on a PRN basis, especially for the patient that has only intermittent discomfort due to osteoarthritis.

Disease-modifying osteoarthritis agents have recently been developed for the treatment of human and veterinary OA patients. These agents have become commonplace in the treatment of OA despite the lack of definitive scientific studies confirming their efficacy. Most of these products contain mixtures of glucosamine and chondroitin sulfate, which supposedly enhance cartilage health by providing the necessary precursors to maintain and repair cartilage. Glucosamine and chondroitin sulfate reportedly have a positive effect on cartilage matrix by enhancing proteoglycan production and inhibiting catabolic enzyme production or activity in OA joints. These properties have contributed to the labeling of these agents as "chondroprotective." With the exception of one product which is a true pharmaceutical by definition (Adequan®, Luitpold Pharmaceuticals, FDA approved in horses and dogs), these agents are marketed as oral nutritional supplements ("nutricueticals") and not "drugs" and as such, the FDA does not require the manufacturer to provide efficacy data for their product. Bioavailability of orally ingested forms of glucosamine and chondroitin sulfate is 87% and 70% in humans and experimental animals, respectively. Limited investigations have been performed on the *in vitro* and *in vivo* activity of glucosamine and chondroitin sulfate separately, but products containing both agents have become popular for treating OA symptoms in humans and other animals. Synergism with glucosamine and chondroitin sulfate has recently been demonstrated histologically and with *in vivo* biochemical analysis in a rabbit OA model.

Glucosamine and chondroitin sulfate are two regular nutricuetical combinations used in many dietary supplenets for dogs and cats. Examples of these formulations are Cosequin® and Dasuquin® (similar to Cosequin® but with the additions of with avocado/soybean unsaponifiables and methylsulfonylmethane (MSM) (Nutramax) and Glycoflex® (Vetri-Science Laboratories). Although clinically noted not to have predictable

efficacy in all dogs, this combination of a precursor glycosaminoglycan and a glycosaminoglycan appears to have a prophylactic effect on the development of OA in dogs. Dogs undergoing a Pond-Nuki model for the development of OA with or without stifle stabilization that were administered Cosequin for five months following surgery subjectively had less OA and less periarticular fibrosis than dogs not receiving Cosequin. Chymopapain- induced acute carpal synovitis was significantly attenuated based on nuclear scintigraphy and lameness evaluation when dogs were pretreated with glucosamine and chondroitin sulfate (Cosequin). Current research suggests that glucosamine and chondroitin sulfate products may be prophylactically beneficial in patients that are prone to develop OA (e.g., canine hip dysplasia [CHD], elbow dysplasia, OCD, cranial cruciate ligament injury, etc.) or patients that may aggravate preexisting OA with activity. Further controlled clinical studies are still warranted to support these statements.

Injectable forms of DMOA available include Adequan, which is a polysulfated glycosaminoglycan (PSGAG) product, and hyaluronic acid (HA), a nonsulfated GAG. The US (Adequan) and European products (Arteparon®) have been used in horses and dogs. Although conflicting evidence exists that PSGAGs have a positive anabolic effect on hyaline cartilage, studies have shown that PSGAG may decrease hyaline cartilage catabolism. In one study, immature dogs prone to hip dysplasia administered Adequan developed better hip conformation than dogs that were not treated with Adequan. A clinical study investigating the use of PSGAG on hip dysplasia patients found no significant difference in orthopedic scores (lameness, range of motion, pain on manipulation of hip joints) compared to PSGAG nontreated dogs. In a meniscectomy model in dogs, PSGAG provided partial protection to articular cartilage damage associated with the meniscectomy. PSGAG has been reported to have chondroprotective properties in joints with a chemically induced articular cartilage damage model versus no effect on a physical articular cartilage damage model in horses. Anecdotal reports have appeared indicating that there may be a positive synergism between injectable PSGAG and oral glucosamine and chondroitin sulfate when administered concurrently to a patient.

Hyaluronic acid (sodium hyaluronate, HA) is a major component of synovial fluid. HA acid is postulated to enhance joint health by increasing the viscosity of the joint fluid and reducing inflammation and scavenging free radicals. A study using a Pond-Nuki model for OA in dogs followed by intraarticular injections of HA did not modify OA and reduced overall proteoglycan concentrations in treated stifles.

Other products reported that have disease-modifying, anti-OA potential include pentosan polysulfate, tetracyclines (doxycycline, minocycline, and modifications of these molecules), methylsulfonylmethane (MSM), capsaicin, and fatty acid ratio manipulation (omega-6:omega-3). S-adenosyl-L-methionine (SAMe) has objectively not been shown to have efficacy in dogs to resolve the clinical signs of OA. Dietary management using omega-3 fatty acids has been reported to improve clinical scores and ground reaction forces in approximately 25–82% of patients. Metaanalysis evaluating the efficacy of various nutritional-based DMOAs concluded that only fatty acid diet modifications appear to have the strongest evidence-based results to ameliorate the clinical signs of OA in dogs. There are several commercially available OA diets that incoroprate the use of omega-3 fatty acid in the dietary formulations with other formulations adding antioxidants such as Vitamin E, C, as well as glucosamine and chondrotin sulfate.

Adjuncts to pharmacologic, exercise/activity, and weight control treatments that can also be considered are the application of heat, cold, massage, hydrotherapy, ultrasound/diathermy, and electrotherapy. Although based on anecdotal observations only, these adjuncts appear to help some patients. Laser, chiropractic, extracorporeal shockwave therapy (EST), and acupuncture are professed to improve canine patients with the clinical signs of OA. EST results reported can be variable with regard to the joint evaluated and to date, acupuncture has not been evaluated to be efficacious in dogs with OA of the hip or elbow. Laser and chiropractic procedures are anecdotally proclaimed to have efficacy in OA patients or at best, may have only limited *in vivo* support for efficacy. Unfortunately, placebo or negative controlled clinical studies are needed to test the supposition that these and other developing modalities (e.g., radiation) have efficacy in veterinary OA patients.

Recently, the use of autogenic tissues such as adipose-derived mesenchymal stem cells and platelet-rich plasma or platelet-enhanced plasma intraarticular injections has been investigated as therapies to attenuate the clinical signs of OA in dogs. Although early results appear promising for these therapies, additional controlled clinical trials are needed to provide better evidence-based proof that they justify their high costs to the owner of an OA patient.

Surgical management for the clinical signs of OA are limited to arthroplasty (via arthroscopy or arthrotomy), arthrodesis, total joint replacement for selected joints, or limb amputation. Nonexcisional arthroplasties will typically require the integration of a multimodal medical approach to provide better long-term function for the patient.

Prognosis

Dogs and cats can be significantly affected by OA; however, new concepts with a balanced multimodal management approach to treat the clinical signs of OA can result in an acceptable quality of life for the majority of OA patients, providing fair to excellent prognoses for lame-free function. Included in the formula for prognosis will be the consideration of a specific joint affected by OA (biomechanics, e.g., shoulder vs tarsus) and the degree of disease present in that joint (e.g., cartilage erosions vs minimal cartilage disease). Nonsurgical management must be considered beyond conventional and nonconventional pharmacologic treatment to include a balance created between exercise/activity and weight control management. Failure to consider this multimodal approach to OA treatment, especially in an individualized medicine approach (i.e., not all dogs or cats will respond the same with the same treatments), will usually result in a poorer clinical response to therapy (surgical and nonsurgical) and quality of life as perceived by the owner of the OA patient.

Excellent progress continues in the development of new pharmaceuticals and other agents to combat or even reverse the degenerative processes of OA. In contrast, research and development into exercise/activity management for the OA companion animal lag significantly behind those of human medicine, but since the mid-1990s, it has become a major treatment focus in veterinary medicine. Nonetheless, large controlled clinical trials are still needed for "evidence-based" treatment protocols (controlled clinical trials) that will allow us to treat our OA patients beyond the individual clinician's clinical experience.

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174

Developmental Orthopedic Diseases

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Developmental orthopedic diseases (DODs), a subset of canine pediatric orthopedic diseases, are a group of bone and joint diseases that initiate and develop during postnatal skeletal growth, mostly during the first 26 weeks of life. During this period, joints attain their adult morphology and bones assume their mature length and shape. Pediatric orthopedic diseases are aberrations of this ordered process (including endochondral ossification), described in more detail in Chapter 172. Most DODs are caused by multifactorial traits, with presumed or demonstrated genetic, nutritional, and environmental risk factors. Developmental orthopedic diseases may affect bones or joints. In this section, we will discuss hip dysplasia, osteochondrosis, patella luxation, Legg–Calvé–Perthes disease, craniomandibular osteopathy, panosteitis, hypertrophic osteodystrophy, and slipped capital femoral epiphysis (SCFE). Although all these diseases develop and usually manifest during the period from birth to skeletal maturity, their long-term clinical effects may be persistent and profound.

Developmental Orthopedic Diseases Affecting Joints

Canine Hip Dysplasia

Etiology and Pathophysiology

Hip dysplasia literally means abnormal development of the hip joint. The abnormal development appears to start with laxity of the hip joint, with subsequent subluxation and abnormal wear and tear of the joint. The joint capsule becomes inflamed, the cartilaginous joint surface is mechanically disrupted, and progressive osteoarthritis (OA) ensues. The condition is usually bilateral.

At birth, the hip joints of puppies that will develop canine hip dysplasia (CHD) are indistinguishable from joints that will develop normally. After birth, laxity has been associated with increased synovial fluid volume, as well as swelling, damage, and excessive lengthening of the ligament of the head of the femur. Dysplastic puppies have a delayed onset and abnormal progression of mineralization of the head of the femur compared to nondysplastic puppies. Muscular development is also abnormal, with predisposed breeds often having reduced pelvic muscle mass, and atypical pectineal muscle fiber composition having been demonstrated in affected dogs.

In dysplastic animals with subluxated joints, greater muscle forces are required to generate equivalent hip motion compared to healthy animals. This, combined with the smaller contact area of the incongruent opposing joint surfaces caused by the subluxation, results in abnormal wear and tear of the articular surfaces with subsequent synovitis and OA.

The etiology of laxity is not fully understood but includes genetic, endocrine, and nutritional factors. Canine hip dysplasia is mostly diagnosed in medium- and large-breed dogs and strong breed predispositions have been identified (Table 174.1). The condition is considered a polygenic trait with a heritability varying from 0.2–0.3 (based mostly on arthritic changes on the ventrodorsal extended hip joint radiographs) to 0.5–0.6 (mostly based on distraction index or dorsolateral subluxation index). Thus, somewhere between 20% and 60% of the phenotype of a patient affected with CHD may be attributed by its genetic make-up. Several quantitative trait loci (QTLs; chromosomal regions

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Table 174.1 Breed predispositions for selected developmental orthopedic diseases (DODs).

Trait	Breeds at increased risk	Comments
DODs affecting bones		
Craniomandibular osteopathy	Cairn terrier, Scottish terrier, West Highland white terrier	Autosomal recessive in West Highland white terriers
Hypertrophic osteodystrophy	Boxer, Chesapeake Bay retriever, German shepherd dog, golden retriever, Great Dane, Irish setter, Labrador retriever, Weimaraner	–
Panosteitis	Afghan hound, akita, American cocker spaniel, American Staffordshire terrier, basset hound, bearded collie, Bernese mountain dog, boxer, bull terrier, bulldog, Chesapeake Bay retriever, chow chow, Dalmation, Doberman pinscher, English Setter, English springer spaniel, giant schnauzer, German shepherd dog, German shorthaired pointer, golden retriever, Great Dane, Great Pyrenees, Irish wolfhound, Labrador retriever, mastiff, Neapolitan mastiff, Newfoundland, Rhodesian ridgeback, Rottweiler, St Bernard, shar-pei, shih tzu, Weimaraner, West Highland white terrier	–
DODs affecting joints		
Osteochondritis dissecans (OCD) shoulder	Bernese mountain dog, border collie, bouvier, boxer, bullmastiff, Chesapeake Bay retriever, Dalmation, English setter, German shorthaired pointer, German shepherd dog, German wirehaired pointer, golden retriever, Great Dane, Great Pyrenees, Irish wolfhound, kuvasz, Labrador retriever, mastiff, Munsterland, Newfoundland, Old English sheepdog, Rottweiler, St Bernard, standard poodle	Polygenic mode of inheritance
OCD elbow	Chow chow, German shepherd dog, golden retriever, Great Dane, Labrador retriever, Newfoundland, Rottweiler	Polygenic mode of inheritance
Fragmented coronoid process	Basset hound, Bernese mountain dog, bouvier, bullmastiff, chow chow, German shepherd dog, golden retriever, Gordon setter, Irish wolfhound, Labrador retriever, mastiff, Newfoundland, Rottweiler, St Bernard	Polygenic mode of inheritance
Ununited anconeal process	Basset hound, Bernese mountain dog, chow chow, English setter, German shepherd dog, golden retriever, Labrador retriever, mastiff, Newfoundland, Pomeranian, Rottweiler, St Bernard, shar-pei	Polygenic mode of inheritance
Hip dysplasia	Airedale, Alaskan malamute, bearded collie, Bernese mountain dog, bloodhound, border collie, bouvier, Briard, Brittany spaniel, bulldog, bullmastiff, Chesapeake Bay retriever, chow chow, English springer spaniel, German shepherd dog, German wirehaired pointer, giant schnauzer, golden retriever, Gordon setter, Great Dane, Great Pyrenees, keeshond, kuvasz, Labrador retriever, mastiff, Neapolitan mastiff, Newfoundland, Norwegian elkhound, Old English sheepdog, pointer, Portuguese water dog, Rottweiler, St Bernard, Samoyed, tree walking coonhound	Polygenic. Heritability of 0.2–0.6
Legg–Calvé–Perthes disease	Australian shepherd, cairn terrier, Chihuahua, dachshund, Lhasa apso, Manchester terrier, miniature pinscher, pug, toy poodle, West Highland white terrier, Yorkshire terrier	Autosomal recessive or multifactorial with high heritability
OCD stifle joint	Boxer, bulldog, German shepherd dog, golden retriever, Great Dane, Irish wolfhound, Labrador retriever, mastiff, Rottweiler	-
Patella luxation (medial and lateral)	Akita, American cocker spaniel, Australian terrier, basset hound, bichon frise, Boston terrier, bulldog, cairn terrier, Cavalier King Charles spaniel, Chihuahua, chow chow, flat-coated retriever, Great Pyrenees, Japanese chin, keeshond, Lhasa apso, Maltese, miniature pinscher, miniature poodle, papillon, Pekingese, Pomeranian, pug, sha-rpei, shih tzu, silky terrier, standard poodle, toy fox terrier, toy poodle, West Highland white terrier, wirehaired fox terrier, Yorkshire terrier	Multifactorial, polygenic. Low heritability
OCD talocrural joint	Labrador retriever, Rottweiler, bullmastiff	-

Source: Modified from LaFond E, Breur GJ, Austin CC. Breed susceptibility for developmental orthopedic diseases in dogs. *J Am Anim Hosp Assoc* 2002; **38**: 467.

containing a gene or group of genes influencing the phenotypic expression of a trait) for CHD and hip OA have been identified on multiple canine chromosomes. Several upgraded genes like *COX-2*, *MIG-6/Gene 33*, *DNCLl*, *LAMS*, and *ATF3* have been identified. Only genetically predisposed animals exposed to certain specific environmental factors may develop clinical hip dysplasia, and dogs not predisposed but exposed to the same environmental factors will not.

The hormones estrogen and relaxin have also been implicated as etiologic factors of CHD. Both are present in colostrum and may be absorbed from the puppy's gastrointestinal tract. Estrogen is probably not a strong etiologic factor, as estrogen fluctuations during the estrus cycle do not result in joint laxity changes. One of relaxin's functions prepartum is to relax the ligaments of the maternal pubic symphysis, and in dogs and humans it is associated with joint laxity. However, the significance of relaxin in the etiology of CHD is unclear.

Rapid growth and body weight have been associated with the development of CHD. In recent studies, heavier puppies developed hip OA requiring treatment at a much younger age than lighter littermates. Similarly, *ad libitum* feeding of Labrador retrievers accelerated the onset of hip OA when compared to a control group fed a restricted diet. High dietary concentrations of calcium and/or vitamin D3 have also been implicated, but not conclusively proven, as etiologic factors. A high dietary anion gap and vitamin C deficiency have also been proposed as causes of CHD, but their clinical significance has not been demonstrated.

Epidemiology

Hip dysplasia is the most commonly diagnosed canine orthopedic condition and in one North American epidemiologic study of canine appendicular musculoskeletal disorders, it comprised 9.6–12.8% of all patients. In this population, the incidence of CHD ranged from 21.1 to 28.1 per 1000 patients, but incidences as high as 50–70% in some large breeds have been reported. Hip dysplasia in cats is thought to be uncommon.

Signalment

Canine hip dysplasia is most commonly diagnosed in medium- and large-breed dogs (see Table 174.1). Male and female dogs are equally affected. Patients younger than 1 year of age are usually presented because of pain and lameness caused by synovitis following hip laxity. As a result of progressive joint capsule fibrosis, older, mature patients usually have minimal laxity but suffer from subsequent hip OA.

History and Clinical Signs

Young patients with hip dysplasia (hip laxity) usually present with uni- or bilateral lameness, bunny hopping, difficulty rising, reluctance to walk, trot, jump, or climb stairs, and exercise intolerance. Hips are often very painful in these animals. Older dogs mostly present with similar signs but with a more chronic presentation due to the slow progression of arthritic changes. Differentials for these signs include panosteitis, iliopsoas myopathy, bilateral cruciate disease, and lumbosacral disease.

Diagnosis

Affected hip joints have a decreased range of motion and pain on extension and abduction, and may exhibit crepitus on manipulation. There is often atrophy of the large muscles round the thigh and hip joint. Hip laxity may be clinically assessed using the Ortolani test. With this test, the presumed lax hip joint is first manually subluxated and then reduced. If the joint is lax, the subluxated hip will reduce with a palpable or audible clunk or click. This evidence of reduction is regarded as a positive Ortolani sign and is suggestive of hip laxity. In the awake, unsedated patient, the Ortolani test can be most easily performed with the dog in lateral recumbency, affected side up. The test may induce pain and should be performed humanely. In the sedated patient, the Ortolani maneuver also can be performed with the patient in dorsal recumbency.

The diagnosis of CHD is confirmed using well-positioned, ventrodorsal extended hip and lateral pelvic radiographs. The lateral pelvic view is mostly evaluated for evidence of lumbosacral disease. The ventrodorsal hip-extended (VD) view is assessed for hip joint laxity, osteophytes, hip remodeling, and enthesophytes of the lesser trochanter suggestive of iliopsoas muscle injury. This view is also helpful in identifying transitional vertebrae, for example sacralization of the last lumbar vertebra. Hip laxity is suspected if on the VD view less than 50% of the femoral head is within the acetabulum or if the cranial half of the joint space is not uniformly wide and diverges medially. Unfortunately, with this technique actual hip laxity may be present in the absence of radiographic signs. Thus this technique has limited sensitivity for the detection of hip laxity as false-negative results may be obtained. Early nonspecific osteoarthritic signs can be found around the femoral head (circumferential femoral head osteophyte) and the femoral neck (caudolateral curvilinear osteophyte = Morgan's line). Osteophytes may also be seen on the cranial and caudal acetabular margins, and sclerosis of the craniodorsal acetabulum may be noted. Later stages of the disease are characterized by varying degrees of remodeling of the femoral head (flattening) and acetabulum (shallowing) and thickening of the femoral neck.

Radiography is also used as a screening tool to identify dogs suffering from CHD and at risk for OA, to predict progression of the disease, and to assist in identifying suitable breeding animals. Several techniques are in use. In the USA, the Orthopedic Foundation for Animals

requires ventrodorsal hip-extended views of the pelvis for their examination. Their evaluation is mostly based on evaluation of arthritic changes, and prediction of future disease and suitability for breeding is based on radiographs of dogs 2 years of age and older. Another US registry for CHD, PennHIP, requires three views: a ventrodorsal hip-extended view, a ventrodorsal hip view with the limb in a neutral, weight-bearing position with the femoral heads pressed into the acetabula (compression view), and a ventrodorsal hip view with the limb in a neutral, weight-bearing position with the femoral heads pulled out of the acetabulum (distraction view). The latter two views are used to determine joint laxity and the "fit" of the femoral heads into the acetabula, respectively. Crucial in the evaluation is the so-called distraction index (DI): a DI >0.3 is suggestive of laxity and an indicator of future disease. The DI can be used as a predictor of CHD in dogs 16 weeks and older.

Prevention

The incidence of CHD may be reduced by selective breeding based on the results of radiographic screening. Restricted dietary intake and perhaps a diet with a low calcium density may reduce the severity and/or slow down the development of hip dysplasia and OA.

Treatment

Treatment may consist of conservative (nonsurgical) or surgical management. The choice of treatment will depend on the severity of clinical signs, the stage of the disease, the patient's age and the owner's commitment and expectations. The goal of nonsurgical management in dogs younger than 1 year of age (predominantly hip laxity) is to control the synovial pain and adjacent muscle spasm and increase muscle mass to stabilize the hip joint. The treatment consists of NSAIDs, skeletal muscle relaxer, weight management, nutritional supplements (omega-3 fatty acids, glucosamine/chondroitin sulfate), exercise control (avoidance of intense/high-impact exercise, roughhousing and stairs; long walks and swimming are beneficial), and physical therapy (electrotherapy, joint manipulation and others). Most young dogs respond well to conservative management and the pain is well controlled although normal hip function is not restored.

If a patient is refractory to conservative management, has evidence of substantial hip dysplasia at young age or is at risk to develop clinical hip dysplasia, surgical intervention may be required. Employed surgical interventions include juvenile pubic symphysiodesis (JPS), triple pelvic osteotomy, intertrochanteric osteotomy, total hip replacement, femoral head and neck ostectomy (FHNO), and pectineal myectomy. Juvenile pubic symphysiodesis, surgically induced premature closure of the pubic symphysis, is recommended for 10–20-week-old dogs with palpable hip laxity and a distraction index of 0.3–0.5. The goal of this procedure is to improve the dorsal acetabular coverage of the femoral head by limiting mediolateral length growth of the cranial pubic rami. In patients between 6 and 11 months of age with no to minimal osteoarthritic changes, a triple pelvic osteotomy (TPO) may be recommended. With this procedure, the acetabular segment of a hemipelvis is rotated to increase the acetabular coverage of the femoral head. Just as with the JPS, this may retard the development of OA.

For patients over 1 year of age with moderate to severe hip dysplasia, a total hip replacement (THR) may be considered. In the past decade, THR has to a large extent replaced TPO. Pectineal myectomy is a procedure that may provide pain relief for patients with hip dysplasia by releasing the tension of the spasmodic muscles across the inflamed synovium, although it will not alter the hip joint congruity and the development of OA. Femoral head and neck ostectomy is a salvage procedure that may be employed if concerted medical management is unsuccessful and THR is not possible. Its outcome is most predictable in patients weighing less than 23 kg.

Dogs over 1 year of age (suffering from predominantly secondary OA) may be treated as any other OA patient with nonsurgical methods as above. If animals become refractory to nonsurgical management, surgical treatment is indicated. The main surgical options are THR and FHNO. Even though FHNO can benefit patient of all body weights, it is most beneficial in patients under 23 kg. In patients over 23 kg, THR is preferred. Denervation of the synovium of the hip joint is a more recently described surgical procedure for the treatment of hip dysplasia. The goal of this procedure is palliative and the procedure is not meant to change the course of the disease. However, the pain relief is variable, and may not be accompanied by improved limb function.

Prognosis

No treatment has been developed that can arrest or revert the pathologic changes associated with hip dysplasia. However, conservative and surgical treatments provide adequate pain relief and acceptable but not normal clinical function.

Osteochondrosis

Osteochondrosis (OC) is a disease of endochondral ossification (EOS), the normal process whereby epiphyseal and growth plate cartilages expand (lengthen the bone) and gradually transform into bone. It is a focal or multifocal disorder with an often bilaterally symmetric distribution, seen in young growing animals and humans. The term most commonly refers to a disturbance of

Table 174.2 Manifestations of osteochondrosis

Widely reported and accepted	Presumptive/proposed
Osteochondrosis in the dog • Caudomedial aspect of the proximal humeral head • Medial aspect of the distal humeral condyle • Lateral or medial femoral condyles • Medial or lateral trochlear ridge of the talus	*Osteochondrosis in the dog* • Caudal glenoid osteochondritis diseccans (OCD) • Ununited caudal glenoid ossification center • Fragmented coronoid process • Ununited anconeal process • "Erosion" of the medial aspect of the humeral condyle • Ununited medial humeral epicondyle • Retained endochondral cores of the distal ulna • Asynchronous growth between radius and ulna • Slipped femoral capital epiphysis • Femoral condylar deformity • Genu valgum • Tibial tuberosity avulsion • Medial tibial trochlea • Lumbosacral OCD • Cervical vertebral malformation-malarticulation *Osteochondrosis in the cat* • Caudomedial aspect of the proximal humeral head • Lateral femoral condyle

Source: Breur GJ, Lambrechts NE. Osteochondrosis. In: Johnston SA, Tobias KM, eds. *Veterinary Surgery: Small Animal*, 2nd edn. St Louis, MO: Elsevier Saunders, 2017, pp. 1299–315. Reproduced with permission of Elsevier.

endochondral ossification of epiphyseal growth centers, resulting in articular cartilage disorders of the shoulder, elbow, stifle or hock joints. Sometimes, disturbances of endochondral ossification of growth plates of long and cuboidal bones are also classified as OC. Generally accepted and proposed manifestations of OC are listed in Table 174.2.

In this section, we will first discuss the common etiology/pathophysiology and epidemiology of all OCs, followed by a description of signalment, history and clinical signs, diagnosis, treatment and prognosis of OC of the shoulder, elbow, stifle and hock joint, and the presumed manifestation of growth plate OC, retained cartilaginous core of the distal ulna.

Etiology and Pathophysiology

Osteochondrosis has a multifactorial etiology with several suggested risk factors playing a role: heredity, rapid growth, dietary factors, and trauma.

Strong breed and bloodline predispositions for the different forms of OC strongly suggest a heritable etiologic component. Reported heritability for these conditions ranges from 10% to 45% and it is thought that most forms of canine OC are inherited as a polygenic trait. In humans and pigs, severity of OC lesions may be associated with certain joint shapes and joint morphology also may be an etiologic factor for canine OC.

Several nutritional factors have been implied in the etiology of OC. The relatively increased growth rate resulting from overnutrition (*ad libitum* feeding) presumably predisposes the development of OC lesions by increasing muscle mass and body weight, resulting in biomechanical overload of structurally weak joint surfaces. However, in a recent review, a direct role of rapid growth from overnutrition in the etiology of osteochondrosis was questioned. Another suggested nutritional predisposition is a diet high in calcium and/or vitamin D3. It is evident that such diets cause a disturbance in endochondral ossification but there is no clear evidence that high dietary calcium concentrations will cause or increase the risk for OC in breeds other than Great Danes.

Both macro- and microtrauma have been implicated in OC etiology. Microtrauma may presumably damage cartilage canal blood vessels at the chondroosseous junction of the epiphysis, thus initiating OC. In dogs, exercise has been suggested as a risk factor for osteochondrosis. There are no studies demonstrating that in dogs macrotrauma will cause or initiate OC. However, studies in pigs and humans suggest that macrotrauma may hasten the conversion from an *osteochondrosis manifesta* to an *osteochondrosis dissecans* lesion (see later).

A series of elegant, primarily histologic studies in horses and pigs have suggested that the primary lesion of OC is a focal necrosis of epiphyseal cartilage canals at

the chondroosseous junction of the epiphysis, resulting in areas of epiphyseal cartilage ischemia and chondronecrosis. Necrotic cartilage cannot undergo EOS. This early lesion is called *osteochondrosis latens*. With progression of the epiphyseal mineralization, the area of ischemic chondronecrosis may become located at the cartilage–bone interface. This stage is called *osteochondrosis manifesta* and the resulting shape change of the subchondral epiphyseal bone may be seen on radiographs. Several sequelae have been proposed. The chondronecrotic focus may heal, may develop into a bone cyst, or may deform, resulting in an altered joint contour and congruency. Commonly, fissures, clefts or cracks may start at the necrotic cartilage lesion and propagate along the osteochondral junction or tide mark. Fissures may further propagate to the joint surface and form a cartilage flap off the underlying subchondral bone, resulting in synovitis, joint effusion, arthralgia, lameness, and OA. At this stage, OC is commonly known as *osteochondritis dissecans* (OCD) or (more physiologically) *osteochondrosis dissecans*. This is the most well-known and described manifestation of OC. Cartilage flaps may reattach, resorb, undergo dystrophic calcification or detach and form a so-called joint mouse.

Epidemiology

In a large epidemiologic study of more than 400 000 canine patients, articular OC was diagnosed in approximately 3.7% of all dogs presented with an orthopedic problem, translating into an incidence of 8.1 cases per 1000 patients. In dogs younger than 1 year of age, OC was diagnosed in approximately 9% of the dogs presented with an orthopedic problem. Male dogs are more commonly affected than female dogs and strong breed predispositions for all forms of OC have been identified (see Table 174.1). Feline OC is very uncommon.

Osteochondritis Dissecans of the Shoulder Joint

Osteochondritis dissecans of the shoulder joint is a common form of epiphyseal OC. The lesion is located on the caudomedial humeral head.

Signalment

The disease is most commonly seen in large- and giant-breed dogs (see Table 174.1), and males are more commonly affected than females. Most dogs are presented between 4 and 10 months of age.

History and Clinical Signs

Most dogs suffering from shoulder OCD develop clinical signs between 4 and 8 months of age, but some dogs only experience discomfort later in life. Most patients present with an insidious unilateral lameness that worsens with exercise and improves with rest. The condition is bilateral in 27–68% of cases but signs will predominate on one side and can shift sides. Differentials include elbow dysplasia, panosteitis, hypertrophic osteodystrophy (HOD), injuries of the shoulder muscles, and cervical nerve root pain. These conditions can occur concurrently with shoulder OCD.

Diagnosis

The presumptive clinical diagnosis is based on signalment, history, and pain on shoulder hyperflexion and/or hyperextension. Crepitus and swelling of the shoulder joint are usually not detected. The final diagnosis is based on characteristic radiographic changes on the mediolateral and craniocaudal view of the shoulder joint. Most radiographic changes are seen on the mediolateral projection and include flattening to saucer-shaped and radiolucent defects of the subchondral bone of caudal humeral head. Occasionally, mineralizations representing dystrophic calcification of the cartilage flaps are evident either over the subchondral lesion if the flaps are still attached, or removed from the lesion if they have detached and become joint mice. These may appear anywhere in the joint, but most commonly are seen in the caudoventral joint pouch or occasionally in the bicipital tendon sheath. Because the disease is often bilateral, both shoulders should be radiographed.

Treatment

Patients diagnosed with shoulder OC may be initially treated with restricted activity, weight control, and NSAIDs. If the patient is refractory to conservative management, the lameness has persisted for more than six weeks, or the patient is older than 6 months of age, surgical treatment in the form of arthrotomy or arthroscopy is indicated. The goal of the procedure is to remove the flap and/or joint mouse, debride necrotic cartilage within the defect, stimulate the formation of fibrocartilage, and remove synovial fluid cytokines and wear debris through joint lavage.

Prognosis

More than 90% of surgically treated patients return to normal limb function. Long term, arthritic changes may develop but these changes usually do not result in serious discomfort and lameness. Because shoulder OC is a heritable trait, the owner should be advised that the patient should not be used for breeding.

Elbow Dysplasia

Elbow dysplasia is an abnormal development of the elbow joint due to fragmented medial coronoid process (FMCP), OCD of the medial humeral condyle, elbow

incongruity, and/or ununited anconeal process (UAP). These diseases have in common that they will cause varying degrees of OA. It is thought that FMCP, OCD of the medial humeral condyle and UAP may be associated with humeroradial and/or humeroulnar joint incongruity secondary to asynchronous growth of the radius and ulna. It has been speculated that activity or exercise-induced microtrauma to a vulnerable medial coronoid process or the growth plate of the anconeal process, due to asynchronous growth of the radius and ulna, could facilitate the initial chondronecrosis associated with FCMP, OCD of the medial humeral condyle, and UAP respectively. It also has been demonstrated that chondronecrosis is associated with a delay of endochondral ossification of the medial coronoid process in animals afflicted with FMCP. All three traits are thought to be multifactorial. The reported heritability of FCMP ranges from 0.18 to 0.31.

Signalment

Large- and giant-breed dogs are most commonly affected and unique breed predispositions for FMCP, OCD and UAP have been identified (see Table 174.1). For all three diseases, males are more often affected than females.

History and Clinical Signs

Dogs affected with elbow dysplasia are usually presented for unilateral forelimb lameness. The lameness usually starts insidiously, worsens with exercise, and improves with rest. Clinical signs often develop between 4 and 8 months of age, but may be missed if the condition is bilateral and the gait is symmetrically affected. Patients also may present at later age, but then clinical signs are usually due to secondary OA. Differentials are similar to those of shoulder OC.

Diagnosis

The presumptive diagnosis of elbow dysplasia is based on the patient's signalment, history, clinical signs, and orthopedic exam findings. Muscles of the affected limb may be atrophied and affected joints may be swollen, initially due to joint effusion but later secondarily to capsular fibrosis. Hyperextension and/or hyperflexion of the joint are painful and a decreased range of flexion and/or extension may be present. Internal rotation of the antebrachium with the elbow joint in 90° of flexion may elicit pain as the medial compartment is compressed (so-called Campbell maneuver). Crepitus may be noted during joint manipulation. The final diagnosis is based on characteristic radiographic or computed tomography (CT) findings. Recommended radiographic views include a neutral and a flexed mediolateral view and a craniocaudal view. Because the condition is often bilateral, both elbows should be radiographed.

Fragmented medial coronoid process and OCD of the medial humeral condyle both are characterized by secondary OA of the medial joint compartment as seen on the craniocaudal view (osteophyte formation on the medial coronoid process and the medial humeral condyle), but osteophytes also can be present on the anconeal process, caudodistal humerus, and the cranial portion of the radial head (mediolateral view). Primary changes of FMCP include fragmentation, blunting or deformity of the medial coronoid process and sclerosis of the subchondral bone of the trochlear notch (mediolateral view). Direct evidence of OCD includes flattening or a radiolucent concavity of the medial humeral condyle (craniocaudal view). Radiography often results in false-negative interpretations for FMCP, OCD and elbow incongruity and therefore oblique elbow views have been suggested. However, CT is a much better technique for visualization of FMCP and OCD defects and elbow incongruity than orthogonal radiographic views. The diagnosis of UAP is made after 22 weeks (the normal time of growth plate fusion), on the basis of a persistent lucent line or zone in the area of the growth plate. This lesion is best seen on the flexed mediolateral radiograph. Comparison radiographs of the opposite elbow may aid with establishing the diagnosis.

Treatment

After an initial diagnosis of FMCP or OCD, the patient may be treated conservatively with rest, weight control, and NSAIDs. However, conservative management will not arrest or retard progression of OA. Surgical intervention may be needed if conservative management does not improve the clinical signs. The goal of the intervention is to remove loose fragments, debride the affected coronoid process down to healthy subchondral bone, stimulate the formation of fibrocartilage in areas with eburnated cartilage, and remove synovial fluid cytokines and wear particles. Recently, repair of OC defects of the medial humeral condyle with osteochondral autografts was reported. Patients with more advanced OA and refractory to medical management may temporarily benefit from surgical intervention to remove loose fragments, wear particles, and cytokines in the synovial fluid. The elbow joint can be approached by open arthrotomy or arthroscopy. Ulnar or humeral corrective osteotomies may be indicated if significant elbow incongruity exists. A total elbow replacement may be considered if a patient with advanced OA has become unresponsive to conservative management.

Dogs with suspected UAP should be treated conservatively with rest, weight reduction, and NSAIDs until the diagnosis can be confirmed when the patient is older than 22 weeks of age. Once the diagnosis is

made, surgical intervention should be considered. Proposed procedures include excision of the ununited anconeal process, ulnar osteotomy, or a combination of ulnar osteotomy and lag screw fixation. Excision controls a major trigger for secondary OA but does not stop its progression. Ulnar osteotomy is an effective treatment of lameness, and in dogs younger than 7–8 months of age may lead to reattachment of the process. These procedures are not recommended for use in older dogs with UAP and advanced OA; these patients should be treated for their OA. If the patient becomes refractory to conservative management, a total elbow arthroplasty may be considered.

Prognosis

The prognosis for FMCP and OCD depends on the extent of articular cartilage damage, the state of joint congruity and severity of the arthritic changes. In cases with minimal cartilage damage and OA, the prognosis may be good. If the articular cartilage damage is more substantial, the prognosis is not as favorable and OA will progress. In these cases, the condition can be particularly debilitating and hard to manage. The prognosis for UAP following surgical treatment in young dogs is usually good if treated before secondary changes develop. However, severe OA may develop, particularly if in combination with FMCP.

Osteochondritis Dissecans of the Stifle Joint (Medial or Lateral Femoral Condyle)

Osteochondritis dissecans of the stifle joint is an uncommon form of epiphyseal OC. The lesion is located on the weight-bearing surface of the medial or lateral femoral condyle.

Signalment

The disease is most commonly diagnosed in large- and giant-breed dogs (see Table 174.1). Males are more commonly affected than females.

History and Clinical Signs

Dogs affected with stifle OCD become lame between 4 and 8 months of age, similar to other forms of joint OC. Some dogs may develop lameness later in life. The lameness may range from mild to severe, and tends to worsen with exercise.

Diagnosis

The presumptive clinical diagnosis is based on signalment, history, and pain on stifle hyperflexion and/or hyperextension. Joint effusion and crepitus are usually present. Mild cranial drawer also may be detected, but an abrupt stop of the cranial drawer motion will suggest that the cranial cruciate ligament is intact. The final diagnosis is based on characteristic radiographic changes on the mediolateral and especially the craniocaudal view of the stifle joint. Lesions are located on the medial or lateral femoral condyle. Oblique views of the stifle may improve visualization of the defect. Radiographic changes range from subchondral bone flattening and subchondral sclerosis to more severe radiolucent concave defects. Effusion is always seen and secondary arthritic changes are usually present.

Treatment

Patients may be treated initially with restricted activity, weight control, and NSAIDs. If the patient does not respond to conservative management, surgical treatment in the form of arthrotomy or arthroscopy is indicated. The purpose of the surgical intervention is to remove the cartilage flap and debride the defect, stimulate the formation of fibrocartilage, and remove synovial fluid cytokines and wear particles. The OC defect also may be repaired with osteochondral autografts, or resurfaced with a single-layer or bilayered implant. Dogs that have developed severe secondary OA unresponsive to conservative management may be treated with a total knee replacement.

Prognosis

Treatment, including surgical treatment, does not change the progression of secondary OA. Conservatively managed dogs usually end up with an intermittent lameness. Surgical treatment usually improves the limb function but lameness may persist, especially after exercise. There is no long-term evidence yet that the currently used osteochondral transplant techniques improve the treatment outcome. The owner should be advised that stifle OC most likely is a hereditary trait and that the patient should not be used for breeding.

Osteochondritis Dissecans of the Hock Joint (Medial or Lateral Trochlear Ridge of the Talus)

Osteochondrosis of the hock joint is an uncommon epiphyseal OC. Lesions are localized on either the medial (most common) or lateral trochlear ridge of the talus. Most patients present between 4 and 10 months of age.

Signalment

Just as with the other articular OCs, this condition is mostly seen in large- and giant-breed dogs, and Rottweilers, retrievers, and Great Danes are most predisposed (see Table 174.1). Male dogs are more commonly affected than female dogs.

History and Clinical Signs

Affected dogs usually present between 4 and 8 months of age, but some dogs develop clinical signs later in life. Affected dogs usually present with an insidious unilateral lameness that worsens with exercise and the patient may be mildly exercise intolerant.

Diagnosis

The presumptive clinical diagnosis is based on signalment, age of presentation, history, and pain on hock hyperflexion and/or hyperextension. A decreased range of motion of the hock joint, as well as joint crepitus and joint swelling/effusion, are often present. The final diagnosis is based on characteristic radiographic changes on a neutral mediolateral and extended craniocaudal view of the hock joint. Flexed mediolateral and craniocaudal views facilitate visualization of the defect if not obvious on the aforementioned views. With OC of the medial ridge of the talus, flattening of the medial trochlear ridge can be seen on both orthogonal views; widening of the medial joint compartment (craniocaudal view) and periarticular mineralizations are also often present. OC of the lateral trochlear ridge is characterized by subchondral fissures at the base of the lateral trochlear ridge. CT may help to establish the diagnosis, particularly with lateral trochlear ridge OC.

Treatment

Patients suffering from hock OC may be initially treated with restricted activity, weight control, and NSAIDs. If the patient does not respond to conservative management, arthrotomy or arthroscopy is indicated. The goal of the procedure is to remove the flap and/or joint mouse, debride the defect and stimulate the formation of fibrocartilage, and remove synovial fluid cytokines and wear particles.

Prognosis

Most dogs will have a fair to good quality of life despite continued lameness. Conservative management usually results in a continuous or intermittent lameness and progressive OA. Surgical management may improve limb function, but progressive OA still may cause exercise-induced lameness. Affected dogs should not be used for breeding as hock OC appears to be a heritable trait.

Retained Cartilaginous Core

Generically, retained cartilaginous core is caused by a failure of endochondral ossification and can occur in any metaphyseal growth plate. It is characterized by the projection of cones of unmineralized growth plate cartilage, predominantly hypertrophic chondrocytes, into the adjacent metaphyseal bone. The local thickening of the growth plate may be caused by vascular events on the epiphyseal or metaphyseal side of the growth plate. Most cartilaginous cores will heal spontaneously and in most growth plates will not have clinical consequences. However, a retained cartilaginous core may have clinical significance in the distal ulnar growth plate, a growth plate with a rapid rate of length growth and with an adjacent paired radius. Here, they may be associated with a reduced length growth of the ulna, leading to angular limb deformities (radial bowing and valgus deformity) and/or elbow incongruity, similar to cases with traumatic closure of the distal ulna growth plate.

Signalment

The condition is most commonly seen in rapidly growing, large- and giant-breed dogs. Most patients are presented between 4 and 10 months of age.

History and Clinical Signs

Patients are presented with angular limb deformity, radial bowing, and/or valgus deformity that developed during adolescence.

Diagnosis

The presumptive diagnosis is based on the patient's signalment, history, clinical signs, and orthopedic exam findings. Angular limb deformity, including radial bowing and/or valgus deformity, is often a prominent feature and elbow incongruity (pain on hyperextension/hyperflexion) also may be present. The final diagnosis is based on radiographic evidence of the presence of a cartilaginous core in the distal ulna (a long-tapering radiolucent triangle based on the physis) in combination with the classic signs of angular deformity. Orthogonal radiographic views of the elbow joint, radius/ulna, and manus are recommended to identify and assess the extent of the deformities. If limb shortening is suspected, radiographs of the humerus and comparative radiographs of the opposite limb are useful.

Treatment

The choice of treatment is dependent on the age of the dog, the remaining growth potential, and the severity of the angular deformity. Treatment may consist of conservative management for patients with mild deformity and limited remaining growth potential, or surgical intervention in patients with more substantial deformity and/or bone shortening and more remaining growth potential. Surgical techniques include ulnar ostectomy (for elbow incongruity and mild deformity), static surgical deformity correction (radial and ulnar osteotomy, followed by deformity correction stabilized with an external fixator or bone plate), and dynamic deformity correction (radial and ulnar osteotomy, followed by deformity correction

and bone lengthening with an adjustable external fixator). Surgical planning can be facilitated by 3D printed (plastic) models of the deformity, based on a CT study of the affected limb.

Prognosis

The prognosis for a normal limb function is good, particularly for patients with mild to moderate deformity. In patients with significant limb shortening and elbow joint incongruity, the prognosis may not be as favorable.

Patella Luxation

Etiology and Pathophysiology

Patella luxation (PL) may occur nontraumatically as a consequence of quadriceps mechanism (quadriceps muscles, patella, and patellar tendon) malalignment with the underlying bone and/or femoral trochlea articular surface secondary to the development of femoral and tibial deformities during skeletal growth. Patella luxation also may be acquired traumatically. The etiology of nontraumatic medial or lateral PL is not well understood. It has been hypothesized that medial PL is initiated by a decreased angle of inclination and a diminished angle of anteversion of the proximal femur early in the postnatal period. The resulting medial malalignment of the quadriceps mechanism produces eccentric forces across growth plates and may cause bone deformities, such as coxa vara, genu varum, distal femoral varus or external torsion, proximal tibial varus or valgus, internal tibial torsion, and medial rotation of the tibial tubercle. The malalignment also may lead to rupture or weakening of periarticular structures, thus facilitating PL. Malarticulation of the patellofemoral joint may result in poor development and shallowness of the trochlear groove, diminishing the normal retention of the patella.

It has been suggested that PL is a multifactorial polygenic disease. Strong breed predispositions have been recognized (see Table 174.1). For instance, according to the Orthopedic Foundation for Animals, 43% of examined Pomeranians had PL. A PL heritability of 0.17 was reported and quantitative trait loci were identified on chromosome 7 and 31 in a Dutch flat-coated retriever population. This moderate heritability suggests that environmental factors play an important role in the development of the disease.

Epidemiology

In general, small-breed dogs are more likely to be affected than large-breed dogs. Medial PL is more common than lateral PL in dogs of all sizes and lateral PL is more often seen in large-breed than in small-breed dogs. Many breeds have strong predispositions (see Table 174.1). In small-breed dogs, females appear to be more commonly affected than males, while the opposite has been reported for large-breed dogs. Bilateral disease is common.

History and Clinical Signs

This condition is often asymptomatic, particularly in small-breed dogs, and may go unrecognized until incidentally discovered. Large-breed dogs are rarely asymptomatic. Dogs suffering from PL may present with lameness, intermittent skipping, a history of short acute pain episodes, and/or exercise intolerance. Differential diagnoses, particularly in small breeds, include cranial cruciate disease, which often occurs concurrently, and intervertebral disc disease.

Diagnosis

The diagnosis of medial or lateral PL is based on the examiner's ability to manually luxate the patella in medial and/or lateral directions. Starting with the leg in full extension, the patella is located and pushed in the medial or lateral direction, while simultaneously slowly flexing the hock and stifle joint and internally or externally rotating the limb respectively. Simultaneously abducting or adducting the limb may further encourage the patella to luxate medially or laterally. This test is considered positive (patella luxation) if during flexion of the stifle joint the patella can be moved medial or lateral to the medial or lateral femoral trochlear ridge. It should be noted that with the stifle in full extension, the patella easily can be moved in medial and lateral direction; this patellar mobility is normal and not indicative of patella luxation.

The disease is classified according to the anatomic relationship of the patella and trochlear groove during the gait cycle. Patients with a grade I PL are usually asymptomatic. Their patella is normally positioned in the trochlear groove but the patella can be manually luxated. Grade II is characterized by a normally positioned patella that may spontaneously luxate and relocate, which may cause acute pain and/or "skipping." The luxated patella may reduce spontaneously or can be manually reduced. With a grade III PL, the patella is found in a luxated position; the patella can be easily reduced manually. In patients with a grade IV PL, the patella is permanently luxated and cannot be reduced. Bone angular deformities and trochlea maldevelopment become more severe with increasing grade of PL.

The main purpose of radiography is to assess the severity of secondary osteoarthritic changes, determine the location of the patella in the trochlear groove (lateral or medially displaced or abnormally proximal or distal to the normal central position, termed patella alta or patella baja, respectively) and elucidate the degree of femoral and tibial deformity. In cases of low-grade PL and mild

skeletal abnormalities, mediolateral and caudocranial views of the stifle will suffice. If more deformity is detected during the orthopedic exam, additional orthogonal ("alignment") views of femur and tibia to characterize the angular deformities are recommended. CT allows better evaluation of the deformities and may be beneficial in patients with severe deformities.

Treatment

Patients with grade I PL are asymptomatic and usually do not require treatment. Grade II PL patients may require treatment if the pain or skipping episodes increase in duration or frequency. If clinical signs are mild, fewer than 2–3 episodes per month, or if the owner is unable to pursue surgical treatment, nonsurgical treatment is a reasonable option. However, just as with grade I luxation, the patient should be reevaluated if the lameness becomes more severe or frequent.

Surgical intervention is indicated for patients with persistent lameness due to grade II, III or IV PL. The purpose of the intervention is to realign the patella and quadriceps complex over the trochlear groove and the long axis of the femur, and to stabilize the patella in the trochlear groove. In most patients with grade II or III PL and mild femoral and tibial deformity, the alignment is obtained with a transposition of the tibial tuberosity in the medial, lateral and/or distal direction. The patella is stabilized in the trochlear groove with a combination of trochleoplasty (deepening of the trochlear groove) and parapatellar soft tissue release and imbrication techniques. Transposition is performed after the apophyseal physis of the tibia has closed. In patients with grade III or IV and more severe deformity, particularly large-breed dogs, corrective distal femoral osteotomies may be needed to obtain adequate alignment, in addition to the aforementioned techniques. In patients with grade III or IV PL and severe osteoarthritic changes refractory to conservative management, a partial or total stifle replacement may be indicated. The long-term utility of partial stifle replacement (trochlea arthroplasty) in clinical patients has yet to be described.

Prognosis

The prognosis for lateral and medial PL is similar and mostly depends on the severity of the deformity. For Grade II and III luxations, the prognosis for return of function is good, while for most grade IV luxations the prognosis is fair to good. However, for some patients with chronic grade IV luxation with severe femoral and tibial deformity, severe OA and/or severe muscle atrophy and contracture, the prognosis is much more guarded.

Legg–Calvé–Perthes Disease

Etiology and Pathophysiology

Legg–Calvé–Perthes disease (LCP) is an uncommon cause of pelvic limb lameness in small-breed dogs. The lameness is associated with lysis, fragmentation, collapse, and deformity of the femoral head, including the joint surface. These changes are the result of avascular necrosis and structural weakening of the bone of femoral head. Synonyms for LCP include osteochondritis coxae juvenilis, osteochondrosis, coxa plana, aseptic necrosis of the femoral head, and avascular necrosis of the femoral head.

The etiology of LCP is unknown but increased intracapsular pressure, abnormal anatomic conformation, infarction of the femoral head, hormonal influences, and heredity have been implicated as etiologic factors. Strong breed predispositions exist (see Table 174.1) and it has been suggested that LCP is a simple autosomal recessive trait in West Highland white terriers and miniature poodles. In Manchester terriers, the trait is a simple autosomal recessive or multifactorial with high heritability.

Epidemiology

In one study, 277 of 33 633(0.82%) patients diagnosed with an appendicular bone diseases were suffering from LCP.

Signalment

Predisposed breeds include terriers and toy-breed dogs, with affected dogs most commonly being presented between 4 and 11 months of age. Males and females are equally represented.

History and Clinical Signs

Patients present with unilateral or bilateral pelvic limb discomfort, lameness, and muscle atrophy. Lameness can be mild to nonweight bearing, although in minimally affected cases the disease may be subclinical. Bilateral involvement occurs in 12–16.5% of cases.

Diagnosis

Orthopedic exam findings may include muscle atrophy, pain on hyperextension and manipulation of the hip joint, and crepitus. An extended ventrodorsal and a mediolateral view of the hip joint that include the proximal femurs are recommended. If positioning for this view is causing discomfort, a flexed ventrodorsal (frog-leg) view of the coxofemoral joint may be used. An additional advantage of this view is that it may help elucidate the defect on radiographs. Early radiographic signs sometimes include increased epiphyseal opacity but more commonly, patients are presented with focal lytic lesions of the femoral head. In later stages of the disease, collapse and flattening of the femoral head and

remodeling of the acetabula, femoral neck lysis, and possible associated compression fractures may be seen. Computed tomography may be beneficial for the detection of small lesions in patients with early-stage disease where LCP is suspected but no radiographic evidence of the disease is seen. Orthopedic examination will rule out common differential diagnoses such as patellar luxation and cranial cruciate ligament rupture. Less common differential diagnoses include septic arthritis, neoplasia, and osteomyelitis.

Treatment

Analgesics and rest result in lameness resolution in less than 25% of cases. Surgical treatment with femoral head and neck excision or total hip replacement is recommended if patients do not respond to conservative management. At the time of surgery, excised tissue should be submitted for histopathology and bacterial culture to rule out neoplasia and osteomyelitis.

Prognosis

Surgery resolves lameness and discomfort in 84–100% of LCP cases. Persistent lameness may be due to the resultant change in biomechanics and reduced range of motion associated with femoral head and neck excision.

Developmental Orthopedic Diseases Affecting Bone

Craniomandibular Osteopathy

Etiology and Pathophysiology

Craniomandibular osteopathy is characterized by unilateral or bilateral irregular symmetric osseous proliferation on mandibles and/or tympanic bullae, causing difficulties opening the mouth. Temporal, frontal, maxillary, and long bones can also be affected. The disease can be self-limiting. Synonyms for craniomandibular osteopathy (CMO) include lion jaw, Scotty jaw, Westie jaw, craniomandibular osteodystrophy, mandibular periostitis, and craniomandibular osteoarthropathy.

In affected mandibulae, lamellar bone is resorbed and new bone originating from the periosteum invades the adjacent connective tissue and muscle fibers. Bone marrow is replaced by a highly vascular fibrous-type stroma and inflammatory cells (lymphocytes, neutrophils, and plasma cells) that surround the lesions. The etiology of the disease is unknown but strong breed predispositions suggest a hereditary etiology. The condition is autosomal recessive in West Highland white terriers. A test to determine genetic predisposition for the test is available.

Epidemiology

The disease has a reported incidence of 1.4 per 100 000 cases. The incidence of the disease is highest in the southern and western regions of the United States.

Signalment

Dogs from many breeds, including large- and small-breed dogs, can be affected (see Table 174.1). Females and males are equally represented. Patients younger than 6 months are at the highest risk for being affected by CMO, while the probability for diagnosis decreases in patients over 12 months of age.

History and Clinical Signs

Patients affected by CMO are most commonly presented with complaints of not eating, difficulty eating or drinking or complete inability to open the mouth. Additional clinical signs that have been reported include discomfort, swelling of the mandibles, intermittent hyperthermia, increased salivation, exophthalmia, and strabismus.

Diagnosis

Clinical signs include inability to partially or completely open the patient's mouth and swelling of the mandibles and/or temporomandibular joint region. The final diagnosis is based on demonstration of osseous proliferation on mandibles and/or tympanic bullae using ventrodorsal, lateral, and oblique radiographs of skull and mandibles. Computed tomography may be useful in identifying small lesions in early stages of the disease and may also allow the extent of the lesions to be more accurately characterized. A complete blood count, serum chemistry, and urinalysis are recommended when systemic signs are present. Fine needle aspirate/biopsy for histopathology and culture are recommended to rule out other diseases, including osteomyelitis, neoplasia, and metabolic bone diseases.

Treatment

There is no known medical or surgical cure for this condition. Treatment is primarily aimed at supportive care. Feeding soft food, gruel food, or syringe-fed food, and/or placement of a feeding tube may be needed for as long as the patient is unable to take in an adequate amount of water and food. The level of treatment is based on the severity of the condition and the patient's ability to drink and eat, so hydration and nutrition must be carefully and frequently evaluated. Analgesics should be prescribed if indicated. During febrile periods, patients may be treated with antibiotics and steroids or NSAIDs. These treatments are empirical and the benefits of these medications are variable. Excision of osseous proliferations and/or rostral hemimandibulectomy may be considered as salvage procedures for severe cases to permit improved alimentation.

Prognosis

The condition is often self-limiting by 11–13 months of age and until this time, supportive care is paramount. There are no predictive factors to determine if the bony proliferations will regress partially or completely. For owners who are unable to provide adequate care, for the rare severe case, and for cases with intractable discomfort, euthanasia is an option.

Panosteitis

Etiology and Pathophysiology

Panosteitis is a self-limiting disease of the bone marrow of fore- and hindlimb long bones. Synonyms for panosteitis include shifting leg lameness, enostosis, and eosinophilic panosteitis.

The earliest changes in affected long bones are seen around the nutrient foramen. Vascular proliferation and bone formation result in vascular congestion and increased intraosseous pressure. In response to the increased intraosseous pressure, dogs develop lameness of the affected limb and form bone in periosteum and medullary cavity. Eventually, the affected bone marrow is replaced by normal, healthy adipose bone marrow. The etiology of panosteitis is unknown but strong breed predispositions (see Table 174.1) suggest a genetic component.

Epidemiology

The reported incidence of panosteitis is 2.6 per 1000 patients. The disease incidence is higher in north central and northeastern regions of the United States, especially in the summer and fall.

Signalment

Panosteitis is primarily a disease of medium- and large-breed pure-bred dogs. However, smaller dogs (either mixed breed or pure bred) such as the American cocker spaniel and the West Highland white terrier can also be affected. Males are more frequently affected than females (4:1), with patients most commonly affected between 5 and 12 months of age. However, patients have been diagnosed as young as 2 months and as old as 5 years. In a study of 100 dogs, the median age of affected dogs was 12.4 months.

History and Clinical Signs

Panosteitis patients are often presented with a history of lameness, often shifting between limbs (shifting lameness). Lameness ranges from mild to nonambulatory. The occurrence can be acute in onset and may run a waxing–waning course. There is a 4:1 ratio of lesions in the forelimbs to hindlimbs, with 42%, 25%, 14%, 11%, and 8% occurrence in the ulna, radius, humerus, femur, and tibia, respectively. The affected bones may be painful on palpation. Systemic signs including fever, anorexia, lethargy, and weight loss may accompany the lameness. The signs may regress and reoccur, but rarely continue past 2 years of age.

Diagnosis

Depending on the disease phase, radiographic findings from orthogonal views of the affected bone(s) may vary from completely normal to the classic blurring and inhomogeneity of the medullary cavity trabecular pattern. The first stage, rarely seen, is characterized by a decrease of the radiodensity of the medullary cavity near the nutrient foramen. In the next stage, an increased medullary opacity with a granular pattern or loss of trabeculation, as well as periosteal bone formation, is seen. In a later stage, changes in the medullary cavity become more diffuse and homogeneous. After 4–6 weeks the lesions regress and a coarse trabecular network develops. It should be noted that radiographic signs are not correlated with patient discomfort or lameness.

Differential diagnoses include elbow dysplasia, OCD, hip dysplasia, and HOD.

Treatment

There are no known medical or surgical cures for this condition. Treatment consists primarily of analgesics (NSAIDs) and rest.

Prognosis

The disease is self-limiting, although recurrences are possible, reportedly even until the patient is 5 years of age.

Hypertrophic Osteodystrophy

Etiology and Pathophysiology

Hypertrophic osteodystrophy (HOD) is a disease of predominantly young, growing large-breed dogs, characterized by metaphyseal swelling of affected bones and lameness. Synonyms for HOD include infantile scurvy, Moller Barlow disease, juvenile scurvy, osteodystrophy II, skeletal scurvy, and metaphyseal osteopathy.

The etiology of HOD is unknown. Proposed theories include overnutrition, vitamin C deficiency, infection, vaccinations, and heritability. In more recent reports, the etiologic roles of overnutrition and vitamin C deficiency have been questioned.

Many large dog breeds are predisposed to HOD (see Table 174.1) and therefore a genetic etiology has been suggested. In a litter of affected Weimaraners, the heritability was estimated to be 0.68.

Several lines of evidence suggest an infectious etiology. Specifically, many affected dogs have a history of, or actually are suffering from, a systemic illness (for instance, a respiratory infection). Active bacteremia (*E. coli*) in an

affected dog has also been reported. Canine distemper virus transcripts have been detected in the metaphysis of dogs with HOD, but a direct relationship with canine distemper has not been demonstrated. More recently, it was reported that clinical signs of HOD developed in six Weimaraner puppies (five of the six were related), 10 days after administration of a modified live vaccine of canine distemper virus and canine adenovirus type 2. It was suggested that the HOD may have been facilitated by an inherited immunodeficiency with low concentrations of circulating immunoglobulins.

Epidemiology

Hypertrophic osteodystrophy is reported to occur in 2.8 per 100 000 cases. In one study, the incidence was highest in the northeastern regions of the United States, and was highest in the fall and lowest in the winter.

Signalment

Several breeds are predisposed to HOD (see Table 174.1). Males are more often affected than females (2.3:1) with patients most commonly being presented between 2 and 6 months of age.

History and Clinical Signs

Hypertrophic osteodystrophy is a disease of young, rapidly growing dogs. The distal radius, ulna, and tibia are the most commonly affected bones but the condition has also been diagnosed in the humerus, mandible, ribs, maxilla, femur, skull, vertebra, and scapula. Affected patients have unilateral or bilateral swelling at the metaphyseal region(s) of affected bone(s). If the distal radius and ulna are affected, an angular limb deformity may be seen if a synostosis develops between radius and ulna. Warmth and varying degrees of discomfort can be appreciated when palpating the swellings, with subsequent lameness ensuing. The lameness may range from mild to a complete inability to stand or walk. Additional systemic clinical signs may include anorexia, depression, hyperthermia, and diarrhea.

Diagnosis

The hallmark radiographic finding is a metaphyseal radiolucent zone with adjacent sclerosis parallel and adjacent to the growth plate. In a later stage, periosteal and endosteal bone proliferation may be noted. Metaphyseal enlargement and irregular widening of the growth plate may be present in advanced disease stages. As the condition resolves, resolution of the radiolucent line and remodeling of the periosteal reaction will occur. In severely affected dogs with a secondary synostosis, an angular limb deformity may develop. If a patient has systemic clinical signs, a complete blood count, serum chemistry and urinalysis, as well as blood or synovial fluid culture, may be indicated. Differential diagnoses include septic polyarthritis, panosteitis, polyarthropathies, polyneuritis, polymyocytis, secondary nutritional hyperparathyroidism, neosporosis, and toxoplasmosis. In Newfoundlands, metaphyseal dysplasia also may be considered.

Treatment

There are no known medical or surgical cures for this condition. Treatment varies depending upon the severity of the disease. In mildly affected dogs, a balanced diet (a nutritional association has been reported) and NSAIDs will be sufficient. In more severely affected dogs, more supportive care may be needed, particularly if the patient is reluctant to eat, hyperthermic, and/or unable to get up. Antibiotics are indicated for patients with bacteremia. Severely affected Weimaraner puppies without bacteremia may respond better to steroids than to NSAIDs.

Prognosis

The prognosis is generally good to excellent for mild to moderate cases. The disease is usually self-limiting, typically within days to weeks, but can persist for months with multiple recurrences possible. In severe cases, death may occur. In cases with intractable disease and/or refractory to treatment, euthanasia should be considered. All owners should be counseled on the potential for secondary angular limb deformities.

Slipped Capital Femoral Epiphysis

Etiology and Pathophysiology

Slipped capital femoral epiphysis (SCFE) is a nontraumatic, slowly progressive lateral slippage of the proximal femoral metaphysis through the growth plate, resulting in separation of the proximal femoral metaphysis from the capital femoral epiphysis, causing pelvic limb lameness. The disease is most commonly seen in mature cats but also has been reported in dogs. Synonyms include spontaneous femoral capital physeal fracture, femoral neck metaphyseal osteopathy, and femoral capital physeal dysplasia.

The etiology of the metaphyseal slippage is unknown. Some have suggested that in cats, the slippage is the result of weakening of the capital physis due to a multicentric dysplasia. Others proposed that SCFE in cats is the result of early (juvenile) castration. The ensuing delayed growth plate closure due to hypotestosteronism, together with obesity, exposes the physis to increased/excessive/supraphysiologic cyclic shear forces during the gait cycle, resulting in spontaneous slippage and separation. The latter hypothesis is consistent with the pathophysiology of SCFE in children and other animal species.

Epidemiology
The disease is uncommon, but an incidence has not been reported.

Signalment
Cats are more commonly affected than dogs. Reported feline cases are almost all neutered overweight males presented when they were 4.5–42 months of age. In one study of 13 cats, 23% were Siamese.

History and Clinical Signs
Clinical signs include uni- or bilateral lameness, decreased ability to jump, weakness, and crepitus and pain during palpation. Lameness can be acute in onset but is mostly insidious and possibly intermittent. It was reported that at initial presentation, 24–38% of cases were affected bilaterally but not necessarily symmetrically.

Diagnosis
Radiographic lesions vary with the stage of the disease. Early on in the disease, the capital growth plate is slightly widened compared to the normal contralateral one and slippage may be demonstrated on extended ventrodorsal pelvic radiographs. In later stages, the proximal femoral metaphysis may be craniodorsally displaced relative to the epiphysis, with resorption and sclerosis of the femoral neck. Ultrasound (slippage and periphyseal fluid accumulation) and/or computed tomography may be helpful in early stages without obvious radiographic signs.

Treatment
The most common method of treatment is femoral head and neck ostectomy because of progressive femoral neck resorption. Successful primary stabilization with Kirschner wire and total hip replacement have been reported.

Prognosis
The prognosis for patients treated with femoral head and neck ostectomy is excellent, although limb function is not normal. Unilateral cases can present with contralateral disease later in life.

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Section 14

Social and Ethical Issues in Veterinary Medicine

175

Canine and Feline End of Life Care

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The Buddhists say "Pain is inevitable; suffering is optional." Our obligation in veterinary medicine is to recognize, relieve, and prevent pain and suffering in the animals entrusted to our care. At no time is this obligation to advocate on behalf of beings who cannot advocate for themselves more imperative than when an animal approaches the end of its life.

Veterinary medicine and human medicine are intimately intertwined. Many of the life-saving procedures now used for human patients had their roots in animal models. Likewise, most pharmaceuticals undergo animal testing before they are brought to trials in human subjects. The flow of medical knowledge, information, technology, and techniques between human and veterinary medicine is bidirectional. Advanced surgical techniques (e.g., arthroscopy), advanced diagnostic technologies (e.g., magnetic resonance imaging [MRI]), and critical care interventions (e.g., mechanical ventilation) have been embraced by veterinary medicine and have proved to be game-changers, allowing countless animals who would otherwise have succumbed to their conditions or been euthanized to be restored to life and health. It is a logical extension of the search for better and broader ways to practice veterinary medicine for veterinarians to recognize the utility of evaluating human palliative medicine and hospice care for application to animal patients.

Companion animals have made a migration of Biblical proportions from the backyard to the bedroom and from the kennel to the couch. The evolving role of pets as members of the family, coupled with advances in preventive and interventive medicine, has resulted in dramatically longer life expectancies among dogs and cats. One consequence of longer lifespans in pets is the emergence of age-related diseases and physiologic breakdowns that were once considered unusual. Examples include multiple joint osteoarthritis, pulmonary hypertension, systemic hypertension, advanced renal disease, and cancers of all types. When pets did not generally live as long as they do now – when their cause of death was an infectious disease or a violent event like being hit by a car – neither veterinarians nor pet owners were faced with the slow, incremental declines so often witnessed now. Squiring companion animals into advanced old age has opened the door to a new discipline of veterinary palliative medicine and hospice care. Human palliative and hospice medicine can provide veterinarians with a template to follow when adapting and adopting these principles and practices for veterinary application.

But a simple translation is not enough. In human end of life care, the patient must, with rare exceptions, die on his or her own. Exceptions at the time of this writing are found in the states of Oregon, Washington, Montana, California, New Jersey, and Vermont where physician-assisted death with dignity has been affirmed as legally available. Of note, however, is that physician-assisted death with dignity remains ultimately the act of the *patient*, generally by refusing food and water or by ingesting a lethal dose of a barbiturate drug previously prescribed by a physician. Only in a few jurisdictions worldwide, most notably the Netherlands, can the physician take an active role in the patient's death by performing voluntary active euthanasia. What that means for the majority of dying humans is that they *must* die on their own.

The gift of euthanasia, translated from the Greek as "good death," remains, at least in the Americas, exclusively in the hands of veterinarians. The single most important caution to the veterinary profession in embracing wholesale the palliative medicine and hospice care model provided by human medicine is to resist the temptation to force animals to suffer to death rather than providing compassionate, humane euthanasia. It is equally important to resist the temptation to force heroic

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interventions with little hope for success on animals who are approaching their end of life. Finally, it is also a veterinarian's obligation to the pet, the pet owner, and the precious human–animal bond not to force or rush euthanasia on a patient whose care has shifted from that of curative to palliative. Ours is a delicate balance to negotiate.

In addition to drawing palliative care strategies from the disciplines of pain management, physical rehabilitation, behavior medicine, and oncology, it is to the discipline of clinical bioethics that the veterinary profession should turn for guidance when evaluating the application of interventive, palliative, or hospice techniques in end of life care. The foundational principles of biomedical ethics – respect for autonomy, nonmaleficence, beneficence, and justice – all have a role to play during the decision making that occurs as an animal approaches the end of its life. Before exploring the application of the principles of biomedical ethics in end of life clinical veterinary medicine, it is appropriate to consider the development and evolution of veterinary palliative medicine and hospice care, as well as the many techniques that can be used to sustain a life-limited pet's comfort and quality of life until the time when humane euthanasia becomes the most reasonable choice.

Veterinary Palliative Medicine and Hospice Care

Veterinary palliative medicine and hospice care derive their basic principles from human palliative and hospice care, both directly and by analogy. Historically, hospices were first places of refuge for travelers, often those on a religious pilgrimage. In the 11th century, the focus shifted to care of the incurably ill who either had no family or could not afford other care. Hospice providers were typically members of various religious orders. In the 19th century, the formal concept of caring for the dying emerged, first in France in 1842. In the late 1800s and early 1900s, several facilities that are still in existence opened in England and Australia to attend to the dying. Religious orders continued to provide care, as this preceded the phenomenon of "medicalizing" the dying process. Hospice in the US began in earnest in the 19th century, mirroring activities in the US and Australia. A leap forward in the development of palliative care and hospice occurred following the 1969 publication of Dr Elisabeth Kübler-Ross' seminal work, *On Death and Dying*. She and others created awareness about the lack of adequate care for the dying, and sharpened the focus on the important role palliative care and hospice can fill.

While the original hospices were *places* for the dying, it is important to understand that hospice is a *philosophy* of caring that "affirms the concept of palliative care as an intensive program that enhances comfort and promotes … quality of life … When cure is no longer possible, hospice recognizes that a peaceful and comfortable death is an essential goal of health care…" This commitment to quality of life and comfort care brought to the patient lends itself well to the veterinary profession. Animal patients can be seen and cared for in many settings, including the clinic and the home. The emergence of ambulatory companion animal veterinary practices clearly demonstrates the response of the veterinary profession to the demand for veterinary care provided in the comfort of the animal's home. This paradigm of sophisticated in-home care further reinforces the opportunity to provide palliative and hospice care to pets who are approaching the end of their lives.

The first formal discussion of hospice for animals was presented at the Delta Society's 10th Annual Conference in Portland, Oregon by Drs Guy Hancock and James Harris, and Ms Bonnie Mader. The presentation, "The hospice concept for animals," was delivered at multiple regional, national, and international conferences by Dr Hancock between 1995 and 2005. Dr Eric Clough, a veterinarian in New Hampshire, alongside his wife, June, a registered nurse with expertise in human hospice, were also pioneers in applying the concepts of animal hospice and palliative care. In 2001, the American Veterinary Medical Association approved the first "Veterinary Hospice Care Guidelines," an open-access document available at www.avma.org. In 2003, the Pet Hospice Volunteer Student Outreach Program was launched by the Argus Institute at the Colorado State University College of Veterinary Medicine and Biomedical Sciences.

During the ensuing years, a clear focus on quality of life during the end of life of companion animals has emerged, leading to the establishment of the International Association for Animal Hospice and Palliative Care (www.iaahpc.org) as well as the provision of postgraduate continuing education on the subject for both veterinarians and veterinary technicians/nurses. Clearly, there is a need for the veterinary profession to understand its critical role in a pet's end of life care. There truly is a "space" between ceasing to pursue a cure and the time when humane euthanasia is in the best interest of the patient. It is also worth noting that while only recently has the term "palliative care" entered the mainstream veterinary vocabulary, veterinarians routinely provide what qualifies as palliative care. Palliative medicine is care that is not focused on a cure but rather on improving and maintaining good quality of life. Pets with many

different conditions enjoy the benefits of this approach long before they are at the end of life, including those with diabetes mellitus, systemic hypertension, and chronic kidney disease.

At the end of life, with the many sophisticated interventional options available, it is appropriate for veterinarians to exercise a more formal approach to the necessary decision making that occurs. Veterinarians must combine the following elements in order to help the pet owner make ongoing care decisions that are in the best interest of the pet approaching its death.

- Regular evaluations of the animal's quality of life in dialogue with the pet owner.
- Regular assessment of the human family's quality of life as they care for the pet.
- Regular reevaluation of the therapeutic goals of care.
- Application of the foundational principles of clinical bioethics (respect for autonomy, nonmaleficence, beneficence, and justice) to both the patient and the human family during decision making to maximize outcomes and to act in the best interest of all parties.

When considering any intervention as a pet approaches the end of its life, it is important to ask the question, "Just because we can, does that mean we should?"

Evaluating and Maintaining Quality of Life in End of Life Care

As soon as a life-limiting disease is diagnosed, it is appropriate to open a dialogue with the pet owner about the anticipated arc of the disease process on the way to the end of the pet's life. Likewise, it is important to lay the foundation for periodic ongoing evaluations of the pet's quality of life. Finally, it is important to consider the effects of pet end of life care on the family's quality of life. Caring for a beloved animal family member at the end of life can become overwhelming and fraught with emotional overload. The veterinarian's obligation is to advocate on behalf of a being who cannot advocate for itself, and that obligation becomes even more critical when choreographing care at the end of life (Figure 175.1).

Quality of life is an exquisitely subjective concept. Quantifying a particular pet's quality of life is equally subjective. Each pet's quality of life must be assessed on a case-by-case basis as every animal is unique. Likewise, every family situation must stand on its own merits in order to assess both the financial and emotional resources that are available for care of the pet approaching its death.



Figure 175.1 A comfort room lends itself well to end of life consultations with pet owners. *Source:* Courtesy of Robin Downing, DVM.

Dr Alice Villalobos has created a Quality of Life Scale to use in dialogue with pet owners to offer a somewhat objective assessment of what is a very subjective experience (Table 175.1). The scale considers seven parameters, each scored 1–10 (10 is best). A score at or above 5 in each category with an overall score of 35 or greater generally suggests an acceptable quality of life. While a particular score is important, the trend of scores over time is a more accurate representation of how the pet is doing. A single low score may illuminate a weakness in the palliative care plan, calling for a fine-tuning of care. On the other hand, a low score in even a single category may signal the time when humane euthanasia is in the pet's best interest. The seven parameters follow the mnemonic HHHHHMM.

- Hurt
- Hunger
- Hydration
- Hygiene
- Happiness
- Mobility
- More good days than bad

Table 175.1 Villalobos Quality of Life (HHHHHMM) Scale

Pet caregivers can use this Quality of Life Scale to determine the success of Pawspice care. Score patients using a scale of 0 to 10 (10 being ideal).

Score	Criterion
0–10	**HURT** – Adequate pain control and breathing ability is of top concern. Trouble breathing outweighs all concerns. Is the pet's pain well managed? Can the pet breathe properly? Is oxygen supplementation necessary?
0–10	**HUNGER** – Is the pet eating enough? Does hand feeding help? Does the pet need a feeding tube?
0–10	**HYDRATION** – Is the pet dehydrated? For patients not drinking enough water, use subcutaneous fluids daily or twice daily to supplement fluid intake
0–10	**HYGIENE** – The pet should be brushed and cleaned, particularly after eliminations. Avoid pressure sores with soft bedding and keep all wounds clean
0–10	**HAPPINESS** – Does the pet express joy and interest? Is the pet responsive to family, toys, etc.? Is the pet depressed, lonely, anxious, bored or afraid? Can the pet's bed be moved to be close to family activities?
0–10	**MOBILITY** – Can the pet get up without assistance? Does the pet need human or mechanical help (e.g., a cart)? Does the pet feel like going for a walk? Is the pet having seizures or stumbling? (Some caregivers feel euthanasia is preferable to amputation, but an animal with limited mobility yet still alert, happy and responsive can have a good quality of life as long as caregivers are committed to helping their pet)
0–10	**MORE GOOD DAYS THAN BAD** – When bad days outnumber good days, quality of life might be too compromised. When a healthy human–animal bond is no longer possible, the caregiver must be made aware that the end is near. The decision for euthanasia needs to be made if the pet is suffering. If death comes peacefully and painlessly at home, that is OK
TOTAL	A total over 35 points represents acceptable life quality to continue with pet hospice (Pawspice)

Dr Alice Villalobos (09/2004), scale format created for author's book (2007), revised for IVAPM (2011) Palliative Care and Hospice Guidelines. Reproduced with permission of Dr Alice Villalobos and Wiley-Blackwell.

Hurt

Adequate pain management is the cornerstone of end of life care, and a key to sustaining an acceptable quality of life. Dr Lloyd E Davis wrote in 1983:

> [o]ne of the psychological curiosities of therapeutic decision making is the withholding of analgesic drugs because the clinician is not absolutely certain that the animal is experiencing pain. Yet the same individual will administer antibiotics without documenting the presence of an infection. Pain and suffering constitute the only situation in which I believe that, if in doubt, one should go ahead and treat.

Because pain is such a major factor in diminished quality of life, excellent, aggressive, and comprehensive (e.g., multimodal) pain management plays a critical role in applying palliative care and hospice principles to pets. While humans have eschewed overt cruelty to animals from Biblical times, it is only within the past several decades that human understanding of nonhuman pain and suffering has expanded to include a more proactive approach to recognizing and relieving that pain. Richard D. Ryder, in his groundbreaking work *Painism: A Modern Morality*, coined the term "panience" to describe the principle that a moral code should be based on the capacity to feel pain. He went on to state that the terms "pain" and "suffering" are interchangeable and "what matters morally is the degree of pain and not who or what experiences it." In Ryder's worldview, pain is the common enemy of all beings. Ryder's work, alongside that of scientists like Marc Bekoff and Frank McMillan, lays the foundation for applying clinical bioethical principles to pet end of life and quality of life considerations. There are several excellent resources for practitioners to access in creating appropriate pain management plans for patients approaching the end of life.

Appropriate pain management at the end of life is a function of striking a balance between risks and benefits. Regardless of the root of the palliative care patient's pain, the practitioner must always start with a careful pain palpation assessment to determine all the uncomfortable areas on the body in order to create as comprehensive a pain management strategy as possible. The ability to breathe falls into this category, and trouble breathing trumps all other concerns about quality of life. Because animals cannot self-report, measurement of oxygen saturation may be an important part of patient assessment if breathing is compromised in any way.



Figure 175.2 Foam steps up to bed. *Source:* Courtesy of Robin Downing, DVM

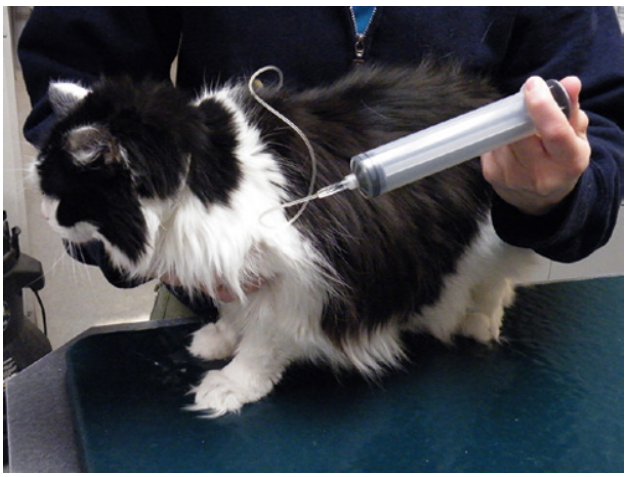


Figure 175.3 Delivering subcutaneous fluids. *Source:* Courtesy of Robin Downing, DVM.

One final consideration for managing pain at the end of life is to use nonpharmacologic strategies. These include modifying the pet's environment and everyday handling in order to maximize comfort (Figure 175.2). Environmental modifications may include:

- raising food and water dishes to shoulder height
- using a form-fitted lift harness for gait assistance
- using a fabric sling under the abdomen for support
- limiting access to stairs
- covering slippery floor surfaces
- using a ramp for vehicle entry and exit.

Many techniques commonly employed in physical medicine lend themselves very well to relieving pain and supporting comfort in veterinary palliative and hospice care patients. Application of heat and cold, stretching, joint mobilizations, massage, neuromodulatory acupuncture, photobiomodulation via therapeutic laser, transcutaneous electrical nerve stimulation (TENS), neuromuscular electrical stimulation (NMES), as well as some proprioceptive retraining and therapeutic exercise, can all contribute to pain relief in this population of patients.

Hunger

Hunger can serve as an important barometer of a pet's quality of life. If the pet remains hungry and willing to eat, it is reasonable to presume that it is still interested in living. On the other hand, a decline in appetite is one part of the natural process as the end of life approaches.

Nutritional support is important if hospice care is to continue, and malnutrition and weight loss occur quickly in an anorectic pet. Hand feeding or feeding a different texture (canned versus dry kibble) may enhance appetite. Appetite stimulants as well as antinausea medications may be indicated, at least in the short term. For an animal experiencing difficulty prehending, chewing, or swallowing food, placing an esophagostomy tube may be appropriate if other quality of life parameters remain high. This is a minimally invasive technique requiring a very short period of general anesthesia, and the contribution to overall quality of life can be significant.

Hydration

Many animals approaching the end of life do not drink enough to sustain metabolic functions. Dehydration not only undermines quality of life, it hastens the decline of all metabolic functions, particularly waste elimination by the kidneys. Many animals readily accept the delivery of subcutaneous (SC) fluids, and this is an easy technique to teach pet owners (Figure 175.3). It is important to link the delivery of SC fluids with something that the pet enjoys, like tasty treats or gentle combing or brushing, in order to minimize any objection the pet may have to receiving fluids. If a pet receiving end of life care vigorously objects to receiving SC fluids in spite of all attempts to make the procedure as comfortable as possible, it is important to respect the animal's expressed preference. To force fluids on an uncooperative hospice patient compromises quality of life.

Hygiene

Good hygiene is an important component of good quality of life. As animals approach the end of their lives, they may develop fecal and/or urinary incontinence, which is the most likely hygiene issue these pet owners will face. Preventing urine and fecal scalding is a priority

in these patients. Keep hair trimmed short around the genitals and anus to facilitate cleaning. It may be worth considering a whole-body trim to make day-to-day grooming easier for both the pet and pet owner. Reusable/washable diapers as well as diapers with replaceable absorbent pads are available for animals whose incontinence is intermittent or unpredictable. Waterproof bedding covers facilitate clean-up. Cats may need to have one side of their litter pan cut away to make entry easy. If the pet has any areas of devitalized tissue that secrete serum and form crusts (e.g., a tumor that cannot be removed), lemon juice in a 1:1 dilution with water can be used to cleanse the area, and absorbent fabrics like cotton T-shirts may be used to help manage exudates. Waterless shampoos also work well to keep immobilized pets clean.

Happiness

Happiness may be the most subjective of the quality of life parameters to be measured during the pet's end of life time, but it is an important one. It is in this area in particular that the veterinarian must listen very carefully to the client's report of how the pet is doing overall. The pet's mental state and psychosocial well-being are critical components of quality of life. Dogs and cats communicate with their eyes, their facial expressions, and their actions. These are social creatures, and their happiness depends upon interaction with "their" humans. Animals engage in many mutual care behaviors that can be mimicked by the human caregiver to contribute to happiness, including stroking and sounds of contentment (e.g., purring while interacting with a cat patient).

Owners of animals receiving end of life care must be instructed to think through the activities the pet has enjoyed over its lifetime, and then to consider how those activities and interactions may be modified to provide joy to the pet. For instance, the author worked with a toy poodle who had been felled by a stroke. She became paralyzed in the rear legs and profoundly paretic in the front legs. Her greatest joy before her stroke was playing tug-of-war with a cloth toy. She would bring the toy to one or another family member and ask them to play. The family simply modified this game by initiating play sessions themselves. This dog obviously derived great joy from these play sessions.

Many end of life pets will cheer up and greatly anticipate their interactions with their human family members. Feeding, grooming, play, simple stroking, and strategic placement so that the pet may watch what the family is doing are all simple strategies for enhancing happiness. McMillan makes a strong case that animals not only do experience happiness, but that their happiness contributes immeasurably to their quality of life. In general, we can equate happiness with the will to live.



Figure 175.4 A cart can restore and maintain mobility. *Source:* Courtesy of Robin Downing, DVM.

Mobility

As the inevitable decline toward approaching death proceeds, animals may lose their ability to move independently. How much of an impact this makes on the pet's quality of life and the family's ability to continue end of life care may depend on the size/weight of the patient as well as the willingness of the pet to accept assistance. There are many mobility assistance options available for pets of all sizes, and simple environmental modification may make a profound impact, allowing a pet to sustain its own ability to get up and down and move around (Figure 175.4). Providing nonskid floor surfaces, preventing unsupervised access to stairs, utilizing ramps for entry and exit from vehicles, as well as slings, supportive vests, and pet wheelchairs are all simple strategies for sustaining mobility. The owners of immobilized end of life pets must be instructed in the details of preventing decubital ulcers. The size of the immobilized pet relative to the size and strength of the pet owner must be considered when deciding whether to proceed with palliative and hospice care versus opting for humane euthanasia.

More Good Days Than Bad

A single "bad day" in the end of life time of a pet is something to be expected, but more than a few bad days in a row suggests that quality of life may be too compromised to continue palliative and hospice care. If the pet is "turned off" to life, is no longer responding to activities in its immediate environment, or is withdrawing from interactions with family members, then quality of life is compromised. The overarching goal in a pet's end of life care is to maintain a healthy, two-way, interactive human–animal bond (Figure 175.5). When the HHHHHMM score drops below 35, it is likely that the end is near. It is the obligation of the veterinarian



Figure 175.5 An end of life care patient quietly resting near family activities. *Source:* Courtesy of Robin Downing DVM

coordinating end of life care to speak on behalf of the dying pet when compassionate, humane euthanasia is in the pet's best interest. It is critical, when there are more bad days than good, not to allow the beloved pet to suffer to death.

Pets Should Not Suffer to Death

Occasionally, the veterinary healthcare team will encounter a client whose personal or religious beliefs prohibit the active ending of a life – any life. If this is the case, then a deep discussion about the need to prevent an agonizing death must be a part of the dialogue between the veterinarian and the owner. In a case like this, it is extremely important to make available powerful pain medication that can provide heavy sedation and relieve any suffering that emerges as death approaches. The flipside of this is the client who wishes to pursue treatments, interventions, and procedures that are futile in the face of the pet's life-limiting disease. In both cases, it is essential to have a back-up plan in place to provide the gift of humane euthanasia at any time of the day or night should the need arise and should the family decide to pursue that option.

Applying the foundational principles of clinical biomedical ethics provides a useful framework and strategy for assisting families to negotiate the emotional minefield that end of life care represents. This formal approach to the decision making involved in end of life care serves all parties – the pet owner, the veterinary health care team, and, most importantly, the pet with a life-limiting condition who is receiving end of life care.

The Four Foundational Principles of Clinical Bioethics

In *Principles of Biomedical Ethics*, Tom L. Beauchamp and James F. Childress describe four foundational principles that may serve as an analytical framework for the formulation of rules guiding medical decision making.

- Respect for autonomy (respecting and supporting autonomous decisions).
- Nonmaleficence (avoiding the causing of harm).
- Beneficence (relieving, lessening, or preventing harm and providing benefits, and balancing benefits against risks and costs).
- Justice (fairly distributing benefits, risks, and costs – distribution of scarce resources).

These four principles, by the authors' assertion, do not constitute a general ethical theory, but rather provide a place to start in order to specify application to a particular patient or case. Application of these four principles of clinical bioethics requires balancing among them to decide what, ultimately, is in the best interest of the patient. These principles have a role to play in clinical veterinary medicine in general, but they should definitely play a role leading up to and during a pet's end of life care in order to maximize outcomes and quality of life for the pets and the families who love them.

A conventional application of the four pillars of clinical bioethics in the context of veterinary end of life care is to the interactions with the pet owner as the surrogate decision maker. It is, after all, the pet owner who ultimately makes all the caregiving decisions and who must carry out all the caregiving activities for the pet approaching the end of its life. Considering each of the four principles as described by Beauchamp and Childress, we begin with respect for autonomy.

Acting autonomously, according to Beauchamp and Childress, involves three steps.

1) Intentionality (to make and follow a plan).
2) Understanding the consequences of decisions that will be made.
3) Freedom from control or undue influence in the decision making process.

Respect for the autonomy of the pet owner during a pet's end of life care is fairly straightforward and hinges on the veterinarian providing the owner with enough information in an understandable form that he or she may act as autonomously as possible at each step of the decision-making algorithm as the pet's dying progresses. While, legally, the pet is property and can be subjected to nearly any decision the pet owner might make, aside from gross negligence or abuse, it is acknowledged that the human–animal bond helps to define us as humans. James Serpell

states that it is "hard to escape the conclusion that the child-like qualities of many animals can evoke in people a strong desire to nurture and provide parental care and protection." The pet owner must make end of life decisions analogous to those made by parents on behalf of children. The information that must be provided to the owner of a dying pet in order for him or her to make autonomous decisions on behalf of that animal includes the expected arc of progression of the co-morbidities the pet possesses as well as the expected cause of death, costs associated with various techniques and/or procedures that may be recommended, statistics for expected outcomes of any interventions, a balanced presentation of the pros and cons of any treatment or interventional options, as well as guidance when humane euthanasia is the better choice for the pet.

The principles of nonmaleficence and beneficence as applied to the owner of the pet approaching death are closely allied and related. According to Beauchamp and Childress, nonmaleficence "obligates us to abstain from causing harm to others" and beneficence "potentially demand(s) more than the principle of nonmaleficence" because it obligates us to "take positive steps to help others, not merely refrain from harmful acts." Nonmaleficence and beneficence in this situation demand full revelation of the facts, costs, and potential consequences of pursuing any particular treatment or care option during the pet's end of life care. The positive obligations of beneficence in veterinary palliative care and hospice include active and ongoing patient and client support by the veterinary healthcare team, a clear outline of the pet-specific care required, and contingency planning for unexpected or unplanned events.

Finally, applying the principle of justice to the owner whose pet has entered end of life care involves full disclosure of the costs and details about the anticipated care to each pet owner equally. Each pet owner and family is unique and must be able to conduct a fair appraisal of the investment (monetary and emotional) that they must make. It is not appropriate for the veterinarian to cherry-pick the information that is provided to the client based on his or her impression of what the client can and cannot afford or accomplish. Justice suggests that it is the veterinarian's obligation to the client to guide the decision making based on what is medically in the dying pet's best interest.

Bioethical Principles and The Life-Limited Pet

Turning our attention to the pet entering end of life care, it is not only appropriate but necessary to consider how at least three of the four foundational principles – respect for autonomy, nonmaleficence, and beneficence – apply, despite the fact that animals cannot participate in the caregiving decisions made on their behalf. This reflects a novel application of clinical bioethical principles in clinical veterinary medicine, and acknowledges that animals can and do express preferences, which can guide caregiving decisions.

In order to apply the principles of clinical bioethics to animals, we must first consider them as moral agents and thus appropriate targets of such an application. This involves issues of consciousness and a need to respect the preferences they express. Darwin himself recognized that animals possess the fundamentals of consciousness. His reasoning was that "if animals show emotion through behavioral expression, then the behavioral expression of emotion in man must share a similar neurobiological evolution with other animals capable of expressing similar emotions." As cited earlier, Richard D. Ryder laid the foundation for considering animals as moral agents in his work *Painism: A Modern Morality*. An updated narrative on the need for humans to recognize the moral agency and emotional richness of animals is presented in the provocative volume *Wild Justice: The Moral Lives of Animals* by Marc Bekoff and Jessica Pierce. They argue compellingly, based on robust behavioral science, that "differences between species are differences of degrees rather than differences in kind." They go on to state that in "including some animals within the sphere of morality, we force a reconsideration of what have been assigned to be the essential ingredients of morality – reflective judgment, agency, and conscience." This and other contemporary work opens the door to applying the principles of clinical bioethics in a serious way to the pets themselves who are entering end of life care.

Animals do express preferences, if only the human is willing to listen. When applying the principles of clinical bioethics to animals receiving end of life care, we accept the limitations presented by beings who do not possess decisional capacity as we strive to achieve optimal outcomes for them, ultimately leading to a peaceful and pain-free death. The animal receiving end of life care must be considered carefully. The pet's personality, willingness to be handled, willingness to take medication – basically, the pet's willingness to participate in its own care – must weigh in the balance. In applying respect for this pet's autonomy, we must evaluate these preferences, as expressed by the pet, before embarking on a complex path of end of life medical management. To force medication or painful wound care on an animal whose response is either anxiety or aggression clearly violates the autonomy the pet can express, independent of its inability to actively choose specific end of life care. McMillan would argue that forced medication or other forced procedures, performed without the animal's cooperation, present

a sufficiently aversive stimulus to activate a powerful sympathoadrenal response that can precipitate negative gastrointestinal and cardiovascular changes.

Nonmaleficence and beneficence are intertwined when applied to the pet receiving end of life care. Nonmaleficence is the requirement to avoid harm, and this principle is in play when considering a procedure or other interventive technique for an end of life patient. On balance, the benefit must clearly outweigh any potential harm to the patient. Beneficence means acting in the patient's best interest. At each decision-making step, it must be considered that the patient may be best served by the compassionate application of humane euthanasia. Nonmaleficence and beneficence are tightly aligned with the pet's willingness to participate in its own care. Without that willingness, the animal itself is expressing its preferences and we have an obligation to heed the message if we are unable to change the circumstances of care to improve quality of life. While animals cannot anticipate or fear their own death, they certainly can and do anticipate and fear pain, and unrelenting pain is a deal-breaker for the continued imposition of care on a dying pet.

McMillan might argue that one barometer of our ability to monitor and measure our success in applying the principles of respect for autonomy, nonmaleficence, and beneficence is the animal's ability to experience and express happiness. As elusive a concept as happiness is, ongoing active engagement with the environment and human family members, the ability to exert some level of control over activities, and modification of activities that had previously brought enjoyment (e.g., tug-of-war games) appear to contribute to an animal's happiness (Figure 175.6). This provides a slightly richer context for consideration of quality of life issues.



Figure 175.6 A healthy human–animal bond is a two-way relationship. *Source:* Courtesy of Robin Downing, DVM.

End of Life Care and The Human–Animal Bond

End of life discussions are among the most difficult for both the pet owner and the veterinary healthcare team, yet they are among the most important. Taking a systematic approach to the practicalities of end of life care allows the veterinarian to exhibit and express compassion while at the same time providing the client and family with a longer view of the arc of care that will be required as the pet's condition deteriorates.

The veterinarian should start with an initial consultation to assess the client's goals, beliefs, concerns, and financial resources/constraints. It is important to discuss all of the pet's co-morbidities to ensure that all relevant issues are addressed to maximize comfort and function. Schedule regular quality of life evaluations and pain reassessments. The trend over time of the quality of life scores is generally more important than individual scores. Provide regular ongoing guidance to the client about comfortable bedding for the pet, safe surroundings, medications, feeding, wound management when necessary, assistive devices, physical medicine techniques to enhance comfort and function, and environmental enrichment. Construct a preparedness plan for the inevitable decline in the pet's health status, including an advanced directive (e.g., "Do not attempt resuscitation" – DNAR) and options for euthanasia at any time of the day or night. Plan for unexpected escalations of pain or discomfort, providing the client with specific steps to take. Plan for in-home euthanasia if that is preferable to the client and available in the community. Plan ahead for preferred body handling when the animal dies. Be ready to refer the client and family for grief support services if that becomes necessary.

Planning ahead for the anticipated and inevitable events that occur at the end of life supports the human–animal bond and helps to prevent the client from being overwhelmed with decisions once the animal's death day arrives.

Conclusion

Veterinary medicine has long prided itself on its commitment to scrutinize advances in human medicine and to evaluate the possible application of those advances to

animal patients. In fact, many of the medical and surgical techniques now utilized in human medicine were first developed in animal models. There exists now a paradigm in human and veterinary medicine that recognizes the importance of interdisciplinary collaboration in order to foster synergistic attention to enhance the care of animals, humans, and the environment. This is the One Health Initiative –www.onehealthinitiative.com/). The mission statement of the One Health Initiative recognizes "that human health (including mental health via the human-animal bond phenomenon), animal health, and ecosystem health are inextricably linked" seeking to "promote, improve, and defend the health and well-being of all species by enhancing cooperation and collaboration between physicians, veterinarians, [and]other scientific and environmental professionals." With such a commitment to cross-pollination between medical disciplines, it is logical to consider ways in which palliative and end of life care options for animals may be expanded.

In pursuing such expansion, however, it is critical also to expand the ethical framework within which palliative and end of life care decisions are made on behalf of pets who are either experiencing life-limiting disease or actively dying. In addition to applying human *medical* principles and practices in end of life care for pets, including aggressive pain management and other palliative care techniques, it is appropriate for veterinary healthcare teams to understand and apply the foundational *clinical bioethical* principles and practices as well. The pet owner is in an analogous situation to the parent of a dying child when making decisions on behalf of the pet. The pet clearly does not possess decisional capacity – that is, the animal cannot weigh the evidence and decide for itself, among the care options, which one is in its best interest. It is up to the pet owner – the "pet parent" – to listen to the explanation provided by the veterinarian and veterinary healthcare team, to weigh the options to try to determine the risk to benefit ratio, and then to decide on behalf of the pet what treatment or procedure will be performed or withheld.

This huge responsibility to act in the best interest of the pet *must* be borne by *both* the owner and the veterinarian coordinating care. In no other context of veterinary care is this shared obligation greater than at the end of life. The veterinarian possesses knowledge about the procedures and probabilities for various outcomes that the owner simply cannot know in the same way. The late physician Edmund Pellegrino, MD, acknowledged to be the father of modern medical ethics, would affirm by analogy that every time a veterinarian sees a patient and client and asks, "What is wrong?" she is committing herself to having the competence to help that animal patient as well as the judgment "to use that competence in the best interests of the patient."

In the end of life time for animal patients, it is especially important for veterinarians to find guidance in the bioethical principles of respect for autonomy, nonmaleficence, and beneficence as applied to their patients in determining what actions – or withholding of actions – are in the best interest of *that* animal at *that* time, in dialogue with the pet's human family. It is important not to reach for euthanasia too early, but equally important not to withhold it when that action reflects the best interest of the animal. Reaching a decision about what will best serve the animal patient at the end of life may, in fact, demand answering the question mentioned earlier in this chapter: "Just because we *can*, does that mean we *should*?"

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Section 15

Preventive Care

176

Role of Immunization

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The immune system is a complex network of interacting cells and molecules. Manipulation of the immune response is an attractive prospect, and has been achieved in part through immunization. Immunization is the process of exposing an animal to whole or parts of microbes in order to stimulate an acquired response. Immunization takes many forms, and continues to advance as a field of research. This chapter focuses on several aspects of immunization in veterinary medicine.

Before one can understand immunization, one must understand the nature of the acquired or adaptive immune response. Acquired immunity is that which is developed after an animal is born and is restricted primarily to the T and B lymphocytes. This is to distinguish it from innate immunity with which an animal is born. This latter form of immunity is nonspecific in nature and involves many cell types and molecules such as cytokines and complement. Acquired immunity is distinct in that it has a high degree of specificity and diversity of antigen recognition, as well as memory. It is this latter trait that is exploited by immunization – the ability to establish an immunologic memory of an encountered foreign antigen.

The major cells involved in the specific immune response, and the only ones that manifest these properties of adaptive immunity, are the lymphocytes. Different lymphocyte lineages are distinguished by cell surface markers and perform different functions in the immune response. The B lymphocytes, the producers of antibodies, or the humoral response, are critical for defense against extracellular pathogens. The cytotoxic T lymphocytes, which force altered and invaded cells to undergo apoptosis, are critical for defense against intracellular pathogens. The overseers of the entire response, T helper lymphocytes, direct and modulate the response using cell surface molecule expression and cytokine production and secretion. It is important to understand how various lymphocyte lineages recognize antigens in order to design or select the most appropriate antigen delivery method.

B lymphocytes are able to detect free and soluble antigens, while T lymphocytes are only able to recognize antigens presented to them "on the pedestal" of the major histocompatibility complex (MHC) structures. For the latter to occur, the foreign antigen must be processed within a cell and displayed on the MHC for T lymphocyte recognition. MHC structures are classified as class I or class II. The former are expressed on all nucleated cells and express only antigens that are produced within that cell. The cytotoxic T lymphocytes recognize antigens presented in MHC I. MHC class II are expressed on antigen-presenting cells (APCs), such as macrophages, dendritic cells, and B lymphocytes. The antigen displayed by these structures is produced outside of and taken up by the APCs via endocytosis or phagocytosis. The antigen is then processed and inserted in MHC II for presentation to T helper lymphocytes. Understanding how lymphocytes differ in this antigen recognition process is critical to designing and selecting efficacious vaccines.

B lymphocytes bear immunoglobulins on their surface for antigen recognition. As mentioned above, these antigens are extracellular, such as free-living bacteria and parasites and the extracellular form of viruses and other intracellular parasites. In response to antigen recognition and assistance from T helper lymphocytes, naive B lymphocytes will proliferate and differentiate into plasma cells, which secrete antibody and are relatively short-lived, or memory cells, which are long-lived cells that are more easily activated and respond more quickly and with higher magnitude and antibody affinity than naive B lymphocytes. Producing a significant population of the latter is the goal of most vaccines. Antibodies, the effector mechanism of B lymphocytes, will opsonize, neutralize, clump for easy removal of, or activate complement to destroy the infecting agent.

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T helper lymphocytes use the T cell receptor to recognize antigens displayed in MHC II by APCs. These antigens originate outside of and are "ingested" and processed by the APCs. Thus, as with B lymphocytes, the antigen is extracellular. In response to antigen recognition, the T helper lymphocytes begin to proliferate and differentiate into cytokine-producing cells. These cytokines, such as interleukin 2, enhance or modulate the immune response. In addition, depending on signals received by the T helper from the APC, the former will direct the immune response in the most appropriate direction – the humoral response for extracellular pathogens or cell-mediated immunity for intracellular pathogens. Thus, the T helper lymphocyte is critical to an effective immune response, whether humoral or cell mediated. T helper memory cells develop, as with B lymphocytes, into long-lived, easily activated cells, and their production is a critical goal of vaccination.

Cytotoxic T lymphocytes detect antigens presented to them in MHC I using T cell receptors on their surface. The antigen displayed in MHC I, as described above, is produced within a cell and displayed on the surface. The presence of foreign peptide from an intracellular invader in MHC I results in induction of apoptosis in the infected cell by the cytotoxic T lymphocyte. This type of response is critical for elimination of an intracellular pathogen, as it is inaccessible to most other defense mechanisms. Thus, for protective immunity against most intracellular pathogens, activation of cytotoxic T lymphocytes must occur; to do this, the vaccinal agent must be replicating in order to produce a peptide for display in MHC I. As with T helper and B lymphocytes, this process leads to proliferation and differentiation of the cytotoxic T lymphocyte into effector and memory cells.

It goes without saying that there are many other components to an effective immune response, including granulocytes, natural killer cells, cytokines such as interferon, and inflammatory mediators. But the goal of vaccination remains lymphocyte stimulation and memory cell production. How this is accomplished depends not only on the antigen presented but how it is delivered. Induction of adequate protection depends on appropriate vaccine selection and immunization protocols. As stated by Shams (2005), "an ideal vaccine should be inexpensive, stable, adaptable to mass administration, and confer a strong and long-lasting immunity with no or minimal adverse side effects in the vaccinated animal."

Antigen Delivery Systems

Vaccines can be divided into two basic groups depending upon whether or not there is transcription/replication of the agent after inoculation, referred to as infectious or noninfectious, respectively. There are an increasing variety of strategies to produce vaccines in both categories, and each has its advantages and disadvantages.

Noninfectious Vaccines

These vaccines may contain inactivated whole organisms or pieces (subunits) of the organism. *Killed* vaccines contain whole organisms that have been altered or inactivated to destroy their ability to replicate. These vaccines are generally inexpensive to produce. *Subunit vaccines* contain purified immunogenic and protective antigens, often microbial proteins. These proteins may be purified from the whole organism or may be generated using molecular technology (recombinantly produced). Conjugation to carrier proteins may be required for the antigen to stimulate an effective response; this is expensive and currently laborious. Peptide vaccines contain immunogenic epitopes that have been generated synthetically. Conjugation to carriers is required for effective immunogenicity of peptide vaccines.

In all cases, the vaccine is nonreplicating; thus, no amplification of the antigenic mass occurs after inoculation. In addition, because no transcription/translation/replication is occurring, MHC I presentation of microbial antigens, in general, does not occur. Thus, these vaccines stimulate primarily humoral immunity. They may require multiple inoculations to be effective, but this is not always the case. Most noninfectious vaccines also require an adjuvant to enhance the immune response. These substances nonspecifically increase the immune response, often by unknown mechanisms. Concern exists, particularly for feline vaccines, about the potential for adverse effects due to adjuvants.

Still, noninfectious vaccines have several advantages. Because they contain killed/inactivated organism or only a portion of the infecting agent, there is no chance for reversion to virulence. In general, they are safe for pregnant animals as well as for animals that may be immunocompromised or have an underlying disease. In addition, noninfectious vaccines are stable in field conditions and are usually inexpensive to produce.

Infectious Vaccines

Infectious vaccines contain metabolically active agents that undergo transcription and translation at a minimum and often the entire replication cycle of the inoculated organism. For infectious whole organisms, the agent is attenuated in some way such that it is no longer virulent while retaining its antigenicity. Examples of infectious vaccines include whole organism live vaccines, recombinant vectors, and DNA vaccines. Because infectious vaccines undergo transcription and translation after

inoculation, presentation of an antigen in MHC I will occur, thus enabling stimulation of cytotoxic T lymphocytes. Meanwhile, the extracellular form of the agent will be detected by B lymphocytes as well as APCs, which will process it for presentation and activation of T helper lymphocytes. Thus, both cell-mediated and humoral arms of the immune response are activated.

Modified Live Vaccines

Modified live vaccines contain organisms altered to remove their disease-causing ability. Attenuation may be accomplished by acquisition of multiple genetic mutations. Alternatively, virulence genes may be removed using recombinant technology. The attenuation process must remove the virulence without altering the immunogenicity of the organism. In addition, the attenuated organism must be genetically stable.

Recombinant Vector Vaccines

These are a variation on the theme of modified live vaccines in which one or more genes encoding immunogenic microbial proteins are engineered into a harmless bacterial or viral carrier. Examples of this technology are the canarypox virus vectored vaccines containing genes of rabies virus or feline leukemia virus. The recombinant vector expresses the cloned gene as well as its own genes during transcription and translation. This technology is useful for pathogens that would otherwise be too unsafe to administer as a live vaccine. DNA vaccines use purified DNA containing microbial genes of immunologic importance. They are taken up by cells after inoculation, and the cloned genes are expressed within the cell and presented in MHC.

Generally, for infectious vaccines, a lower antigen mass is required, and no adjuvant is needed to achieve a protective response. There are drawbacks to infectious vaccines. Attenuated organisms can potentially revert to a virulent state, though this is very uncommon. For recombinant vectors and DNA vaccines, reversion to virulence is not possible. Infectious vaccines may be less stable in field conditions than noninfectious vaccines. Finally, infectious vaccines are not generally recommended for pregnant or immunocompromised animals.

Vaccine programs may vary with each patient and client. Core vaccines, those recommended to be given routinely to all dogs and cats, are outlined in the guidelines published by various organizations, including the AAFP, AAHA, AVMA, and WSAVA (see list at end of chapter). Additional vaccines are available for a number of pathogens, including feline immunodeficiency virus and *Chlamydia* for cats, and *Leptospira*, Lyme, and canine influenza for dogs. Administration of these vaccines varies with epidemiology of the organism and risk of exposure to the animal. Also severity of disease, cost and efficacy of the vaccine, and potential for adverse reactions should be considered.

Vaccine administration for the majority of vaccines is parenteral, with subcutaneous being the route of choice for most vaccines. When multiple vaccines are given at the same visit, it is recommended that administration be done at different sites so that local adverse reactions can be documented for the specific vaccine that induced them.

Vaccine Failures

Vaccine failures do arise and have several potential causes. The most common reason in puppy- and kittenhood is interference from maternal antibodies. For the majority of puppies and kittens, the amount of maternal immunity present at any point in time is unknown. Thus, vaccination generally begins at the earliest point when most will begin losing protection from maternal antibodies and continues through the latest point at which the majority of animals do not have significant levels of interfering antibodies. The booster vaccine given during this period is actually a misnomer, as multiple vaccines are given not to boost preexisting immunity but to insure that the animal responds to at least one vaccine in the series. Because we do not know at what time point this occurs for each animal vaccinated, and it is not feasible to measure antibodies multiple times throughout this period, we give multiple vaccines with the intention that one of the series will work. For example, some puppies may have immunity that has waned by 6–7 weeks of age; these pups will respond to the vaccine given at 8–9 weeks of age. In reality, this would be the only vaccine necessary (for live vaccines) if we knew for certain that maternal immunity had waned and the pup had responded to the vaccine. The vaccines that follow at 12 and 16 weeks will in fact be neutralized by the antibodies induced from vaccination. If maternal immunity does not wane until 13–14 weeks of age, only the 16-week vaccine will induce full protection. Because we do not know the individual status at multiple time points for each animal and against multiple pathogens, we start at the early end of the susceptibility window and continue through the late end of this window.

Other causes of vaccine failure that are host related include immunosuppressive disorders and occurrence of a genetic nonresponder. The former should likely not be vaccinated with live vaccines until the disorder is corrected. For the latter, vaccinating with a different strain of the agent may be able to overcome the nonresponsiveness.

Vaccine factors also play a role in vaccine failures. Vaccine design, strain variation, and route of administration

may all factor in to the level of protection induced. Human error is also a concern, including improper storage, preparation, and administration.

Duration of immunity is likely much longer than current revaccination recommendations. Studies have shown duration of immunity of years, and in many cases it is likely lifelong, especially following infectious vaccines. Detectable antibody levels to administered vaccines have been found as long as 14 years after vaccination for canine distemper virus and canine parvovirus in dogs. Challenge studies in dogs vaccinated for canine distemper and canine parvovirus have shown protection as long as nine years post vaccination. Similar results have been reported in cats. Current guidelines recommend revaccinating every three years, but some are electing not to boost senior animals that have a strong vaccination history.

How young is too young? Generally, most live vaccines cannot safely be administered to neonatal animals, as they may cause disease in the neonate. Noninfectious vaccines can be used as can intranasal live vaccines. However, in the very young, the response may be less than adequate due to immaturity of the immune system and interference from maternal antibodies. The exception to this interference is the intranasal vaccines which can be used in high-risk settings where the history of the neonate may not be known.

How old is too old? This is a difficult question to answer, and varies with each animal. Health status of the animal, previous vaccination history, and exposure of the animal to infection all must be considered when vaccinating senior animals. Rabies requires adherence to local vaccination policies.

Conclusion

Vaccination remains an important tool in preventive veterinary medicine. Against the common pathogens affecting dogs and cats, their use has led to decline in disease prevalence. Canine rabies, for example, has been eradicated from the USA, though rabies from wildlife still occurs in dogs and cats. There are many choices among current vaccines, and selection of vaccines is an important action for any practitioner. The practitioner must remain vigilant as new strains of pathogens emerge and new vaccines appear on the market.

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Vaccine Recommendations

AAFP: www.catvets.com/guidelines/practice-guidelines/feline-vaccination-guidelines

AAHA (canine): www.aaha.org/aaha-guidelines/vaccination-canine-configuration/vaccination-canine/

WSAVA (canine and feline): www.wsava.org/guidelines/vaccination-guidelines

177

Behavior Triage for Internists and the General Practitioner

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All veterinarians are behaviorists to some degree, whether they care for the mind or the body. Because we treat nonverbal species, our patients cannot tell us what hurts or how they feel. We rely upon behavioral observations – either our clients' or ours – to determine if a pet is ill and to evaluate its response to treatment.

Just as physical illness may produce behavioral changes, mental illness may also generate somatic signs. For example, anxiety may trigger compulsive behaviors such as psychogenic polydipsia or a proinflammatory response as in feline urologic syndrome. It is important that veterinarians recognize this mind–body interaction and be able to address the behavioral component when necessary.

The objectives of this chapter are to help veterinarians recognize the interplay between internal and behavioral medicine and to provide an algorithm and recommendations for triaging behavior cases. Diagnosis and treatment of specific behavioral problems are beyond the scope of this chapter. Recommended clinical small animal behavioral medicine texts which discuss the diagnosis, treatment, and prevention of canine and feline behavior problems are listed at the end of the chapter.

Behavioral Presentations

The relationship between internal and behavioral medicine is more complex than one may assume at first glance. In addition to physical illnesses triggering behavioral problems and vice versa, medical treatments may also affect a pet's behavior. Likewise, a pet's misbehavior may hinder the veterinarian's ability or the client's willingness to run diagnostic tests or implement treatment plans. Examples of ways in which the diagnosis and treatment of physical ailments may be influenced by the pet's behavior are listed below.

Physical Illness Causing a Behavioral Problem

While treating a pet for a physical problem, veterinarians may learn from the client that the pet has started to misbehave. For example, a polyuric cat may have urinated outside the litter box or a dog with pancreatitis may have begun growling when his owner picks him up. Although the behavior problem should resolve once the underlying physical cause has been addressed, the client may become frustrated with their pet's behavior during the treatment process. As such, veterinarians should query clients regarding behavioral changes at each appointment and be able to provide short-term treatment recommendations to alleviate them.

Ruling Out Physical Causes for a Behavior Problem

Clients may bring their pet to you to determine whether there is a physical explanation for their pet's behavior. When a behavioral change is the first or only clinical sign that the client observes, it is often unclear whether or not a physical ailment is to blame. Physical causes for behavioral problems should always be ruled out before assuming the issue is purely psychological in nature. At minimum, a complete physical exam, baseline bloodwork (i.e., complete blood count [CBC], chemistry panel, total thyroid level), urinalysis and any other indicated diagnostics tests (e.g., fecal exam for a pet defecating in the house; radiographs or other imaging if pain is elicited on physical exam) should be performed.

The likelihood of finding a physical cause for a behavior problem varies widely and depends in part on the clinical signs and history. For example, the odds of diagnosing a physical cause for a cat's sudden onset of house soiling are much higher than finding a medical reason for a dog's eight-year history of aggressive behavior toward strangers.

Of course, physical illness, if diagnosed, must be addressed. However, if no such cause is determined or if

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Companion website: www.wiley.com/go/bruyette/clinical

the behavior persists despite medical treatment, veterinarians should be prepared to offer behavioral treatment recommendations.

Behavioral Problem Causing a Physical Illness

A pet may present with a physical illness that was caused, either directly or indirectly, by a behavioral problem. The link between the pet's mental and physical ailments may be straightforward. Examples include toxicity or vomiting due to pica, polyuria secondary to psychogenic polydipsia, and hair loss caused by psychogenic alopecia. Because a psychological diagnosis for a behavior problem depends on excluding potential physical causes, it is extremely important to discuss the necessity of diagnostic testing with clients.

In other cases, the connection between the physical clinical signs and behavioral problem is less obvious. For example, a cat presenting for rodenticide toxicity may be hunting outdoors because he housesoils and is no longer allowed inside. A dog with unexplained weight loss may be suffering from separation anxiety, his weight loss occurring because he does not eat and constantly paces when home alone for 10 hours. In such cases, the client may be unaware that their pet's behavior plays a role in their physical ailment. The veterinarian should look beyond the presenting complaint to explore potential psychological or behavioral issues that may be contributing to the disease. If the underlying behavioral cause is not determined and addressed, it is very likely that the pet will present for the same issue on subsequent occasions.

Medical Treatment Causing a Behavioral Problem

Unfortunately, medical treatment may cause undesirable behavior in some cases. Patients may have idiosyncratic reactions to certain medications. For example, acepromazine may trigger aggressive behavior in some patients, while opioids and metoclopramide may elicit various behavioral changes, including agitation, in others. Steroid-induced polyphagia may result in counter-surfing, trash-raiding or resource-guarding behavior. Similarly, frequent veterinary visits, physical handling, restraint and manipulation, and constant medication administration may trigger anxiety, depression or aggressive behavior in pets that do not understand that the veterinary staff and their owners are trying to help them. In these situations – especially if the treatment cannot be discontinued or altered – veterinarians must provide behavioral recommendations to alleviate these behaviors or risk poor compliance with their treatment plan.

Preexisting Behavior Problem Hindering Medical Diagnostics and/or Treatment

Clients and veterinary staff may simply be unable to perform diagnostic tests or treatments because of the pet's behavior and temperament. The most common scenario is the client who is unable to give oral medication to his or her cat because the cat becomes aggressive when restrained and is too finicky to consume medication hidden in food. Clients may find it impossible to administer insulin injections to their diabetic dog that bites. A client living in a busy household may not be able to conduct a food trial if her dog knocks down her two-year-old son to steal cookies out of his hand. Similarly, veterinarians and staff may not be able to provide the best care to a patient that is fractious or difficult to work with. Clients may also hesitate to bring their pet to the hospital if the pet does not travel well (e.g., hides from the carrier; is agitated or anxious during car rides) or is fearful or aggressive at the clinic. If the veterinarian or client is unable to implement the ideal diagnostic or treatment plan because of behavioral reasons, discuss other treatment options or behavioral management solutions that may entail environmental changes, behavior modification and training and/or referral to a behavior practitioner.

Client Declines Diagnostics or Treatment Because of a Preexisting Behavioral Problem

The most insidious way in which behavior affects the veterinary practice occurs when the human–animal bond has been broken due to a pet's problematic behavior. Clients may elect to not pursue diagnostic or treatment options because their pet's poor behavior factors into their decision. In the client's mind, it may be difficult to justify spending money to treat a pet that bites, destroys their house, runs away or is a nuisance. Because clients rarely admit to this aspect of their decision-making process, it is especially important that veterinarians screen for behavioral problems at each visit, as part of a general "systems check." Behavioral problems can be caught early and dealt with before the human–animal bond has been affected.

Behavioral Triage

Once a behavior problem has been identified, obtaining complete medical and behavioral histories and conducting a physical exam and ancillary diagnostic tests will allow the veterinarian to determine whether the behavior is normal or aberrant/abnormal and whether it is physical or psychological in origin. The veterinarian may then recommend an appropriate course of treatment, which may include referral to an appropriate behavioral

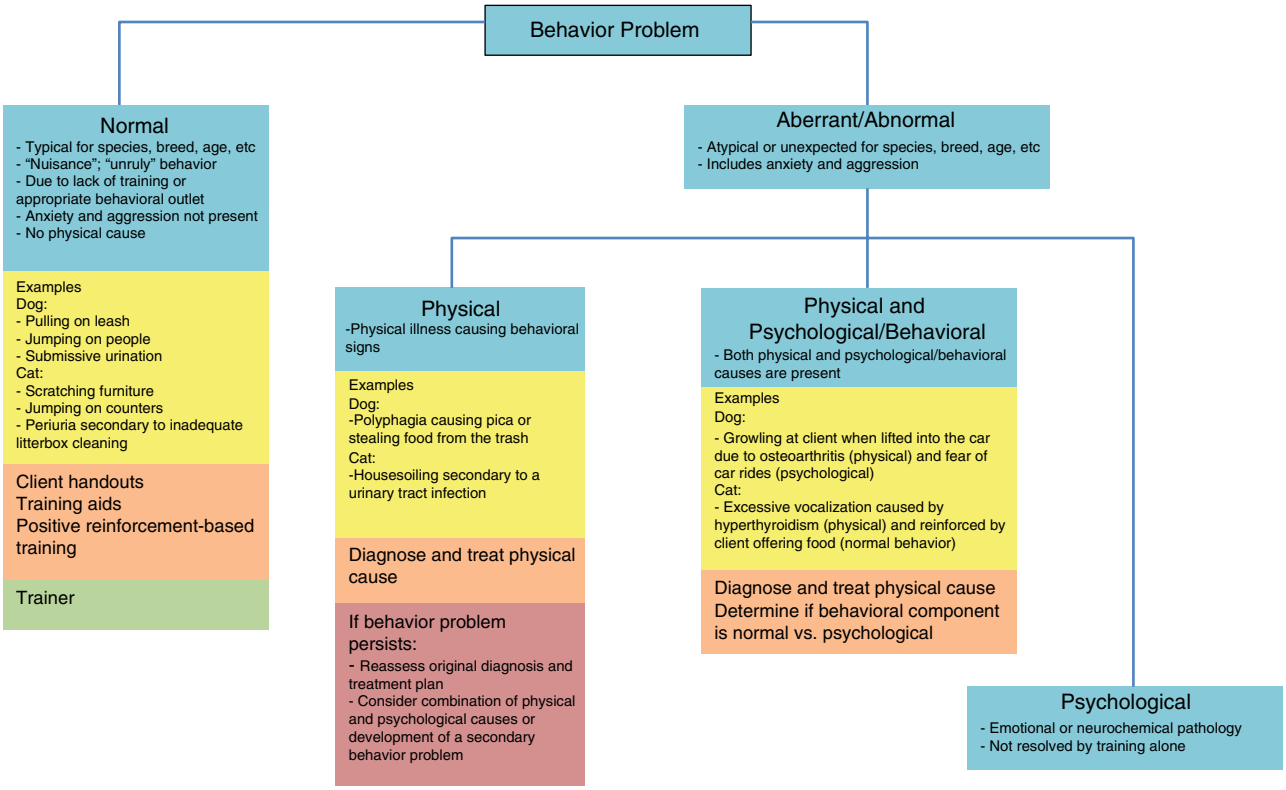


Figure 177.1 Behavioral triage algorithm.

professional depending on the type and severity of the issue. The algorithm in Figure 177.1 may help veterinarians triage behavioral issues they encounter.

1) Determine if the behavior is normal or abnormal.
   – *Normal*. These are behaviors you would expect from another animal of similar species, breed, age, lifestyle, experience, etc. These behavior problems arise because normal expression of canine or feline behavior is often incompatible with human rules. Labeled "nuisance" or "unruly" behaviors, these problems are often due to inadequate or inappropriate training or a lack of appropriate outlets for the expression of species-typical behavior. Anxiety and aggression are not present. An underlying medical cause is not present.

     Problems stemming from normal behaviors are extremely common and remain a frequent cause of relinquishment and euthanasia. It is important to identify these issues early and provide owners with treatment resources. Client handouts outlining treatment protocols are available in veterinary behavior textbooks and from veterinary, shelter, and training websites. Depending on the particular behavior, appropriate use of training aids such as head halters, body harnesses, puzzle toys, etc. may also provide clients with a "quick fix." Because the problem does not have an underlying physical or psychological cause, referral to a qualified trainer or other behavior professional is an appropriate measure.
   – *Aberrant/Abnormal*. An animal of similar species, breed, age, lifestyle, experience, etc. would not be expected to exhibit these behaviors. This category includes but is not limited to anxiety and aggression. Anxiety and aggression are normal behaviors when expressed in rational contexts and with appropriate intensity (e.g. cat hisses when a painful limb is manipulated). They are included in this category because anxiety and aggression may be clinical signs of an underlying physical and/or psychological disorder.
2) If the behavior is aberrant/abnormal, determine if the primary cause is physical, psychological or a combination of both.
   – *Physical*. If the primary cause of the behavior problem is determined to be physical, diagnose and treat the underlying physical cause of the behavior and continue medical management until both the physical and behavioral clinical signs have resolved.

     If the behavioral signs do not resolve or new behavior problems arise, reassess your original diagnosis and medical management and follow Step 1 accordingly. Consider the possibility that the original behavior problem had both physical and

psychological causes and that medical treatment only addressed the former. For example, a cat that continues to urinate outside the litter box despite elimination of its cystic calculi may have concurrent feline urologic syndrome (physical cause), litter box aversion due to inadequate cleaning by the client (normal behavior) or a learned litter box aversion because urination in the box had been associated with pain (psychological cause).

- *Both physical and psychological*. Diagnose and treat the physical component. Assess whether the behavioral clinical signs are normal or abnormal and follow Step 1 accordingly. For example, a dog that is aggressive when he is lifted into the car may be painful due to osteoarthritis (physical cause) but also fearful of car travel (psychological cause). Similarly, an elderly cat that vocalizes at night might have hyperthyroidism (physical cause) but has also been reinforced by his owners because they fed him when he cried (normal, learned behavior).
- *Psychological*. A primarily psychological etiology is diagnosed once physical causes have been ruled out or addressed. Unlike problems due to normal behaviors, "abnormal" behavioral problems typically stem from an underlying emotional (e.g., fear or anxiety) or neurochemical pathology rather than a lack of training or opportunities to express species-typical behavior. Simply reinforcing commands in these situations is unlikely to alter the animal's underlying emotional response to a situation they find threatening. These cases should be referred to a behavior professional both adept at interpreting canine or feline body language and behavior and who understands the clinical applications of learning theory.

3) If you prefer not to manage the behavioral aspects of the case yourself, determine the type of behavior professional to refer to based on the presence or absence of aggressive behavior, the severity of the behavior problem, and whether the behavior itself is common or atypical.
   - *Human-directed aggression*. Ideally, cases involving human-directed aggression should be referred to a veterinary behaviorist or a veterinarian experienced in treating aggression cases. Aggression cases often require extensive and protracted care, including an honest discussion with the owners regarding risk assessment, development of a treatment plan tailored to the owner and pet and ongoing communication – potentially for months to years – to assess and monitor the response to treatment. Because clients frequently inquire about the role medication might play in treating their pets' aggression, referral to a veterinarian with expertise in using and ability to prescribe behavior-modifying medications is best. Additionally, cases involving human-directed aggression may be at risk of future legal involvement. Documented referral to a veterinary specialist or another veterinarian who establishes their own veterinarian–client–patient relationship may be preferable to referring to a nonveterinarian in these cases. If a veterinary behaviorist or veterinarian with behavior experience is not locally available, consider a veterinarian-to-veterinary specialist consultation via phone to discuss treatment and/or referral to another behaviorist.
   - *Common problems (mild)*. A common behavior problem is one that, while abnormal, occurs frequently in that species. When they are mild in severity, common behavior problems typically do not require behavior-modifying medication and may be addressed through consistent behavior modification and environmental changes. Although it is always appropriate to refer to a veterinary behaviorist, these cases suitable for referral to a well-qualified trainer or nonveterinary behaviorist.
   - *Common problems (moderate to severe) or atypical problems*. This category includes any behavior that is moderate to severe in intensity, frequency or duration, atypical for that species or signalment, or for which a typical trigger or pattern cannot be discerned (e.g., behaviors that are idiopathic or occur "out of the blue"). These are cases in which medication and extensive, long-term behavior modification may be necessary. These cases should be referred to a veterinary behaviorist or veterinarian experienced with behavior cases.

Referrals

Clients have become increasingly educated regarding animal behavior and are seeking the advice of veterinarians when their pets misbehave rather than resorting to relinquishment or euthanasia. Whether or not to refer depends entirely on the individual veterinarian's comfort level and experience (Figure 177.2). "Normal" behavior problems or mild forms of common behavior problems may easily be addressed by the veterinarian "in house." Guidance on how to diagnose and treat canine and feline behavior problems is available in various texts (see the Further Reading list at the end of the chapter). If the veterinarian does not feel comfortable treating behavior problems or lacks the time or interest to do so, many referral options exist.

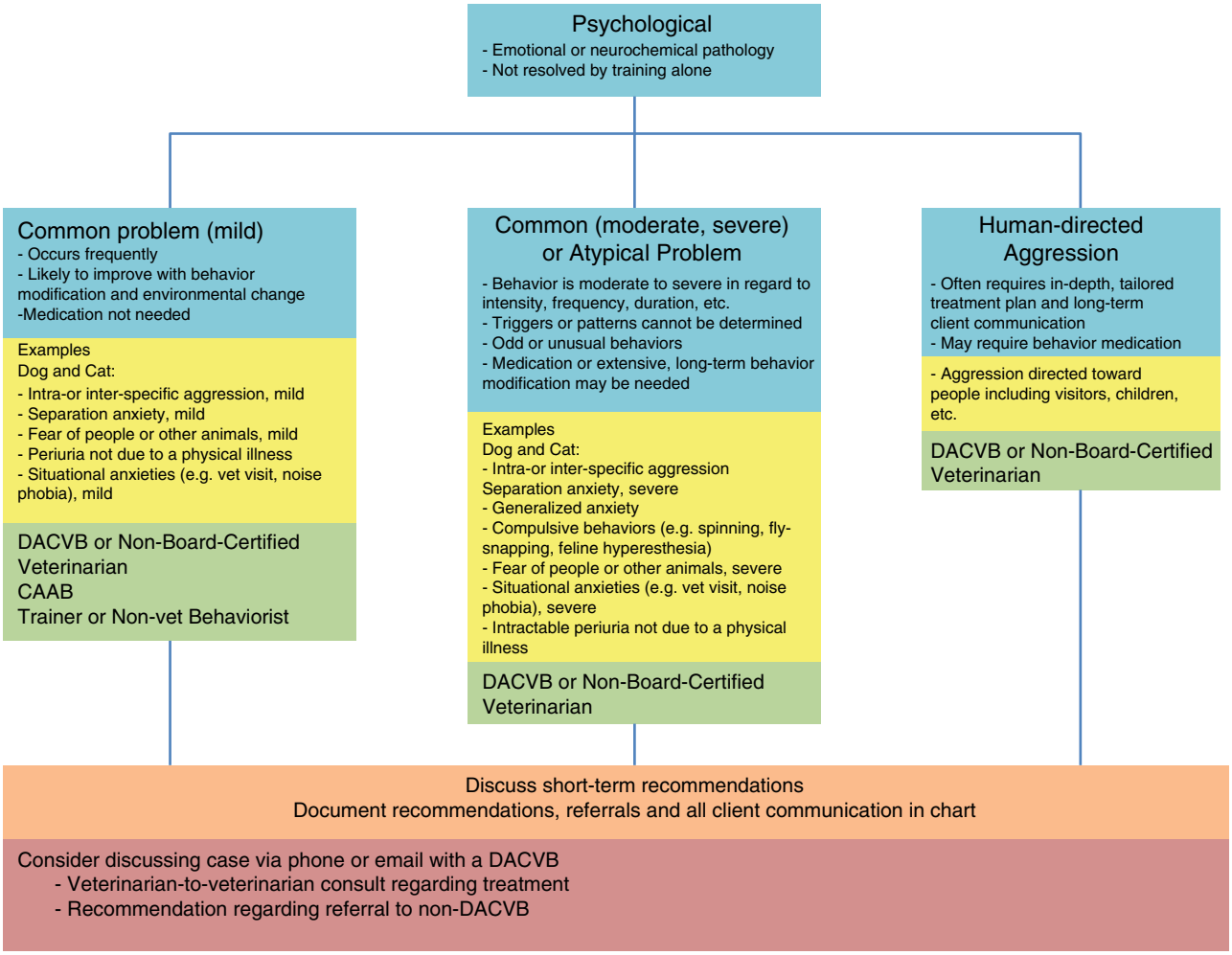


Figure 177.2 When to seek consultation with a veterinary behaviorist.

Veterinary Referrals

Veterinary Behaviorists

Board-certified veterinary behaviorists (Diplomates of the American College of Veterinary Behaviorists [ACVB]) are veterinarians who have completed a residency training program, published behavioral research and passed a qualifying exam covering medicine, ethology, pharmacology, and clinical behavior of domestic and nondomestic species. As specialists, they have a breadth of clinical experience and advanced knowledge of behavioral treatment options. Referral to a veterinary behaviorist is always appropriate and may be preferable in certain situations (Box 177.1).

If a board-certified veterinary behaviorist does not practice within a reasonable distance of your clinic, consider a veterinarian-to-veterinary specialist consult via phone or email to discuss the case or refer to a nonboarded veterinarian with behavioral experience in your local area.

Nonboarded Veterinarian with Behavioral Experience

These are veterinarians who are not board certified but are experienced with behavior cases. This category includes, but is not limited to:

- current veterinary behavior residents or residency-trained veterinarians. These are veterinarians currently in their university or private practice residency programs or who have completed their residency but have not yet passed their board-administered examination
- nonresidency-trained veterinarians with extensive behavior education and experience. There are many excellent veterinarians who have devoted their careers to the study and practice of veterinary behavior but have not completed a formal residency. They may have behavior-only private practices or see behavior cases as part of their general practice.

The American Veterinary Society of Animal Behavior (AVSAB) is an organization consisting of veterinarians and research professionals whose mission is to promote

Box 177.1 Situations in which referral to a board-certified veterinary behaviorist is warranted

Involvement of a board-certified veterinary behaviorist may be preferable over that of a nonveterinarian when one or more of the following factors are present.

- Human-directed aggression, particularly if aggression is severe or involves children
- Moderate to severe interdog or intercat aggression, especially if fights have resulted in injuries to pets or people
- Physical illness affecting the pet's behavior or treatment
  - Interplay between physical and behavioral issues warrant close monitoring
  - Medical issues may affect behavioral treatment or vice versa
- Possible use of behavior-modifying medication
  - Behavior is severe enough to warrant consideration
  - Owner inquires about medication
- Legal issues: ongoing or possible legal action
- Concerning client–patient dynamic
  - Human-animal bond is affected and/or euthanasia is a consideration
  - Client appears to be in denial regarding the severity of behavioral problem or risk involved

applied animal behavior and animal welfare. Many nonboarded veterinarians with behavior experience belong to the AVSAB.

Individual veterinarians' background training, experience level, and continuing education vary widely. Before referring to a nonboarded veterinarian, ask for a copy of their curriculum vitae and speak to them directly to discuss the case.

Nonveterinary Referrals

Certified Applied Animal Behaviorists (CAAB)

Most CAABs are not veterinarians but have a Master's or PhD degree in behavioral science, multiple scientific publications, hands-on experience with animals and have met coursework and experience requirements for certification as set forth by the Animal Behavior Society. Their scientific background makes CAABs knowledgeable about learning theory, ethology, and animal behavior. However, the amount of clinical or practical experience working with animals may vary by individual. Inquire as to their level of hands-on experience with clinical cases prior to referral.

Because most CAABs are not veterinarians, their insight into the interaction between physical and behavioral illness may be limited. It is therefore important that the referring veterinarian and CAAB work in partnership so physical issues are not overlooked. CAABs cannot prescribe medication and must refer cases back to a veterinarian for a prescription. It is the prescribing veterinarian's duty to ensure that the medication prescribed is appropriate for the patient and behavior being addressed. If the prescribing veterinarian is not familiar with psychopharmaceutical medications, it is appropriate to ask the CAAB for supporting documentation (in the form of journal articles, book references, etc.). The prescribing veterinarian must also obtain informed consent from the client, including discussing potential physical and behavioral adverse effects and conducting appropriate tests to ensure the health of the patient prior to starting medication.

Trainers and Animal Behaviorists

Many skilled, professional trainers and nonveterinary/non-CAAB animal behaviorists are available to help veterinarians, clients, and patients. These individuals may provide a range of services that veterinary and CAAB behaviorists do not, including private, in-home training, group classes, board and train, etc. Additionally, trainers are often able to work with clients and their pets on a more frequent and regular basis than a veterinary or CAAB behaviorist could. This is extremely helpful especially for clients who require extensive, hands-on training or encouragement to consistently comply with a treatment plan.

As a group, trainers and nonveterinary/non-CAAB behaviorists are a valuable resource. However, it is important to remember that individuals vary widely in regard to their knowledge, experience, training techniques, and ethics. This spectrum exists because there is no agency or governing body that oversees or regulates the qualifications of these professions. Anyone may label themselves a trainer or animal behaviorist regardless of their background. Animal behavior and training certifications can be obtained through various programs, some of which are more rigorous and require more education and experience than others. Training philosophies, such as the use of positive reinforcement versus punishment-based training techniques, also differ from school to school.

Always research the individual before recommending any trainer or animal behaviorist, veterinary or nonveterinary. Both the ACVB and AVSAB have published guidelines for selecting and working with trainers on their websites. These recommendations should be applied to any behaviorist, veterinary or nonveterinary, you may refer a client to. Because experience, training methods, and skillsets of trainers and behaviorists vary

widely, it is advisable to create different referral lists depending on the needs of the clients and patients. For example, some individuals may be highly accomplished trainers (able to teach basic obedience, agility, nosework, etc.) but do not have the background or education to treat behavior problems. Other behaviorists may feel comfortable treating "normal," training-related behavior problems but not "aberrant/abnormal" cases such as aggression or anxiety disorders. Some behaviorists specialize only in a particular species.

Summary

A team effort is required to successfully treat behavior problems. Every member of the team – referring veterinarian, behaviorist, and client – should feel comfortable working with each other for the pet's benefit. Ask your clients for feedback regarding their experience with the behaviorist or trainer they worked with so you know whom to refer to in the future. No matter to whom you refer, referrals reflect on you and your practice.

Safety and Avoidance: Short-Term Recommendations

Unless they have an interest in behavioral medicine, the veterinarian should not feel obligated to provide a comprehensive behavioral treatment plan to the client. However, the veterinarian should provide short-term, interim recommendations geared toward keeping the pet and people safe and to prevent the pet's behavior from worsening until referral to a qualified individual occurs.

- Treat physical conditions that affect the pet's behavior. Encourage clients to treat any medical problem that may contribute to the behavioral disorder.
- Avoid situations that cause the undesirable behavior to occur. Avoiding situations that cause anxiety or aggression may be necessary to prevent the pet from becoming self-injurious or harming other animals or people. Avoidance also prevents the pet from developing a progressively stronger averse response to the situation due to repeated exposure (sensitization). Rather than simply instructing clients not to let their dog or cat become anxious or aggressive, provide specific avoidance recommendations tailored to the pet and behavior problem. Relevant guidelines may be found in behavior textbooks.
- Recognize early signs of fear, anxiety, and aggression. Pets often exhibit subtle signs of discomfort before their anxiety or aggression intensifies. Teach clients to recognize physical cues such as pinned ears, crouched body posture and tucked or lashing tails as well as behavioral signs including refusing treats, not following commands and displacement behaviors like yawning, lip licking, and grooming. Handouts on canine and feline body language (available in behavior textbooks) may be sent home with clients to aid identification. To reduce the frequency and severity of subsequent undesirable behaviors, clients should remove their pet from the situation as soon as they recognize the initial signs of impending aggression or anxiety.
- Do not use punishment or confrontational training techniques as these may exacerbate fear, anxiety, and aggression. Warn clients that physical corrections – such as hitting, swatting, kicking, forcibly holding the pet down ("alpha rolling"), choke or prong collar use, scruffing, etc. – foster negative associations with the client and create anxiety and mistrust. If incorrectly used, punishment-based techniques may physically harm the pet and worsen their behavior. For additional information on the hazards of punishment-based training, see the AVSAB Position Statement on the use of punishment for behavior modification in animals available on the AVSAB website.
- Reward the pet for desirable behaviors. Encourage clients to reward their pet when it behaves appropriately (positive reinforcement). Recommend that clients think proactively rather than reactively by identifying desirable behaviors, creating situations that allow their pet to behave in an appropriate manner and rewarding it when it does so. For example, rather than punishing a dog for jumping on them, the client may preemptively instruct the dog to sit before he jumps up, and then reward him with attention while he is seated.

Encourage clients to formally train their pets. Training provides clients and their pets with a common language in which to communicate. Dogs and cats can be taught simple commands such as "sit," "down," "stay," and "come" which are used to facilitate behavior modification techniques such as desensitization and counterconditioning to specific triggers. When positive reinforcement training techniques are used, the pet enjoys interacting with the client and its anxiety decreases because interactions are consistent, predictable, and rewarding.

Managing Client Expectations

Many clients have unrealistic goals such as wanting their pet "to be friendly with every person and animal" or "to never to be anxious or aggressive again." Alternatively, clients may not realize that their dog or

cat's behavior puts the pet, people or other animals at serious risk of injury. A frank discussion regarding risk assessment and realistic prognosis may be necessary before the client invests time, money, and emotional effort in treating their pet's behavior.

An in-depth discussion of risk assessment is beyond the scope of this chapter but is addressed in several behavioral texts (see Further Reading).

Prognosis depends on the individual case but is usually guarded since most behavior problems cannot be "cured." Abnormal behavior problems not due to physical illness are caused by emotional and/or neurochemical disease states that cannot be fully eliminated. The goal of treatment is remission – management of the behavior and reduction in symptom severity and frequency such that the pet and client have an improved quality of life.

In most situations, consulting with a behavior professional and compliance with a behavior modification plan will improve the pet's behavior. The veterinarian or behavior professional should establish reasonable short-term and long-term goals for the pet. Ongoing communication between the behavior professional and client along with periodic recheck appointments are essential to ensure that the treatment plan is successful or, if not, to adjust the recommendations accordingly.

Conclusion

The goals of both behavioral and internal medicine are the same: establish a diagnosis and alleviate clinical signs of the disease. When behavioral issues complicate physical illness or vice versa, diagnosis and treatment will not be successful without identifying and addressing both. Once a behavioral cause has been established, veterinarians must be prepared to triage these cases and provide the clients with short-term recommendations and referral to the appropriate behavior professional. This multidisciplinary approach addresses both the physical and behavioral components of the disease process and provides the best prognosis for successful resolution of clinical signs, thus improving the quality of life for the pet and client.

Further Reading

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Websites

American College of Veterinary Behaviorists (ACVB): www.dacvb.org

- Information about the College of Veterinary Behaviorists including practice location and contact information for diplomates
- Handouts including "ACVB Guidelines for Working with a Trainer"

American Veterinary Society of Animal Behavior (AVSAB): https://avsab.org/

Information about AVSAB including a referral list of veterinarians and behavior professionals who have a special interest in clinical animal behavior, searchable by zipcode

- AVSAB Position Statements on punishment, dominance, puppy socialization and breed-specific legislation are available to the public
- Members have access to a forum where they can ask questions about cases, review notes from past veterinary behavior symposia and access the newsletter and blog

Academy of Veterinary Behavior Technicians (AVBT): www.avbt.net

- Information about AVBT, including a list of technicians who have obtained the Veterinary Technician Specialist (Behavior) designation
- Resources for behavior information, especially for technicians interested in animal behavior and training

Certified Applied Animal Behaviorists (CAAB): www.corecaab.org

- Information about CAABs including a membership directory
- Additional information on applied animal behavior and CAAB requirements may be found at the Animal Behavior Society website: animalbehaviorsociety.org

Included below are websites containing additional information about nonveterinary/non-CAAB trainers and behaviorists. The veterinarian is highly encouraged to research both the individual trainer and certifying organization prior to referral

www.iaabc.org – International Association of Animal Behavior Consultants
www.ccpdt.org – Certification Council for Pet Dog Trainers
www.KarenPryorAcademy.com – Karen Pryor Academy
www.apdt.com - Association of Pet Dog Trainers (APDT)

Section 16

Laboratory Support

A list of commonly used veterinary laboratories with links to their websites for information concerning test offerings, sample submission, and interpretation.

Idexx
www.idexx.com/en/veterinary/reference-laboratories/tests-and-services/
http://www.idexx.co.jp/pdf/ja_jp/smallanimal/vetlab/catalyst/JP-SAH-Catalyst-reference-ranges.pdf

Antech Diagnostics
www.antechdiagnostics.com

Michigan State University Veterinary Diagnostic Laboratory
www.dcpah.msu.edu/sections/endocrinology/

University of Tennessee College of Veterinary Medicine – Clinical Endocrinology Service
https://vetmed.tennessee.edu/vmc/dls/endocrinology/Pages/default.aspx

Colorado State University – Veterinary Diagnostic Laboratories
http://csu-cvmbs.colostate.edu/vdl/Pages/default.aspx

Cornell University – Animal Health Diagnostic Center
https://ahdc.vet.cornell.edu

MiraVista Veterinary Diagnostics
https://miravistavets.com

ZNLabs Veterinary Diagnostics
https://znlabs.com

Phoenix Lab
http://phoenixlab.com

North Carolina State University College of Veterinary Medicine Vector Borne Disease Diagnostics
https://cvm.ncsu.edu/research/labs/clinical-sciences/vector-borne-disease/

Marshfield Labs
www.marshfieldlabs.org/lab-services/vet-lab

PennGen Laboratories
www.vet.upenn.edu/research/academic-departments/clinical-sciences-advanced-medicine/research-labs-centers/penngen

Texas A&M University – Gastrointestinal Laboratory
http://vetmed.tamu.edu/gilab

Auburn University College of Veterinary Medicine – Molecular Diagnostics (FIP)
www.vetmed.auburn.edu/academic-departments/dept-of-pathobiology/diagnostic-services/molecular-diagnostics/

UC Davis School of Medicine – Coccidiodomycosis Serology Laboratory
www.ucdmc.ucdavis.edu/medmicro/cocci-lab.html

Washington State University Clinical Pharmacology Laboratory (MDR-1)
https://vcpl.vetmed.wsu.edu

Cornell University – Gastroenterology Research Department of Veterinary Clinical Studies (FISH)
www2.vet.cornell.edu/research-departments/labs/simpson-laboratory

Galaxy Diagnostics (Bartonella)
www.galaxydx.com

Kansas State University Clinical Immunology (Platelet and RBC Surface Antibody)
www.ksvdl.org/laboratories/clinical-immunology/

Index

Page locators in **bold** indicate tables/boxes. Page locators in *italics* indicate figures. This index uses letter-by-letter alphabetization.

6MWT *see* six-minute walk test

a

AAFP *see* American Association of Feline Practitioners
AAHA *see* American Animal Hospital Association
ABC *see* airway, breathing, and circulation; ATP-binding cassette
abdominal distension 121, 449
abdominal focused assessment with sonography for trauma (AFAST) 406, 449
ABG *see* arterial blood gas
abnormal involuntary movements (AIM) *see* movement disorders
ABP *see* aminobisphosphonates
abscesses
  hepatobiliary disease 666–667
  nonhemotropic *Mycoplasma*, *Ureaplasma*, and L-form bacteria 934
  prostatic diseases 1161–1163
ABT *see* aortic body tumors
AC *see* activated charcoal
A/C *see* assist/control
acanthomatous ameloblastoma 1253, 1256
accelerated gastric emptying 567
ACCF/AHA *see* American College of Cardiology Foundation and American Heart Association
ACCP *see* American College of Clinical Pharmacology
ACE *see* angiotensin-converting enzyme
ACEI *see* angiotensin-converting enzyme inhibitors
acetate tape impressions 1391, 1457–1458
acetylcholine (ACh) 460, 803–808
AChEI *see* anticholinesterase inhibitors
acid–base balance
  acute kidney injury 1096
  chronic kidney disease 1172
  critical care setting 350
  dialysis 1178
  urolithiasis 1132
Acinetobacter spp. 1060
acne 1465–1466, *1465*
acoustic enhancement 663
acoustic shadowing 664
acquired hepatic dysfunction 107–108
acquired megaesophagus 558–559
acquired portosystemic shunts (APSS) 713–720
  cirrhosis 706–708
  classification and anatomy 713–714
  diagnosis 716
  etiology 713
  history and clinical signs 716
  liver disease 643
  pathophysiology 714–715, **714**
  portal hypertension 715
  prognosis 720
  signalment 715
  treatment 717–720
acral lick dermatitis (ALD) 1467, *1467*
acromegaly 99–100
ACTH *see* adrenocorticotropic hormone
actinomycosis 977–979
  diagnosis 978
  epidemiology 977
  etiology/pathophysiology 977
  history and clinical signs 977–978
  pleural effusion 340–341
  public health implications 979
  signalment 977
  treatment and prognosis 978, **978**
activated charcoal (AC) 442–443
acupuncture 1204
acute blindness 90, *90*
acute hypoperfusion 680
acute kidney injury (AKI) 1089–1099
  acid–base balance 1096
  diagnosis 1092–1094
  dialysis 1098, 1176–1178, *1176–1177*
  diuretics 1095–1096
  electrolyte balance 1096–1097
  epidemiology 1089–1091, **1091**
  etiology/pathophysiology 1089, **1090**
  fluid therapy 1095
  history and clinical signs 1091–1092
  hypoadrenocorticism 83
  imaging 1093
  laboratory tests 1092–1093
  leptospirosis 946, 948
  motility disorders 572
  nutritional support 1097–1098
  phosphorus homeostasis and disorders 1083–1085
  prognosis 1098
  septic shock 423–424
  signalment 1091
  treatment 1094–1098, **1094**
Acute Kidney Injury Network (AKIN) 1091
acute lung injury (ALI) 423

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acute lymphoblastic leukemia (ALL) 1223–1225, *1225*
acute moist dermatitis 1461–1462, *1462*
acute myeloid leukemia (AML) 1225–1227
acute neutrophilic cholangitis (ANC) 687, 690
acute phase proteins (APP) 874, 1208
acute poisoning 437–444
  blood decontamination 443–444
  certain exposure to a known toxin 438–440
  certain exposure to an unknown toxin 441
  clinical approach 437–441
  decontamination 441–444
  diagnostic testing 437–438
  dialysis 1179
  gastrointestinal decontamination 441–443
  history 437
  ocular decontamination 441
  physical examination 437
  topical decontamination 441
  uncertain exposure to a known toxin 440–441
  see also venomous snake bites
acute respiratory distress syndrome (ARDS)
  acute respiratory failure 390
  mechanical ventilation 393, 397
  respiratory monitoring in critical care 379
  septic shock 423
acute respiratory failure 381–391
  diagnosis 387
  epidemiology 386–387
  etiology/pathophysiology 381–386
  history and clinical signs 387
  hypercapneic respiratory failure 381–383, 388–389
  hypoxemia 397–398
  hypoxemic respiratory failure 383–386, **384**, *385*, 389–390, **390**, 397–398
  prognosis 390
  signalment 387
  treatment 387–390
acute spinal cord dysfunction 818–819
ACVB *see* American College of Veterinary Behaviorists
ACVIM *see* American College of Veterinary Internal Medicine
Adams modified staging system 1257, **1257**
Addison disease *see* hypoadrenocorticism
adenohypophysis 35–36
adenoma/adenocarcinoma
  gastritis and gastric ulceration 550
  intestinal cancers 1287–1290, 1292
  nonmelanoma skin cancers 1354
  ocular adnexal tumors 1262
adenomatous polyps 1288, 1292
adenosine diphosphate (ADP) 446
adenosine triphosphate (ATP)
  biology of cancer and cancer genetics 1209–1210
  heart failure 182
  magnesium homeostasis and disorders 1086
  phosphorus homeostasis and disorders 1079, 1082
  shock 404
  trauma and burns 446
ADH *see* alcohol dehydrogenase; antidiuretic hormone
adhesions 495–496, *496*
ADP *see* adenosine diphosphate
adrenal-dependent hyperadrenocorticism (ADH) 55, 56
adrenalectomy 57, 91
adrenal tumors 220
adrenocortical function testing 45
adrenocorticotropic hormone (ACTH)
  autoimmune polyglandular syndromes 114
  endocrine manifestations of cancer 1213
  endocrinology 29–32
  esophageal disorders 559
  feline acromegaly 45
  hypoadrenocorticism 81, 84–89, 91
  hypoglycemia 110
  motility disorders 564
  neuroendocrinology 39
  pituitary-dependent hyperadrenocorticism 49–51, **53–54**, 54–62
  polyuria and polydipsia 67
  septic shock 428
advanced life support (ALS) 367–369
adverse food reactions *see* cutaneous adverse food reactions
AEC *see* articular-epiphyseal complex
AED *see* antiepileptic drugs
AF *see* atrial fibrillation
AFAST *see* abdominal focused assessment with sonography for trauma
afterload 176
AG *see* aminoglycosides
aggression 893, 1574
aggressive diuresis 1149–1150
AIM *see* movement disorders
AIP *see* aryl-hydrocarbon-receptor interacting protein
air embolism 356
airway, breathing, and circulation (ABC)
  acute poisoning 437
  acute respiratory failure 382–383
  cardiopulmonary resuscitation 367
  mechanical ventilation 399
  respiratory pattern-based approach to dyspnea 289
  spinal cord injury 745
  trauma and burns 448–449
airway cancers 1277–1278
  diagnosis 1277–1278
  epidemiology 1277
  etiology/pathophysiology 1277
  history and clinical signs 1277
  prognosis 1278
  signalment 1277
  treatment 1278
AKI *see* acute kidney injury
AKIN *see* Acute Kidney Injury Network
alanine aminotransferase (ALT) *see* enzyme markers of liver disease
albumin
  chronic enteropathies 630–632
  critical care setting 349
  fluid therapy 360, 363
  liver disease 649
  trauma and burns 451
alcohol dehydrogenase (ADH) 440
ALD *see* acral lick dermatitis
aldosterone 81, 89–92
aldosterone antagonists 183
alimentary lymphoma 1235–1239
alkaline phosphatase (ALP) *see* enzyme markers of liver disease
alkalinization therapy 1172
ALL *see* acute lymphoblastic leukemia
allergen-specific immunotherapy 1411–1412
allergen testing 1407–1408, *1407*
allergic skin diseases 1413–1417
  contact dermatitis 1414–1415, *1415*
  flea allergy dermatitis 1415–1417, *1416*
  urticaria and angioedema 1413–1414, *1414*, **1414**
alopecia 1433–1439

abnormal hair growth 1434–1435, *1435*
alopecia X 1435, *1436*
anagen/telogen defluxion 1437
approach to the dermatologic patient *1386*
atopic dermatitis *1406*
autoimmune and immune-mediated skin disease *1424*, *1426*
bacterial pyodermas *1463–1464*
cutaneous manifestations of systemic disease 1488–1489, *1489*
cyclic flank alopecia 1436, *1436*
diagnosis 1438
distribution and pattern of alopecia 1437–1438
ease of epilation 1437
etiology/pathophysiology 1433–1437
exocrine pancreatic cancer 1293
hair cycle arrest 1435
history and clinical signs 1437–1438
inflammation-induced alopecia 1433, *1434*, **1434**
noninflammatory alopecia 1434–1437, *1436*
onset of alopecia 1437
paraneoplastic syndromes 1221–1222
patterned alopecia 1436, *1436*
postclipping hair follicle arrest 1436–1437, *1437*
prognosis 1438–1439
signalment 1437
trauma-induced alopecia 1433
treatment 1438, **1438**
alpha-1-proteinase inhibitors 633
alpha-agonists 451, 1184
alpha-fucosidosis 775
ALS *see* advanced life support
ALT *see* alternative lengthening of telomeres
alternative lengthening of telomeres (ALT) 1206
alveolar dead space 383
alveolar gas equation 376–377
amanita mushrooms 684
amaurosis 823
ambulatory 24-hour Holter recording 213
amebiasis 1019
American Animal Hospital Association (AAHA) 1064
American Association of Feline Practitioners (AAFP)
bartonellosis 924
feline leukemia virus 881
kennels and multicat environments 1064
American College of Cardiology Foundation and American Heart Association (ACCF/AHA) 177
American College of Clinical Pharmacology (ACCP) 321
American College of Veterinary Behaviorists (ACVB) 1575
American College of Veterinary Internal Medicine (ACVIM)
canine myocardial disease 254, 259–262
heart failure 177–178
pituitary-dependent hyperadrenocorticism 53
valvular heart disease 247–250
American Veterinary Dental College (AVDC) **534**
American Veterinary Society of Animal Behavior (AVSAB) 1575, 1577
amino acid-derived hormones 30
aminobisphosphonates (ABP) 1331–1332
aminoglycosides (AG) 957, 1041–1044
AML *see* acute myeloid leukemia
ammonium urate urolithiasis 1128–1129, *1128*, 1141–1142
amputation 617–618, 1330–1331
amyloidosis
cutaneous manifestations of systemic disease 1483–1484
hepatobiliary disease 665–666
metabolic diseases 680–681
anagen defluxion 1437
analgesia 735
see also pain and pain management
anal sac adenocarcinoma 609–610
anal sacculectomy 610–611
anal sac impaction 610–611
analysis of variability 9
anaphylactic/anaphylactoid hypersensitivity reactions 462–463
anaplasmosis *see* ehrlichiosis and anaplasmosis
anatomic shunting *see* right-to-left shunting
ANC *see* acute neutrophilic cholangitis
anemia
acute kidney injury 1092
antimicrobials 1047
chronic kidney disease 1170–1171
feline leukemia virus 878
liver disease 652–653
metabolic diseases 680
paraneoplastic syndromes 1219–1220
shock 405
anesthesia
esophageal disorders 560–561
mechanical ventilation 397
rectoanal diseases 616
surgical, traumatic, and bite wound infections 1031, 1034
trauma and burns 451–452
angioedema 1413–1414, *1414*, **1414**
angiogenesis 1208–1209
angiography
congenital heart disease 240, *242*
pleural effusion 342–343
pulmonary thromboembolism 319–320
angiotensin-converting enzyme (ACE) 179–180
angiotensin-converting enzyme inhibitors (ACEI)
canine myocardial disease 259–262
chronic kidney disease 1168–1170, *1169*
congenital heart disease 240–243
feline myocardial disease 273
glomerular disease 1104–1105
heart failure 183, 186, 188–190, 193, 197
systemic hypertension 222–224
valvular heart disease 248–250
angiotensin receptor blockers (ARB)
chronic kidney disease 1168–1170, *1169*
glomerular disease 1104–1105
systemic hypertension 222, 224
Animal Trauma Triage (ATT) Score 455, **456**
anion gap 1092
anisocoria 737, 824
anorexia 255, 679–680
Anrep effect 176
antacids *see* gastroprotectants
anthrax 971–975
diagnosis 973
etiology/pathophysiology 971–972
history and clinical signs 972–973
prevention 974–975
public health implications 974
signalment 972, **972**
treatment 973–974, **973**

antiangiogenic therapy 1343–1344
antiarrhythmics
  canine myocardial disease 260–265
  supraventricular arrhythmias 212–214, 217
  ventricular arrhythmias 200–204
antibacterials *see* antimicrobials; *individual classes/agents*
antibiotic-responsive diarrhea (ARD) 627, 629, 636
antibiotics *see* antimicrobials; *individual classes/agents*
antibody/antigen detection
  canine brucellosis 964
  feline coronavirus 874
  feline leukemia virus 879–880
  fungal infections 986, 991–992, 994–995
  leptospirosis 946–947
  Lyme borreliosis 942
  protozoal and arthropod-borne infections 841–843
  protozoal and protozoa-like infections 1004–1005
  spotted fever and typhus group *Rickettsia* 939
  tularemia 957
  viral infections 843–844
  yersiniosis 953
anticholinesterase inhibitors (AChEI) 805–806
anticoagulant rodenticide 439
anticoagulants 321–322
antidiuretic hormone (ADH)
  heart failure 180
  hypothermia 432
  neuroendocrinology 39
  pituitary-dependent hyperadrenocorticism 52
  polyuria and polydipsia 65, 67
  sodium and water homeostasis 1069–1076, **1072**
  syndrome of inappropriate antidiuretic hormone secretion 1214
antiemetics 1167–1168
antiepileptic drugs (AED) 761–766, **767**, 771
antifungals *see* antimicrobials; *individual classes/agents*
antigen delivery systems 1568–1569
antigenemia 878–880
antigen-presenting cells (APC) 1208, 1567, 1569
antihistamines
  allergic skin diseases 1414
  atopic dermatitis 1409
  feline bronchial asthma 302
  miscellaneous skin diseases 1499
antihypertensives 1105–1106, **1105**
antiinflammatory drugs
  bacterial pyodermas 1467
  canine chronic bronchitis 308
  cutaneous adverse food reactions 1422
  meningoencephalitis and meningomyelitis 800–801, **800**
  principles of therapy of dermatologic diseases 1399–1400
  spotted fever and typhus group *Rickettsia* 939–940
  see also nonsteroidal antiinflammatory drugs
antimicrobials
  actinomycosis 978, **978**
  anthrax 973–974, **973**
  antimicrobial resistance 1030, 1045–1047
  antimicrobial susceptibility tests 845
  atopic dermatitis 1410–1411
  bacterial pyodermas 1462, 1464–1470
  bartonellosis 924
  canine chronic bronchitis 310
  canine distemper virus 853–854
  canine herpesvirus 856
  canine infectious respiratory disease complex 1037
  canine inflammatory liver disease 700–701, 703
  canine parvovirus type 2 859
  chronic enteropathies 627, 629, 636
  cirrhosis 710
  coccidia 1024–1026, **1025**
  common classes of antifungal agents 1049–1053, **1050**
  common classes of antimicrobial agents 1041–1048, **1042–1043**
  critical care setting 351
  dysbiosis 625
  ehrlichiosis and anaplasmosis 911
  esophageal disorders 559–560
  exocrine pancreatic insufficiency 588
  feline inflammatory liver disease 690–691, **691**
  feline leukemia virus 880
  feline viral upper respiratory tract disease 888
  forebrain disorders 783–784
  formulation, indications, and side-effects **1050**
  fungal infections 986, 988–990, 992–993, 995, 997–999
  gallbladder and extrahepatic biliary ducts 725
  gastritis and gastric ulceration 554
  hemotropic *Mycoplasma* 929
  leptospirosis 947–948
  Lyme borreliosis 943
  meningoencephalitis and meningomyelitis 799, **799**
  miscellaneous skin diseases 1497–1498, 1505–1506
  motility disorders 577
  mycobacteriosis 982–983, **983**
  nocardiosis **978**, 979–980
  nonhemotropic *Mycoplasma*, *Ureaplasma*, and L-form bacteria 934
  optimizing antimicrobial therapy 1041, 1048
  oral cavity and salivary glands 536, 543–544
  otitis externa 1474–1476, **1476**, 1478–1479, **1479**
  parasitic skin diseases 1451–1460
  pleural effusion 340–341
  portosystemic shunts and microvascular dysplasia 717
  principles of therapy of dermatologic diseases 1400–1402
  prostatic diseases 1162, **1162**
  protozoal and protozoa-like infections 1005–1006, 1008–1009, 1014–1015, 1018–1019
  Q fever 960
  salmon poisoning disease 914
  septic shock 427–428
  side-effects and drug–drug interactions **1044**
  spotted fever and typhus group *Rickettsia* 939–940
  surgical, traumatic, and bite wound infections 1030, 1032–1034
  tetanus 968
  trauma and burns 454
  urinary tract infections 1191–1195
  valvular heart disease 251
  venomous snake bites 463
  Wolbachia pipientis infection 918

yersiniosis 953
see also individual classes/agents; nocosomial and multidrug-resistant infections
antioxidants
canine inflammatory liver disease 700–701
chronic kidney disease 1172
gallbladder and extrahepatic biliary ducts 725
antiplatelet agents 322–323
antipruritic agents 1400
antithrombin 315, 316
antithrombotics **188**, 191–192, 1105
antithyroid drugs 78
antitoxin therapy 807–808
antivenins 462–464, 808
antivirals *see* antimicrobials; *individual classes/agents*
anuria 1177–1178
anxiety 197
aortic body tumors (ABT) 1271
aortic insufficiency 147, *156–157*
aortic thromboembolism (ATE) 320
APC *see* antigen-presenting cells
apheresis 1369–1372
bone marrow transplantation 1371
cell separator machines 1369
companion animal apheresis 1370–1372
leukopheresis 1370, 1371
physician-based applications 1369–1370
plateletpheresis 1369, 1372
apocrine gland adenoma/carcinoma 1354
APP *see* acute phase proteins
appetite 584–585, 1167–1168
APS *see* autoimmune polyglandular syndromes
APSS *see* acquired portosystemic shunts
ARAS *see* ascending reticular activating system
ARB *see* angiotensin receptor blockers
ARD *see* antibiotic-responsive diarrhea
ARDS *see* acute respiratory distress syndrome
arginine 678–679
arginine vasopressin (AVP) *see* antidiuretic hormone
arrhythmias *see* electrocardiography; supraventricular arrhythmias; ventricular arrhythmias
arrhythmogenic right ventricular cardiomyopathy (ARVC)
canine myocardial disease 263–265
cardiogenic shock 414
diagnosis 264–265
epidemiology 263–264
etiology/pathophysiology 263, *263*
feline myocardial disease 267, 269–272
history and clinical signs 264
prognosis 265
signalment 264
treatment 265
arterial blood gas (ABG)
critical care setting 350
pulmonary thromboembolism 316
respiratory monitoring in critical care 376–377, **376**
respiratory pattern-based approach to dyspnea 293
shock 407–408
surgical approaches to thoracic disease 328
arterial thromboembolism (ATE) 269, 270–271, 273
arterioportal fistulae 673
arthritis
Lyme borreliosis 941–943
nonhemotropic *Mycoplasma*, *Ureaplasma*, and L-form bacteria 933
see also osteoarthritis
arthropod-borne infections 839–843
see also individual agents/diseases
arthroscopy 1531, *1532*, 1542–1545
articular-epiphyseal complex (AEC) 1511–1512
artifactual hypoglycemia 104–105
ARVC *see* arrhythmogenic right ventricular cardiomyopathy
aryl-hydrocarbon-receptor interacting protein (AIP) 43–44
ascending reticular activating system (ARAS) 731, 753
ascites
cirrhosis 705–706, 709–710
feline inflammatory liver disease 688, 693
pathophysiology 643
portosystemic shunts and microvascular dysplasia 715–716
aspartate aminotransferase (AST) *see* enzyme markers of liver disease
aspergillosis 995–997
diagnosis 996
epidemiology and signalment 995–996
etiology/pathophysiology 995
history and clinical signs 996, *996*
public health implications 997
treatment and prognosis 997
aspiration pneumonia 558, 559
aspiration pneumonitis 292
assist/control (A/C) ventilation 394, 396
association measures 12–15
asthma *see* feline bronchial asthma
astrocytomas 779
asymptomatic bacteriuria 1191
ataxia 732
ATE *see* arterial thromboembolism
atelectasis 325
atopic dermatitis 1403–1412
allergen-specific immunotherapy 1411–1412
approach to the dermatologic patient 1376
diagnosis 1406–1408, *1407*
epidemiology 1403–1404
etiology/pathophysiology 1403
feline bronchial asthma 300
history and clinical signs 1404–1406, *1404–1406*
medical therapy 1408–1411
otitis externa 1471–1472
prognosis 1412
signalment 1404
treatment 1408–1412
ATP *see* adenosine triphosphate
ATP-binding cassette (ABC) proteins 1046
atresia ani 611–612, *611*
atrial enlargement
cardiovascular disease 130, *134–137*
electrocardiography 172, **173**, *174*
feline myocardial disease 271, 273
valvular heart disease 246–247
atrial fibrillation (AF) 212–215
canine myocardial disease 255–256
cardiogenic shock 415, 419–420
diagnosis 213, *214*
epidemiology/signalment 212–213
etiology/pathophysiology 212
history and clinical signs 213
treatment and prognosis 213–215
atrial septal defect (ASD) 231–233, 237, *239*, 241–243
atrioventricular (AV) block, cardiogenic shock 413–414, 419

atrioventricular block 211–212
diagnosis 211, *212*
epidemiology/signalment 211
etiology/pathophysiology 211
history and clinical signs 211
treatment and prognosis 212
atrioventricular septal defects (AVSD) 233, 243
ATT *see* Animal Trauma Triage
atypical hypoadrenocorticism 87–88
auscultation
cardiovascular disease 122–125, *122*, **124–125**
congenital heart disease 235–237, **237**
pleural effusion 335
respiratory auscultation 124–125
respiratory pattern-based approach to dyspnea 291–292
trauma and burns 448
valvular heart disease 247
autoagglutination 1219
autoimmune and immune-mediated skin disease 1423–1431
autoimmune subepidermal blistering diseases 1427–1428, *1427*
canine familial dermatomyositis 1423, *1424*
cutaneous lupus erythematosus 1424–1427, *1426*
erythema multiforme 1423–1424
pemphigus complex 1428–1430, *1429*
toxic epidermal necrolysis 1424
uveodermatologic syndrome 1430–1431
autoimmune polyglandular syndromes (APS)
canine 113–116
diagnosis and prognosis 114
etiology/pathophysiology 113–114
history and clinical signs 114
treatment 114–115
autologous mesenchymal stem cell therapy 538
autonomic nervous system (ANS) 404
autonomy principle 1561–1563
AV *see* atrioventricular
AVSAB *see* American Veterinary Society of Animal Behavior
AVSD *see* atrioventricular septal defects
azoles/triazoles 1050–1052
azotemia
acute kidney injury 1092
acute poisoning 438, 440
dialysis 1176–1177
feline hyperthyroidism 79
glomerular disease 1103, 1106
hypoadrenocorticism 83, 90

b

BA *see* bile acids
babesiosis 1016–1017
diagnosis 1017
epidemiology 1016
etiology/pathophysiology 1016
history and clinical signs 1016–1017
hypoglycemia 108
signalment 1016
treatment and prognosis 1017
bacillary angiomatosis 921, *922*
Bacillus anthracis see anthrax
bacteremia 923, **923**, 951
bacterial infections
approach to the dermatologic patient 1393
bacterial meningoencephalitis 784
laboratory diagnosis 844–845
principles of therapy of dermatologic diseases 1400–1401
see also individual agents/diseases
bacterial pyodermas *see* pyoderma
BAL *see* bronchoalveolar lavage
ballooning 561
bandages *see* wound care
barium-impregnated polyethylene spheres (BIPS) 568, 572
barometric whole-body plethysmography (BWBP) 299
baroreceptors 404
bartonellosis 919–924
diagnosis 922–923, *922–923*, **923**
epidemiology 919–920
etiology/pathophysiology 919, **920**
history and clinical signs 920–921, *921–922*, **921**
hypoglycemia 109
prognosis 924
public health implications 924
signalment 920
treatment 923–924
valvular heart disease 250–251
basal cell tumors *see* trichoblastomas
basal energy requirement (BER) 362, 452–453
basic life support 366–367
basophilic leukemia 1228–1229
Bates bodies 492, *492*
bats
Ebola virus 901
rabies 891–892, 894–896
BB *see* beta-adrenergic blockers
Bcl-2 proteins 75–76, 1207
behavioral problems 1571–1579
causing a physical illness 1572
diagnostics/treatment declined because of preexisting problem 1572
human-directed aggression 1574
managing client expectations 1577–1578
physical etiologies 1573–1574
preexisting problem hindering diagnostics/treatment 1572
presentations 1571–1572
psychological etiologies 1574
rabies 893
referrals 1574–1577, *1575*, **1576**
safety and avoidance: short-term recommendations 1577
secondary to medical treatment 1572
secondary to physical illness 1571–1572
triage for internists and general practitioners 1572–1574, *1573*
beneficence principle 1561–1563
benign masses *see* mass lesions
benign nodular hyperplasia 668
benign prostatic hyperplasia (BPH) 1157–1160
diagnosis 1158–1159, *1159*, **1160**
etiology 1157
history and clinical signs 1157
prognosis 1160
treatment 1159–1160
benzodiazepines 710, 1187
BER *see* basal energy requirement
beta-adrenergic blockers (BB)
canine chronic bronchitis 308
canine myocardial disease 260
cardiogenic shock 419
congenital heart disease 240
feline bronchial asthma 300
heart failure 183, **187**, 190–191
supraventricular arrhythmias 212, 214, 217
systemic hypertension 222–223
ventricular arrhythmias 204
beta-lactams 1045

BHD *see* Birt–Hogg–Dubé
bias 8, 23–24
biceps reflex 735
bile acids (BA) 651–652
bile duct tumors 685, 1303–1304, 1306
biliary cystadenoma 667, *668*
biliary system
  canine inflammatory liver disease 700
  feline inflammatory liver disease 688, *689*
  hepatobiliary disease 659–660, 664, 668–670, *669–670*
bilious vomiting syndrome (BVS) 549, 567
bilirubin
  feline inflammatory liver disease 688
  gallbladder and extrahepatic biliary ducts 723
  liver disease 651, 653
  metabolic diseases 677, 680
  pleural effusion 338, 343
bilirubinuria 653
bilothorax 343
bioethical principles 1561–1564
biofilms 1029–1030
biologic safety levels (BSL) 900
biopsy
  approach to the dermatologic patient 1394–1396
  autoimmune and immune-mediated skin disease 1423–1424, 1426–1430
  bone and joint tumors 1329
  canine inflammatory liver disease 698–699, *699*
  chronic enteropathies 633–635
  cirrhosis 708–709
  endoscopy 510–511, 526–527, *527*
  esophageal and stomach cancers 1284
  feline inflammatory liver disease 689
  glomerular disease 1103
  intestinal cancers 1289
  liver disease 656–658
  lymphomas 1236–1237
  mast cell tumors 1361
  miscellaneous skin diseases 1496–1497, 1503–1504
  neuromuscular junction diseases 805
  nonmelanoma skin cancers 1355
  ocular adnexal tumors 1262
  pancreatic endocrine tumors 1300
  pancreatitis 604
  pericardial disease 279
  prostatic diseases 1158–1159
  soft tissue sarcomas 1334
  sterile nodular panniculitis 1445–1446
  superficial necrolytic dermatitis 1492
  see also histology/histopathology
bioterrorism
  anthrax 974
  disease monitoring and surveillance 833
  tularemia 956
BIPS *see* barium-impregnated polyethylene spheres
birds 973
Birt–Hogg–Dubé (BHD) syndrome 1317
BISC *see* bowenoid *in situ* carcinoma
bisphosphonates 1207, 1245
bite wounds
  diagnosis 1033
  epidemiology 1033
  etiology/pathophysiology 1033
  history and clinical signs 1033
  pleural effusion 340
  prognosis 449, 451–452, 454–457
  public health implications 1034
  septic shock 424
  signalment 1033
  treatment and prognosis 1033–1034
  wound infections 1033–1034
  see also venomous snake bites
black widow spider envenomation 808
bladder tumors 1307–1308, **1309**
blastomycosis 989–990
  antifungal therapy 1050, 1052
  diagnosis 989–990, *990*
  epidemiology and signalment 989
  etiology/pathophysiology 989
  history and clinical signs 989
  public health implications 990
  treatment and prognosis 990
blood chemistry/serology
  acute kidney injury 1091–1093
  acute poisoning 437
  antimicrobials 1047
  apheresis 1369–1372
  approach to the cancer patient 1201
arthropod-borne infections 841–843
bacterial infections 844
bartonellosis 920, 922–923
bone and joint tumors 1328
canine brucellosis 964
canine myocardial disease 256, 258–259, 264
cardiogenic shock 417
chronic kidney disease 1165, **1166**
ehrlichiosis and anaplasmosis 909–910
endocrine manifestations of cancer 1214–1215
feline coronavirus 874
feline immunodeficiency virus 884
feline viral upper respiratory tract disease 888
fungal infections 846, 991, 994, 996
gallbladder and extrahepatic biliary ducts 723
glomerular disease 1102
hemotropic *Mycoplasma* 928
hepatobiliary tumors 1305–1306
intestinal cancers 1289
leptospirosis 946
liver disease 653
Lyme borreliosis 942–943
lymphomas 1233
markers of liver function 649–652
meningoencephalitis and meningomyelitis 797
metabolic bone diseases 1523, 1525–1526
myopathies 812
neuromuscular junction diseases 804, 805
pancreatic endocrine tumors 1298, 1300
pancreatitis 602
plasma cell disorders 1243–1245
portosystemic shunts and microvascular dysplasia 714, 716, 719
prostatic diseases 1158
protozoal and protozoa-like infections 841–843, 1004, 1006, 1008–1009, *1009*, 1011, 1014–1015
pulmonary thromboembolism 318–319
rabies 894
salmon poisoning disease 914
seizures and movement disorders 762

blood chemistry/serology (*cont'd*)
shock 406, 410
spotted fever and typhus group *Rickettsia* 939
sterile nodular panniculitis 1445
surgical, traumatic, and bite wound infections 1031
tularemia 957
urolithiasis 1133
viral infections 843–844
Wolbachia pipientis infection 918
yersiniosis 952
see also enzyme markers of liver disease; *individual biomarkers*
blood decontamination 443–444
blood glucose monitoring **100**
blood pressure monitoring
cardiogenic shock 418
chronic kidney disease 1165, **1167**
critical care setting 349
direct arterial blood pressure measurement 221–222
hypothermia 433
shock 405–406, 411
surgical approaches to thoracic disease 327
see also hypertension; hypotension
blood products 410
bloodstream infections (BSI) 1058, 1060
blood transfusion 453, 1014
blood urea nitrogen (BUN) 714, 716, 719
blue algae 684
blunt trauma
respiratory pattern-based approach to dyspnea 294
septic shock 424
trauma and burns 446–449, 452, 454–457
B lymphocytes 1567, 1569
BMD *see* bone mineral density
BMP *see* bone morphogenetic proteins
bone and joint tumors 1327–1332
diagnosis/staging 1328–1330, *1329*
epidemiology 1328
etiology/pathophysiology 1327–1328
history and clinical signs 1328
prognosis 1332
signalment 1328
treatment 1330–1332, **1330**
bone cement 1516
bone marrow aspiration
mast cell tumors 1361
paraneoplastic syndromes 1219
plasma cell disorders 1244, *1244*
bone marrow suppression 1044
bone marrow transplantation 1371
bone mineral density (BMD) 1523–1524, 1526–1527
bone morphogenetic proteins (BMP) 1515
bones *see* skeletal development and homeostasis
Bordetella bronchiseptica 1035–1037
Borrelia spp. 4
see also Lyme borreliosis
botulism
diagnosis 969–970
epidemiology 969
etiology/pathophysiology 969
history and clinical signs 969
neuromuscular junction diseases 807–808
public health implications 970
signalment 969
treatment and prognosis 970
bougienage 561
Bowditch staircase effect 177
bowenoid *in situ* carcinoma (BISC) 862–863
box and whisper plots 12, *12*
BP *see* bullous pemphigoid
BPH *see* benign prostatic hyperplasia
bradycardia
cardiogenic shock 413, 415
heart failure 185
magnesium homeostasis and disorders 1088
shock 405
trauma and burns 448
urethral obstruction 1110
brain hemorrhage 749
brain herniation 750, *750*
brain injury 748–750, *750*
brainstem reflexes 752–753
brain tumors 778–780
branching mineralization 663
Brazilian spotted fever 937
breath sounds 448
breath tests 569, 574
bronchoalveolar lavage (BAL)
canine chronic bronchitis 307, **310**
canine infectious respiratory disease complex 1036–1037
feline bronchial asthma 299
bronchodilators
canine chronic bronchitis 308
feline bronchial asthma 300–302
supraventricular arrhythmias 208
bronchopneumonopathy 307
bronchoscopy 298–299, 307
Brucella canis see canine brucellosis
BSI *see* bloodstream infections
BSL *see* biologic safety levels
B-type natriuretic peptide (NT-proBNP)
atrial septal defect 239–240
canine chronic bronchitis 306
canine myocardial disease 256, 259
feline bronchial asthma 298
feline myocardial disease 271, 273
pulmonary thromboembolism 318–319
buboes 952–953
bullous pemphigoid (BP) 542, 1427
BUN *see* blood urea nitrogen
burns *see* trauma and burns
butterfly-type catheters 355
BVS *see* bilious vomiting syndrome
BWBP *see* barometric whole-body plethysmography

C

CAAB *see* Certified Applied Animal Behaviorists
calcinosis cutis 1481–1482, *1482*
calcitonin 1218, 1521–1522
calcitriol 1079–1081, 1172
calcium channel blockers (CCB)
heart failure **188**, 191, 193
supraventricular arrhythmias 213–214, 217
calcium homeostasis and disorders
acute kidney injury 1096–1097
endocrinology 31–32
heart failure 175–176, 181–182
hypercalcemia 1217–1218, 1242, 1244
hypercalcuria 1126
hypocalcemia 1096–1097
metabolic bone diseases 1521–1527
paraneoplastic syndromes 1217–1218
plasma cell disorders 1242, 1244
urolithiasis 1124–1127, 1129–1130, 1142–1143
calprotectin 634
calvarial herniation 750
Canadian Veterinary Urolith Centre (CVUC) 1124–1132
cancellous bone 1513
cancer *see individual cancer types*; malignancies and neoplasia

candidiasis 997–998
diagnosis 998
epidemiology and signalment 997
etiology/pathophysiology 997
history and clinical signs 997–998
public health implications 998
treatment and prognosis 998
canine acidophil cell hepatitis virus 695
canine adenovirus (CAV/CAV-2) 696, 1035, 1037
canine brucellosis 963–965
diagnosis 964
epidemiology 963
etiology/pathophysiology 963
history and clinical signs 963–964
prognosis 965
public health implications 965
signalment 963
treatment 964–965
canine chronic bronchitis (CCB) 305–311
airway sampling techniques 307, **309–310**
diagnosis 306–308, **306**, *307–308*
differential diagnosis **306**
epidemiology 305
etiology/pathophysiology 305, **306**
history and clinical signs 305–306
prognosis 310
respiratory pattern-based approach to dyspnea 290–291
treatment 308–310
Canine Chronic Enteropathy Clinical Activity Index (CCECAI) 629–630, **631**
canine circovirus **858**
canine distemper virus (CDV) 851–853
canine infectious respiratory disease complex 1035, 1037
canine viral enteritis **858**
clinical signs 852
cutaneous manifestations of systemic disease 1484–1485
diagnosis 852
epidemiology 852
etiology/pathophysiology 851–852
forebrain disorders 782
prevention 853
prognosis 853
public health implications 853
signalment 852
treatment 852–853
canine enteric coronavirus **858**
canine familial dermatomyositis 1423, *1424*
canine heartworm disease 414, 415
canine hepacivirus (CHV) 696
canine herpesvirus (CHV) 855–856
canine infectious respiratory disease complex 1035, 1037
diagnosis 855–856
epidemiology 855
etiology/pathophysiology 855
history and clinical signs 855
prognosis 856
public health implications 856
signalment 855
treatment 856
canine hip dysplasia (CHD) 1537–1540
diagnosis 1539–1540
epidemiology 1539
etiology/pathophysiology 1537–1539
history and clinical signs 1539
prevention 1540
signalment 1539
treatment and prognosis 1535–1536, 1540
canine histiocytic disorders 1441–1444
cutaneous histiocytosis 1441–1442, *1442*
histiocytic sarcoma complex 1443–1444
systemic histiocytosis 1442–1443
canine hypothyroidism 71–74
additional considerations 72–73
ancillary testing 73
diagnosis 71–73
etiology/pathophysiology and epidemiology 71
history and clinical signs 71
laboratory diagnosis 71–72
prognosis 73
treatment 73
canine idiopathic large bowel diarrhea (CILBD) 572, 576–577, **578**
canine idiopathic vestibular disease 791
canine infectious respiratory disease (CIRD) complex 1035–1038
canine chronic bronchitis 305
diagnosis 1036
epidemiology 1036
etiology/pathophysiology 1035–1036
history and clinical signs 1036
prognosis 1037
public health implications 1037–1038
signalment 1036
treatment and prevention 1036–1037
canine inflammatory liver disease 695–703
acute hepatitis 695, 702–703
autoimmunity 696
chronic hepatitis 695–703
copper storage diseases 696–697, 701
diagnosis 698–699, *699*, 703
epidemiology 697, 702
etiology/pathophysiology 695, 702
history and clinical signs 697–698, 703
imaging 698, 703
infectious causes 695–696
prognosis 702, 703
signalment 697, **697**, 702–703
treatment 699–702, 703
canine influenza virus (CIV) 865–867
canine infectious respiratory disease complex 1035–1037
diagnosis 866
epidemiology 865–866
etiology/pathophysiology 865
history and clinical signs 866
prognosis 867
public health implications 867
signalment 866
treatment 866–867
canine kobuvirus **858**
canine malignant melanoma (CMM) 1347–1351
canine pancreatic lipase (cPL) 594, 633
canine parvovirus type 2 (CPV-2)
canine viral enteritis 857–860
diagnosis 859
epidemiology 857
etiology/pathophysiology 857, **857**
feline parvovirus 869–870
history and clinical signs 859
prevention 859
prognosis 859
public health implications 859
signalment 857–859
treatment 859, *860*
canine respiratory coronavirus (CRCoV) 1035, 1037
canine rotavirus **858**
canine viral enteritis *see individual viruses*
capillary refill time (CRT) 360, 405, 448

capnography
  cardiopulmonary resuscitation 370–371
  head trauma 756, 757
  respiratory monitoring in critical care 377
capsule endoscopy *531*, 532
CAR *see* cortisol-to-ACTH ratio
carbamate toxicity 808
carbapenem-resistant Enterobacteriaceae (CRE) 1059
carbapenems 1045
carbohydrate metabolism 650
carcinoma
  male reproductive system tumors 1312
  mammary cancer 1322–1323
  nonmelanoma skin cancers 1354–1355
carcinoma *in situ* 1288
cardiac cachexia 261
cardiac neoplasia 1271–1275
  diagnosis 1272–1273
  epidemiology 1271–1272
  etiology/pathophysiology 1271
  history and clinical signs 1272
  prognosis 1274–1275
  signalment 1272
  treatment 1273–1274
cardiac output (CO) 403–405, 407–408, 413–414, 417
cardiac troponin (cTn) 318–319
cardiogenic shock 413–420
  diagnosis 416–417
  epidemiology 414–415
  forward and backward failure 413
  history and clinical signs 415–416
  pathophysiology 413–414
  prognosis 420
  signalment 415
  treatment 417–420
cardiomegaly 249
cardiopulmonary arrest (CPA) 365, 366, 370, 417–418
cardiopulmonary resuscitation (CPR) 365–371
  advanced life support 367–369
  airway 367
  basic life support 366–367
  chest compressions 366–367
  critical care setting 347, 348
  defibrillation 369–370
  diagnosing cardiopulmonary arrest 366
  discontinuing CPR 371
  incidence of cardiopulmonary arrest 365
  monitoring during CPR 370
  open cardiac massage 370–371
  postresuscitation care 371
  principles of CPR 365–366
  ventilation 367, 371
cardiovascular disease (CVD) 119–125
  abdominal distension 121
  advanced ultrasound techniques **152**, *161–162*
  auscultation 122–124, *122*, **124–125**
  cardiac radiography 127–134
  case history and owner complaints 120–121
  common abnormal cardiac radiographic patterns 130–132, **133**, *134–139*
  conventional Doppler echocardiography 137–151, *152–160*
  conventional echocardiography 134–137, *140–144*, *146–150*, **150**
  critical care setting 349
  cyanosis 121
  diagnostic imaging 127–164
  dyspnea, tachypnea, and cough 120
  evaluation of fluid accumulation 122
  exercise intolerance, weakness, wasting, and syncope 120–121
  generalized or localized heart enlargement **133**
  left atrial enlargement 130, *134–137*
  left-sided congestive heart failure 131–132, *134*, *136–137*
  left ventricular enlargement 130, *134–135*, *137*
  mucous membranes 121
  normal thoracic radiography 127–130, *128–130*, **128**, **131**, *132*
  palpation of the precordium 122, *122*
  peripheral arterial pulsations 121–122
  physical examination 121–125
  plasma cell disorders 1242
  respiratory auscultation 124–125
  right-sided congestive heart failure 132
  right ventricular enlargement 132, *134*, *138*
  signalment 119
  systemic veins 121
  vertebral heart score 128–130, *130*, **131**
  see also individual diseases
carnitine 678–679
CARS *see* compensatory antiinflammatory response syndrome
case–control studies 16, 18, 21–23
castration 1312, 1314
cataracts 95–96, *95*
catecholamines
  endocrinology 30
  hypothermia 432
  trauma and burns 447–448
cathartics 443
catheters and catheterization
  constrictive pericarditis 284–285
  fluid therapy 355–356
  mechanical ventilation 400
  nocosomial and multidrug-resistant infections 1058
  urethral obstruction 1111–1113, *1113–1114*, 1117
cat scratch disease (CSD) 924
caudal vena cava (CVC) 671, *671*
caval syndrome 414, 420
CAV/CAV-2 *see* canine adenovirus
cavernous sinus syndrome 827–828
CBD *see* common bile duct
CBF *see* cerebral blood flow
CCB *see* calcium channel blockers; canine chronic bronchitis
CCECAI *see* Canine Chronic Enteropathy Clinical Activity Index
CDC *see* Centers for Disease Control and Prevention
CDI *see* central diabetes insipidus
CDV *see* canine distemper virus
CDVD *see* chronic degenerative valvular disease
CE *see* chronic enteropathies; cranberry extract
cecal intussusception 504, *504*
cell death 1206–1207
cell separator machines 1369
cell surface receptors 30–31
cellular energetics 1209–1210
cellular transplantation therapy 746
cellulitis 934
Center for Food Security and Public Health 1065
Centers for Disease Control and Prevention (CDC)

anthrax 973
bartonellosis 924
rabies 892, 896
central diabetes insipidus (CDI) 65, 68, 1071
central nervous system (CNS)
acute poisoning 437, 442
antifungal therapy 1051
forebrain disorders 781–784
fungal infections 986, 989–990, 992–993
head trauma 748–758, *750*, **751–752**, *752*, *754*
meningoencephalitis and meningomyelitis 795–801
myelopathy 816, 821
neurologic assessment 732
nonhemotropic *Mycoplasma*, *Ureaplasma*, and L-form bacteria 933
rabies 891
septic shock 424
spinal cord injury 741–748, *742–745*, **745–746**, *747*
spotted fever and typhus group *Rickettsia* 938–939
vestibular disease 789–790, 792–794
central nervous system (CNS) tumors 1247–1252
diagnosis 1248–1249, *1249*
etiology/epidemiology/signalment 1247–1248
history and clinical signs 1248
lymphomas 1237–1238
treatment and prognosis 1249–1252, **1251**
central pontine demyelination (CPD) 1073
central venous oxygen saturation 411–412
central venous pressure (CVP) 327, 364
cephalosporins 1045
cerebellar ataxia 732
cerebellar-related tremors 770
cerebral blood flow (CBF) 748
cerebral edema 749
cerebral perfusion pressure (CPP) 748, 755
cerebrospinal fluid (CSF)
central nervous system tumors 1248
forebrain disorders 775, 782–784, 787–788
head trauma 749–750
meningoencephalitis and meningomyelitis 795, 797–799
myelopathy 820
protozoal and protozoa-like infections 1004–1006
seizures and movement disorders 771
cerebrovascular accidents (CVA) 785–787
Certified Applied Animal Behaviorists (CAAB) 1576
ceruminous gland adenoma *1474*
CH *see* cutaneous histiocytosis
Chagas disease 1007–1008
CHD *see* canine hip dysplasia; congenital heart disease
chemical burns 544
chemical load 382–383, 388–389
chemoembolization 1202
chemoradiotherapy 541
chemoreceptors 404
chemotherapy
airway and lung cancers 1278, 1280
approach to the cancer patient 1202, 1203
biology of cancer and cancer genetics 1206, 1209
bone and joint tumors 1331
cardiac neoplasia 1273–1274
central nervous system tumors 1252
esophageal and stomach cancers 1285
exocrine pancreatic cancer 1294
gynecologic cancers 1318–1320
hemangiosarcoma **1342**, 1343–1344
hepatobiliary tumors 1306
intestinal cancers 1290–1291
intraocular tumors 1267
lymphoid leukemias 1225
lymphomas 1233–1235, **1234**, 1238–1239, **1238**
male reproductive system tumors 1312, 1315
mammary cancer 1322–1324
mast cell tumors 1363–1364, **1363**
melanoma 1349
myelodysplastic syndromes 1230
myeloid neoplasia 1227
nasal tumors 1258
nonmelanoma skin cancers 1356–1357
oral tumors 1255–1256
orbital and optic nerve tumors 1269
plasma cell disorders 1245–1246
soft tissue sarcomas 1336–1337
urinary tract tumors 1308, 1310
chest compressions 366–367
chest wall 294–295
cheyletiellosis 1456–1457
diagnosis 1457
etiology/pathophysiology 1456–1457, *1456*
history and clinical signs 1457, *1457*
treatment and prognosis 1457
CHF *see* congestive heart failure
CHI *see* congenital hyperinsulinism
Chiari-like malformation 1488
chigger mites *see* trombiculosis
cholangitis 669, *669*, 721–722
cholangitis-cholangiohepatitis *see* feline inflammatory liver disease
cholecentesis 724–725
cholecystitis 670, *670*
choleliths 721, 724
cholestasis 641–642
cholesteatoma 791
cholesterol 83, 650–651
chondrocytes 1510–1511
chondrosarcoma (CSA) 1327, 1332
choroidal melanocytoma/melanoma 1264–1265
choroid plexus papillomas 779
chronic degenerative valvular disease (CDVD) 178
chronic enteropathies (CE) 627–637
adjunctive therapy 637
antibiotic-responsive diarrhea 627, 629, 636
antiinflammatory and immunosuppressive therapy 636
calprotectin and S100A12 634
canine pancreatic lipase 633
classification 627
C-reactive protein 633
diagnostic imaging 635
diagnostic work-up 629–630, **630**, **631**
diet and nutrition 635–636
epidemiology 629
etiopathogenesis 627–629, *628*
fecal alpha-1-proteinase inhibitor 633
food-responsive diarrhea 627–629, 634–637

chronic enteropathies (CE) (*cont'd*)
genetics and genetic testing 627–628, 634–635
histology and WSAVA scoring 635
history and clinical signs 629–630, **629**
immunohistochemistry for P-glycoprotein 634
intestinal microbiota 628–629
intestinal mucosal immune system 628
perinuclear antineutrophilic cytoplasmic antibodies 634
polymerase chain reaction for antigen receptor rearrangement 633
prognosis 637
serum albumin concentration 630–632
serum and fecal markers of disease 630–635
serum cobalamin concentration 632
severe protein-losing enteropathy 636–637
steroid-responsive diarrhea 627, 629, 634
supplementation recommendations for cobalamin 632
treatment 635–637
work-up and diagnostic tests 635
chronic gastric outlet 485, *485–486*
chronic kidney disease (CKD) 1165–1173
alkalinization therapy 1172
anemia 1170–1171
antinausea and appetite stimulant therapy 1167–1168
antioxidant therapy 1172
calcitriol 1172
dialysis 1178–1179
diet and nutrition 1166
disease staging 1165, **1166**, **1167**
enteric dialysis and the microbiome 1172
feline hyperthyroidism 79
fluid therapy 1170
gastritis and gastric ulceration 551
hypokalemia 1171
leptospirosis 946, 948
medical management 1166–1172
metabolic bone diseases 1522
mineral and bone disorder: hyperphosphatemia 1171, **1171**
monitoring CKD patients 1172–1173
motility disorders 572
phosphorus homeostasis and disorders 1083–1085
polyunsaturated fatty acids 1169, 1172
prognosis 1173
proteinuria 1165, **1166**, 1168–1170, *1169*
systemic hypertension 220–221, 1165, **1167**, 1168–1170
chronic lymphocytic leukemia (CLL) 1223–1225, *1224*
chronic myelogenous leukemia (CML) 1227–1228
chronic, recurrent pyoderma 1464–1465
CHV *see* canine hepacivirus; canine herpesvirus
chylothorax 338, 341–343, *342*
CILBD *see* canine idiopathic large bowel diarrhea
CIRCI *see* critical illness-related corticosteroid deficiency
circulating biomarkers *see* blood chemistry/serology
CIRD *see* canine infectious respiratory disease
cirrhosis 705–711
acquired portosystemic shunts 706–708
ascites 705–706, 709–710
coagulation disturbances 706–707, 711
cytology and fluid analysis 708
diagnosis 707–709
diagnostic imaging 666
etiology/pathophysiology 705–706, *706*
gastrointestinal ulceration 706, 710–711
hepatic encephalopathy 706, 710
hepatobiliary disease 673
hepatoprotectants 711
histopathology 708–709
history and clinical signs 707
imaging 708
laboratory testing 707–708
metabolic diseases 681–683
monitoring 711
portal hypertension 705, 711
prognosis 711
signalment 707
treatment 709–711
cisterna chyli ablation 343
CIV *see* canine influenza virus
CK *see* creatine kinase
CKD *see* chronic kidney disease
cleaning and disinfection
endoscopy 511–512, *511–512*
kennels and multicat environments 1064–1065
nocosomial and multidrug-resistant infections 1061
client communication
approach to the dermatologic patient 1396
behavioral problems 1577–1578
critical care setting 348
clindamycin 783–784
Clinical and Laboratory Standards Institute (CLSI) 1192–1193
clinical decision making 17–25
case–control studies 18, 21–23
clinical trials 23–25
cohort studies 19–21, *20*
cross-over trials 24–25
hospital-based cross-sectional studies 17–18
longitudinal observational studies 18–25
randomized masked clinical trials 23–24
clinical trials
clinical decision making 23–25
cross-over trials 24–25
randomized masked clinical trials 23–24
clipping 615
CLL *see* chronic lymphocytic leukemia
Clostridium spp. 768–769, 807–808
see also botulism; tetanus
clot-labeling techniques 319
clotting times 689
CLSI *see* Clinical and Laboratory Standards Institute
CML *see* chronic myelogenous leukemia
CMM *see* canine malignant melanoma
CMO *see* craniomandibular osteopathy
CO *see* cardiac output
coagulation and coagulopathies
acute poisoning 438, 439
canine inflammatory liver disease 698
cirrhosis 706–707, 711
critical care setting 350
heat stroke 436
liver disease 644, 650, 656
mast cell tumors 1362
pathophysiology 644
septic shock 423, 426

trauma and burns 445
venomous snake bites 461, 463–464
cobalamin deficiency/supplementation
chronic enteropathies 632
exocrine pancreatic insufficiency 583, 588–589
liver disease 650
pancreatitis 607–608
coccidia
Cryptosporidium spp. 1025–1026
Cystoisospora spp. 1023–1025
microspora 1026
coccidioidomycosis 994–995
diagnosis 994–995, *995*
epidemiology and signalment 994
etiology/pathophysiology 994
history and clinical signs 994
public health implications 995
treatment and prognosis 995
cohort studies 19–21, *20*
cold packing 462
colitis
gastrointestinal imaging 500, *501*
motility disorders 577
rectoanal diseases 614
collarettes *1385*, *1463*
colloid oncotic/osmotic pressure (COP) 357–360, 363, 451
colonic intussusception 504, *504*
colonic volvulus/torsion 504, *505*
colonoscopy 524–525, *525*, 616
colopexy 618
comedones *1387*
comfort rooms *1557*
COMMD1 gene 681–682
common bile duct (CBD) 721–726
diagnosis 723–725
epidemiology 722
etiology/pathophysiology 721–722, *722*
history and clinical signs 722–723
prognosis 726
signalment 722
treatment 725
compensatory antiinflammatory response syndrome (CARS) 422, 445
complement activation 445
complementary therapy 1344
complete blood count (CBC) *see* hematology
complicated urinary tract infections 1194
compression bandages 462
computed tomography (CT)
airway and lung cancers 1278–1279
biology of cancer and cancer genetics 1210
bone and joint tumors 1329–1330
canine chronic bronchitis 307, *307*
central nervous system tumors 1248–1249
cirrhosis 708
developmental orthopedic diseases 1543–1548
esophageal and stomach cancers 1284
esophagus 476, 478
feline acromegaly 45
forebrain disorders *776*, 781, 783–786
fungal infections 996
gallbladder and extrahepatic biliary ducts 724
gastrointestinal tract 469, 471–472, *472*
head trauma 753–754, *754*
hepatobiliary disease 659, 674
large intestine 500, *500*
leptospirosis 946
meningoencephalitis and meningomyelitis 798
metabolic bone diseases 1523–1524
motility disorders 569
myelopathy 819
nasal tumors 1257–1258
oral tumors 1254
orbital and optic nerve tumors 1268
osteoarthritis 1531
pancreatitis 594, 605
pericardial disease 280
pituitary-dependent hyperadrenocorticism 57
pleural effusion 336–337, 340
rectoanal diseases 609, 619
spinal cord injury 743, *743–744*
stomach 488–489
urolithiasis 1135
see also dual-phase computed tomography angiography
computed tomography pulmonary angiography (CTPA) 319, *319*
concentric hypertrophy 180–181
confounders 22
congenital heart disease (CHD) 231–244
angiography 240, *242*
atrial septal defect 231, 232–233, 237, *239*, 241–243
atrioventricular septal defects 233
auscultation 235–237, **237**
cross-sectional imaging 240, *242*
cyanotic heart disease 234
diagnosis 235–240
echocardiography 237, 240, *241*
electrocardiography 237–238, *238*
epidemiology 235
etiology 231–234
history and clinical signs 235
mitral and tricuspid valve stenosis 234
patent ductus arteriosus 231, 235–237, 241–244
prognosis 244
pulmonary valve stenosis 231, 233–235, *238*, *241*, 243–244
signalment 119, 235, **236**
subaortic stenosis 231, 233, 237, 243
surgical and interventional therapy 243, *243*
tetralogy of Fallot 234, 243
thoracic radiography 237, 238, *239*
treatment 240–243
tricuspid valve dysplasia 231, 234, 237
vascular ring anomalies 234
ventricular septal defect 231, 232, 237, 241–243
congenital hepatic disease 103, 105
congenital hyperinsulinism (CHI) 108–109
congenital hypoplasia 673
congenital megaesophagus 558
congenital portosystemic shunts (CPSS) 713–720
classification and anatomy 713–714
diagnosis 716
diagnostic imaging 670–672, *671–672*
etiology 713
history and clinical signs 716
liver disease 644–645, 650, 653
pathophysiology 714–715, **714**
portal hypertension 715
prognosis 720
signalment 715
treatment 717–720
congestive heart failure (CHF)
canine myocardial disease 254–255, 259–263
cardiogenic shock 413
case history and owner complaints 120–121

congestive heart failure (CHF) (*cont'd*)
feline myocardial disease 267, 271, 273
left-sided 131–132, *134*, *136–137*
management 185–197
right-sided 132
sodium and water homeostasis 1071
valvular heart disease 246–250
conjunctiva 1261–1262
consciousness 448, 753
constant rate infusion (CRI)
acute poisoning 444
cardiogenic shock 418
fluid therapy 363
phosphorus homeostasis and disorders 1083
trauma and burns 451
venomous snake bites 464
constipation 572, 575–580, 612–613
constrictive pericarditis 284–285
diagnosis 284–285
etiology/pathophysiology 284
history and clinical signs 284
signalment 284
treatment and prognosis 285
contact dermatitis 1414–1415, *1415*
continuous common source epidemic curves 835, *835*
continuous positive airway pressure (CPAP) 388, 395–396, 402
continuous renal replacement therapy (CRRT) 1098, 1150, 1175–1176
continuous spontaneous ventilation (CSV) 394
contractility
canine myocardial disease 253–254
cardiogenic shock 418
heart failure 177
hypothermia 433
contrast radiography
esophageal disorders 558, 561–562
gastrointestinal imaging 469–471, *470*, 480–483, *481*, 490–491, *491*, 499
motility disorders 564–565, 572, **573**, 576–577
COP *see* colloid oncotic/osmotic pressure
copper storage diseases
canine inflammatory liver disease 696–697, 701
cirrhosis 709
metabolic diseases 681–683
corneal tumors 1261–1262
corticosteroids
canine inflammatory liver disease 699–700, 703
gastritis and gastric ulceration 549
hemotropic *Mycoplasma* 929
metabolic bone diseases 1517
miscellaneous skin diseases 1498–1500
neuromuscular junction diseases 806
respiratory pattern-based approach to dyspnea 291
septic shock 425, 428
spinal cord injury 745
venomous snake bites 464
corticotroph cell marker 51
corticotrophy differentiation markers 51
corticotropin-releasing hormone (CRH) 50, 81
cortisol 30, *30*, 81, 84–85
cortisol-to-ACTH ratio (CAR) 84
cotton-tipped applicator smears 1391–1392
cough
canine chronic bronchitis 305–310
cardiovascular disease 120
feline bronchial asthma 297–298, 303
gastrointestinal imaging 478
heart failure 194
respiratory pattern-based approach to dyspnea 290–291
valvular heart disease 246–247
cough-drop syndrome 306
COX/COX-2 *see* cyclooxygenase
Coxiella burnetii see Q fever
CPA *see* cardiopulmonary arrest
CPAP *see* continuous positive airway pressure
CPD *see* central pontine demyelination
cPL *see* canine pancreatic lipase
CPP *see* cerebral perfusion pressure
CPR *see* cardiopulmonary resuscitation
CPSS *see* congenital portosystemic shunts
CPV-2 *see* canine parvovirus type 2
crackles
cardiovascular disease 125
pleural effusion 335
respiratory pattern-based approach to dyspnea 289, 292
cranberry extract (CE) 1194
cranial nerves
cranial nerves IX, X, and XII 739
facial and trigeminal neurons 738–739
head trauma 752–753
neurologic assessment 735–739
nystagmus 738
palpebral fissure and third eyelid 737
strabismus 737–738
vestibular disease 789–790
vision - menace and pupils 736–737
craniomandibular osteopathy (CMO) 1548–1549
CRCoV *see* canine respiratory coronavirus
CRE *see* carbapenem-resistant Enterobacteriaceae
C-reactive protein (CRP) 633
creams 1398, 1469
creatine kinase (CK) 461, 812
creatinine 1165, **1166**
CRH *see* corticotropin-releasing hormone
CRI *see* constant rate infusions
cricopharyngeal chalasia 474
cricopharyngeal dysphagia 474
critical care setting 347–353
albumin 349
analgesia 351–352
assessment 348
bandage and wound care 352
blood pressure and perfusion 349
cardiac function 349
client communication 348
coagulation 350
drug metabolism and dosage 351
electrolyte and acid–base balance 350
euthanasia 352
fluid therapy 347–349
gastrointestinal motility and integrity 351
glucose 350
history 348
immune status and antibiotic coverage 351
mentation and intracranial pressure 347, 350
motility disorders 571–572
nursing care and patient mobility 352
nutrition 351
oncotic pull 349
oxygenation and ventilation 350
physical examination 347–348
record keeping 348
red blood cell and hemoglobin concentration 350–351
referral 348–349

renal function and urine output 351
respiratory monitoring in critical care 373–380
Rule of 20, 349–352
tender loving care 352
critical illness-related corticosteroid deficiency (CIRCI) 428
cross-over trials 24–25
cross-sectional imaging 240, *242*
cross-sectional studies 17–18
CRP *see* C-reactive protein
CRRT *see* continuous renal replacement therapy
CRT *see* capillary refill time
crusts
approach to the dermatologic patient *1386*
atopic dermatitis *1406*
autoimmune and immune-mediated skin disease *1426*, 1428–1429, *1429*
cutaneous adverse food reactions *1420*
superficial necrolytic dermatitis *1492*
cryosurgery 1263–1264
cryotherapy 863
cryptococcosis 992–994
diagnosis 993, *993*
epidemiology and signalment 992
etiology/pathophysiology 992
history and clinical signs 992–993
public health implications 994
treatment and prognosis 993–994
Cryptosporidium spp. 1025–1026
diagnosis 1026
epidemiology 1026
etiology/pathophysiology 1025
history and clinical signs 1026
public health implications 1026
signalment 1026
treatment and prognosis 1026
crystallization-inhibition theory 1123
crystalloid fluids 358–359, 409
acute kidney injury 1095
glomerular disease 1106
head trauma 755
septic shock 426
trauma and burns 450–451
urethral obstruction 1112
crystalluria 1132, 1136
CSA *see* chondrosarcoma
CSD *see* cat scratch disease
CSF *see* cerebrospinal fluid
CSV *see* continuous spontaneous ventilation
CT *see* computed tomography
CTL *see* cytotoxic T lymphocytes
cTn *see* cardiac troponin
CTPA *see* computed tomography pulmonary angiography
cumulative incidence 13–14
Cushing disease *see* pituitary-dependent hyperadrenocorticism
Cushing reflex 748, 755
cutaneous adverse food reactions 1419–1422
acute poisoning 441
choice of elimination diet 1421
diagnosis 1421–1422
duration and execution of elimination diet 1421–1422
etiology/pathophysiology 1419, **1420**
history and clinical signs 1419–1420, *1420*
interpretation of outcome of elimination diet 1422
prognosis 1422
treatment 1422
cutaneous histiocytosis (CH) 1441–1442, *1442*
cutaneous lupus erythematosus 1424–1427, *1426*
cutaneous lymphoma 1235
cutaneous manifestations of systemic disease 1481–1490
gastritis and gastric ulceration 551
hormonal and metabolic disorders 1481–1484
immune-mediated systemic diseases 1487–1488
neoplastic and paraneoplastic disorders 1488–1490
neurologic disorders 1488
nutritional disorders 1486–1487
systemic infectious disease 1484–1486
cutaneous trunci reflex 735
Cuterebra spp. 785, 788
CVA *see* cerebrovascular accidents
CVC *see* caudal vena cava
CVD *see* cardiovascular disease
CVP *see* central venous pressure
CVUC *see* Canadian Veterinary Urolith Centre
cyanosis 121
cyanotic heart disease 234
cyanuric acid urolithiasis 1132, *1132*
cyclic flank alopecia 1436, *1436*
cyclooxygenase (COX/COX-2) inhibitors
biology of cancer and cancer genetics 1208
gynecologic cancers 1320
male reproductive system tumors 1313
melanoma 1349
nonmelanoma skin cancers 1356–1357
osteoarthritis 1533
urinary tract tumors 1308
cystic lesions 667
cystine urolithiasis 1130–1131, 1134, *1136*, 1143
cystocentesis 1112, 1117, 1191
Cystoisospora spp. 1023–1025
diagnosis 1024, *1024*
epidemiology 1023–1024
etiology/pathophysiology 1023
history and clinical signs 1024
public health implications 1025
signalment 1024
treatment and prognosis 1024–1025, **1024**, **1025**
cystotomy tubes 1308
Cytauxzoon felis see feline cytauxzoonosis
cytochrome P450 (CYP450) enzymes
antifungal therapy 1051
antimicrobials 1044, 1046
atopic dermatitis 1410–1411
autoimmune polyglandular syndromes 113
cytology
acute kidney injury 1094
approach to the dermatologic patient 1385
bacterial infections 844
bone and joint tumors 1328–1329
canine chronic bronchitis 307, *308*, **309–310**
canine distemper virus 852
canine histiocytic disorders 1441, 1443–1447
cardiac neoplasia 1273
cirrhosis 708
exocrine pancreatic cancer 1294
feline bronchial asthma 299
fungal infections 845–846, *846*, 985–991, *990–991*, 994–996, *995*, 998–1000, *999*
gallbladder and extrahepatic biliary ducts 725
hemangiosarcoma 1341
hemotropic *Mycoplasma* 928

cytology (*cont'd*)
liver disease 655–656
lymphoid leukemias 1224, *1224–1225*
lymphomas 1232
mammary cancer 1322
mast cell tumors 1359–1360, *1360*, 1365–1366
meningoencephalitis and meningomyelitis 798–799
miscellaneous skin diseases 1496, 1504
mycobacteriosis 982, *982*
nonmelanoma skin cancers 1355
otitis externa 1474, *1474–1475*, **1475**, 1476
pancreatitis 596–597
pleural effusion 340, *340*, 342, *342*
prostatic diseases 1159, **1160**, 1162
protozoal and arthropod-borne infections 839–841
protozoal and protozoa-like infections 1009
rectoanal diseases 609
viral infections 843
yersiniosis 953
cytoscopic-guided basket removal 1147
cytoscopy 1183
cytotoxic T lymphocytes (CTL) 1568

d

DAG *see* diacylglycerol
Darrow–Yannet diagram 1069–1070, *1070*
DC cardioversion 217–218
DCM2 mutation 253, 259
D-dimers 315, 316
debridement 1031
defibrillation 369–370, 419–420
degenerative myelopathy (DM) 820
dehydration *see* hydration and dehydration; sodium and water homeostasis
delayed gastric emptying 567
delayed resuscitation 361
demodicosis 1449–1454
approach to the dermatologic patient 1376, 1392–1393
canine 1449–1452
diagnosis 1451, 1453
etiology/pathophysiology 1449, *1450*, 1452–1453
feline 1452–1454
history and clinical signs 1449–1451, *1450–1451*, 1453, *1453*
treatment and prognosis 1451–1452, 1453–1454
demyelinating leukoencephalomyelitis (DL) 851–852
dentigerous cysts 539
deranged nitrogen metabolism 714
Dermanyssus gallinae 1458–1459
diagnosis 1459
etiology/pathophysiology 1458
history and clinical signs 1458
treatment and prognosis 1459
dermatologic disease
antibacterial agents 1400–1401
antifungal agents 1401
antiinflammatory agents 1399–1400
antiparasitic agents 1401–1402
antipruritic agents 1400
approach to the dermatologic patient 1375–1396
biopsy and histopathology 1394–1396
categories and indications for therapeutic approach 1399–1402
common formulations of topical agents 1397–1399
cutaneous manifestations of systemic disease 1481–1490
diagnostic tests and techniques 1383–1396
distribution of lesions 1383, **1388–1391**
epidemiology 1375
history and clinical signs 1375–1381, 1396
immunosuppressive agents 1400
miscellaneous skin diseases 1495–1506
morphology of lesions 1382, **1382–1383**, *1383–1387*
physical examination 1381–1383
principles of therapy of dermatologic diseases 1397–1402
pruritus 1376
screening tests 1385–1394
signalment 1375–1376, **1377–1381**
systemic medications for hormonal disorders 1402
systemic therapy 1399
tests of noncutaneous organs 1396
therapeutic plan and client education 1396
topical therapy 1397–1399
treatment trials 1394
see also individual conditions/agents
dermatomyositis (DM) 1423, *1424*
dermatophytosis 987–988
approach to the dermatologic patient 1393–1394
diagnosis 987
epidemiology and signalment 987
etiology/pathophysiology 987
history and clinical signs 987, *987*
public health implications 988
treatment and prognosis 988
descriptive statistics 10–12, *11–13*
detrusor atony 1186
detrusor hyperreflexia 1186
detrusor urethral dyssynergy (DUD) 1186–1187
developmental orthopedic diseases (DOD) 1537–1551
breed dispositions **1538**
canine hip dysplasia 1534–1540
craniomandibular osteopathy 1548–1549
elbow dysplasia 1542–1544
hypertrophic osteodystrophy 1549–1550
Legg–Calvé–Perthes disease 1547–1548
osteochondrosis 1540–1542, **1541**
osteochondrosis dissecans of the hock joint 1544–1545
osteochondrosis dissecans of the shoulder joint 1542
osteochondrosis dissecans of the stifle joint 1544
panosteitis 1549
patella luxation 1546–1547
retained cartilaginous core 1545–1546
slipped capital femoral epiphysis 1550–1551
DEXA *see* dual-energy X-ray absorptiometry
dexamethasone suppression testing *see* high-dose dexamethasone suppression; low-dose dexamethasone suppression
dextrans 359
DFA *see* direct fluorescent antibody
DGGR-based lipase activity 593, 604–605, 608

DI *see* diabetes insipidus; distraction index
diabetes insipidus (DI) 65–66, **66**, 68
diabetes mellitus (DM) 93–102
  autoimmune polyglandular syndromes 113–115
  cataracts 95–96, *95*
  classification 93
  diabetic ketoacidosis 100
  diabetic neuropathy 96, *96*
  diagnosis 96–97
  endocrinology 32
  epidemiology 94
  etiology/pathophysiology 93, **94**
  feline acromegaly 43–48
  hepatic lipidosis 678
  hepatomegaly 95
  history and clinical signs 94–96, *95*, *96*
  insulin resistance 93, 99–100
  pancreatitis 608
  polyphagia 94
  polyuria and polydipsia 65
  polyuria and polydypsia 94, 96
  prognosis 100–101
  signalment 94
  sodium and water homeostasis 1071
  superficial necrolytic dermatitis 1491–1493
  systemic hypertension 220
  treatment **94**, 97–100, **98–100**
  weight change 94
diabetic ketoacidosis (DKA) 100, 592
diabetic neuropathy 96, *96*
diacylglycerol (DAG) 179
dialysis 1175–1180
  acute intoxications and therapeutic plasma exchange 1179–1180
  acute kidney injury 1098, 1176–1178, *1176–1177*
  availability and prognosis 1180
  azotemia/uremia 1176–1177
  chronic kidney disease 1172, 1178–1179
  continuous renal replacement therapy 1098, 1150, 1175–1176
  fluid overload/oliguria/anuria 1177–1178
  hyperkalemia 1177–1178
  intermittent hemodialysis 1149–1150, 1175–1176
  modalities 1175–1176
  peritoneal dialysis 1175–1176
  severe acidemia 1178
diaphragm 295
diarrhea
  chronic enteropathies 627–629, 634–637
  exocrine pancreatic insufficiency 584–585
  feline inflammatory liver disease 688
  feline parvovirus 870
  motility disorders 570–572, 574–577
  nocosomial and multidrug-resistant infections 1058
  rectoanal diseases 615
DIC *see* disseminated intravascular coagulation
diet and nutrition
  acute kidney injury 1097–1098
  atopic dermatitis 1409–1410
  canine inflammatory liver disease 701, 703
  chronic enteropathies 627–629, 634–637
  chronic kidney disease 1166
  cirrhosis 710
  critical care setting 351
  cutaneous adverse food reactions 1419–1422
  cutaneous manifestations of systemic disease 1486–1487
  developmental orthopedic diseases 1540–1541, 1548
  diabetes mellitus 97–101
  dysbiosis 623
  end-of-life care 1559
  enteral nutrition 452–453, 679, 1097
  exocrine pancreatic insufficiency 583, 589
  feline hyperthyroidism 76, 78–79
  feline inflammatory liver disease 691–693
  forebrain disorders 780
  gastritis and gastric ulceration 554
  glomerular disease 1105
  heart failure **188**, 192
  metabolic diseases 679, 682–683
  motility disorders 577
  osteoarthritis 1532–1533
  pancreatic endocrine tumors 1299–1300
  pancreatitis 597–599, 606–608
  phosphorus homeostasis and disorders 1079–1080, 1085
  pleural effusion 342
  polyuria and polydipsia 66
  portosystemic shunts and microvascular dysplasia 717
  rectoanal diseases 610, 612, 614, 616, 619
  septic shock 428
  superficial necrolytic dermatitis 1492–1493
  urolithiasis 1137–1144
  vestibular disease 793–794
diffuse iris melanomas 1265, *1265*
diffuse parenchymal disease 665–666
diffusion impairment 386
1,25-dihydroxyvitamin D 1521–1522, 1525–1527
dilated cardiomyopathy (DCM)
  canine myocardial disease 253–262
  cardiogenic shock 413–415
  cardiovascular disease 119, 122–124, *137*
  diagnosis 255–259, *255–257*, **258**
  electrocardiography *174*
  epidemiology 254
  etiology/pathophysiology 253–254
  feline myocardial disease 267, 269–271
  heart failure 178, 189–190, 192, 194, 196
  history and clinical signs 254–255
  lymphomas 1234
  prognosis 262
  signalment 254
  treatment 259–262, **260**
  ventricular arrhythmias 200, *201*
dilated pupil syndrome 828
direct fluorescent antibody (DFA) test 894, 953
direct oral anticoagulants (DOAC) 321
discoid lupus erythematosus (DLE) 1424–1425, *1426*
disease-modifying osteoarthritis agents (DMOA) 1534–1536
disease surveillance 4
disinfection *see* cleaning and disinfection
displacement of the colon 505
disseminated intravascular coagulation (DIC)
  cirrhosis 706
  Ebola virus 901
  hyperthermia 434

disseminated intravascular coagulation (DIC) (*cont'd*)
liver disease 644
pulmonary thromboembolism 316–317
septic shock 423, 426
trauma and burns 445, 453–454
yersiniosis 952
distraction index (DI) 1540
distribution 10–12, *11–13*
distribution-free tests 10
disuse osteoporosis 1527
diuretics
acute kidney injury 1095–1096
acute respiratory failure 388–389
canine inflammatory liver disease 701
cardiogenic shock 417
feline myocardial disease 273
glomerular disease 1106
head trauma 756
heart failure 186, **187**, 192–196, **195**
magnesium homeostasis and disorders 1088
pericardial disease 280
urolithiasis 1138–1139
valvular heart disease 249
diverticulum 505
DKA *see* diabetic ketoacidosis
DL *see* demyelinating leukoencephalomyelitis
DLE *see* discoid lupus erythematosus
DM *see* degenerative myelopathy; dermatomyositis; diabetes mellitus
DMOA *see* disease-modifying osteoarthritis agents
DOAC *see* direct oral anticoagulants
DOD *see* developmental orthopedic diseases
dopamine
acute kidney injury 1098
heart failure 196
neuroendocrinology 41
pituitary-dependent hyperadrenocorticism 50–51
supraventricular arrhythmias 212
dopaminergic D2 antagonists **575**, 579–580
Doppler echocardiography 137–151
advanced ultrasound techniques **152**, *161*
basic principles 138
color flow mode 139
common abnormal flow patterns 145–151, *155–160*
mitral and triscuspid diastolic inflows 141–142, 147–149, *153*, *158–159*
nonvalvular abnormal flows 149–151, *160*
normal transvalvular flows 139–145, *152–154*
physiologic regurgitations 144, *154*
pulmonary and aortic systolic flows 141, 145–147, *152*, *155–156*
pulsed-wave and continuous-wave modes 138–139, **145**
quantitative measurements 144–145, *159*
standard Doppler modes 138–139, **145**
Doppler sphygmomanometry 221–222
double balloon enteroscopy 531–532
double-contrast crystography 1134, *1135*
DPCTA *see* dual-phase computed tomography angiography
dried solidified blood calculi 1131
drug/drug metabolite urolithiasis 1132
drug-induced neuromuscular blockade 808
drug-induced osteoporosis 1527–1528
drug-induced tremors 770
drug metabolism and dosage 351
drug toxicity
antifungal therapy 1049, 1051–1052
antimicrobials 1041–1048, **1044**
neuromuscular junction diseases 808
toxic diseases of the liver 683–684
vestibular disease 792–794
dual-energy X-ray absorptiometry (DEXA/DXA) 1523–1524
dual-phase computed tomography angiography (DPCTA) 716, 718, 720
DUD *see* detrusor urethral dyssynergy
duodenograstric reflux 567
duodenoscopy 520–522, *521–522*
duodenum 487, *488*
DXA *see* dual-energy X-ray absorptiometry
dysautonomia 570, 828, 1188
dysbiosis 621–626
antibiotics 625
chronic enteropathies 628–629
chronic kidney disease 1172
clinical data on probiotics in veterinary medicine 625–626
etiology/pathophysiology 622–623, *623*
exocrine pancreatic insufficiency 583, 588, 622
healthy dogs and cats 621–622
importance of gastrointestinal microbiota 621
inflammatory bowel disease 621–622, *623*, 624–625
probiotics, prebiotics, and synbiotics 623–624
selection of probiotics 624–625
therapeutic approach 623–625
dysphagia
esophageal disorders 557
gastrointestinal imaging 473–474
neuromuscular junction diseases 807
dysphonia 807
dyspnea
cardiovascular disease 120
chest wall 294–295
diaphragm 295
feline bronchial asthma 297
initial approach and examination 289
lower airway 290–291
nonrespiratory causes 295
pleural effusion 338
pleural space 291–292
pulmonary parenchyma 292–293, **293**
pulmonary thromboembolism 293–294
respiratory monitoring in critical care 373, 375–376
respiratory pattern-based approach 289–296
surgical approaches to thoracic disease 329
upper airway 289–290, **290**
dysregulated immunity 422
dystrophic mineralization 661–663, *662*

e

ear canal tumors 1355–1356
ear clean solutions 1398–1399, 1474–1475, *1476*, 1478
EBA *see* epidermolysis bullosa acquisita
EBC *see* exhaled breath condensate
Ebola virus 901–902
clinical signs 902

diagnosis 902
epidemiology 901–902
etiology/pathophysiology 901
prognosis 902
public health implications 902
treatment 902
E-cadherin 1210
eccrine gland adenoma/carcinoma 1354
ECF *see* extracellular fluid
ECG *see* electrocardiography
echinocandins 1052
echocardiography
advanced ultrasound techniques **152**, *162*
canine myocardial disease 255, 257–258, *257*, **258**
cardiac neoplasia 1273
cardiogenic shock 416–417
cardiovascular disease 134–137
congenital heart disease 237, 240, *241*
feline myocardial disease 270, *272*
fungal infections 995
general principles and technique 134–136
main parasternal long-axis views 136–137, *146–150*, **150**
main parasternal short-axis views 136, *140–144*
M-mode imaging 134–135, 137, *151*
pericardial disease 278–279, *279–281*, 284
pulmonary hypertension 227, *228–229*
pulmonary thromboembolism 315, 318, *318*
respiratory pattern-based approach to dyspnea 293–294
supraventricular arrhythmias 210, 211, 216
two-dimensional imaging 134–137, *140–144*, *146–150*, **150**
valvular heart disease 247, *247*, 249, 251, *251*
see also Doppler echocardiography
ECLE *see* exfoliative cutaneous lupus erythematosus
ECM *see* extracellular matrix
ECV *see* effective circulating volume
edema 463–464
see also pulmonary edema
educated guesses 1135–1136, *1136*
EEG *see* electroencephalography
effective circulating volume (ECV) 360
effect measures 12–15
effusion fluid 874
EGF *see* epidermal growth factor
EGFR *see* epidermal growth factor receptor
EHBO *see* extrahepatic biliary obstruction
EHL *see* intracorporeal lithotripsy
ehrlichiosis and anaplasmosis 903–912
diagnosis 909–911, **909–910**
epidemiology 905–908, *905*, *907*
etiology/pathophysiology 903–905, *903*, **906**
history and clinical signs 908, **908**, *909*
prognosis 911
public health implications 911–912
signalment 908
treatment 911
Einthoven's triangle 165, *165*
elbow dysplasia 1542–1544
diagnosis 1543
etiology/pathophysiology 1542–1543
history and clinical signs 1543
signalment 1543
treatment and prognosis 1543–1544
electrical cardioversion 419
electric burns 544, *545*
electrocardiography (ECG) 165–174
canine myocardial disease 255–256, *255*, 263, *263*
cardiac neoplasia 1272
cardiogenic shock 416, 419–420
conduction abnormalities or bundle branch block 172–173, *172–174*
congenital heart disease 237–238, *238*
criteria for heart enlargement 172, **173**, *174*
ECG paper, sensitivity, and speed of recording 169, *169*
Einthoven's triangle 165, *165*
evaluation of the ECG 168–172
feline hyperthyroidism 76–77
genesis of ECG deflections 167
heart rate 169–170, *170*
hemangiosarcoma 1341
hypoadrenocorticism 84–85, 89
indications for ECG recordings 165
lead terminology and acquisition technique 165–167
mean electrical axis 170–173, *171–172*
pericardial disease 279, *282*
precordial/chest leads and electrode positions 166, **167**
PR interval 167–168
pulmonary hypertension 227, *228*
pulmonary thromboembolism 319
P-wave 167, 170, 173, *174*
QRS complex 168, 170–173, *171–174*
rhythm 170, **170**
six limb leads and terminals 165–166, *166*, **166**
supraventricular arrhythmias 205, 207, *207–208*, 210–216, *210*, *212*, *214–215*
surgical approaches to thoracic disease 327
trauma and burns 454
T-wave 168, 170
urethral obstruction 1110, *1110*
venomous snake bites 461–462
ventricular arrhythmias 200, *201–203*
waveform morphology and intervals 167–168, *167*, **167**, **169**
electroencephalography (EEG) 762, 777
electrolytes
acute kidney injury 1096–1097
critical care setting 350
ff 357
forebrain disorders 777–778
heart failure 195–196
hypoadrenocorticism 83
metabolic diseases 680
motility disorders 564
sodium and water homeostasis 1073, 1076
urethral obstruction 1111–1112, 1115
electromyography (EMG)
myopathies 812–813
neuromuscular junction diseases 804–805, 807
seizures and movement disorders 768, 770–771
tetanus 969
electronic medical records 17
electroretinography (ERG) 823
elimination diets 1421–1422

ELISA *see* enzyme-linked immunosorbent assay
EM *see* erythema multiforme
emesis *see* vomiting
EMG *see* electromyography
EMP *see* extramedullary plasmacytoma
emptying disorders
  detrusor atony 1186
  dysautonomia 1188
  functional urethral obstruction/detrusor urethral dyssynergy 1186–1187
  micturition and associated disorders 1186–1188
  neurogenic functional urethral obstruction 1187
EN *see* enteral nutrition
encephalitis 781–782
Encephalitozoon caniculi 1026
endocarditis 920–921, *921*
endochondrial ossification (EO) 1509–1511, 1540–1542
endocrine manifestations of cancer 1213–1216
  Cushing syndrome 1213–1214
  erythrocytosis 1214–1215
  syndrome of inappropriate antidiuretic hormone secretion 1214
  Zollinger–Ellison syndrome 1215–1216
endocrinology 29–33
  alopecia 1438
  amino acid-derived hormones 30
  approach to the dermatologic patient 1396
  chemical classes of hormones 29–30
  endocrine disease 32
  hormone receptors 30–31
  hormones in circulation 30, *30*
  measurement of hormones 32–33
  protein/polypeptide hormones 29
  regulation of hormone secretion 31–32, *32*
  septic shock 423
  steroids 30
  see also neuroendocrinology
end-of-life care 1555–1564
  approach to the cancer patient 1204
  bioethical principles 1561–1564
  esophageal and stomach cancers 1285
  evaluating and monitoring quality of life 1557–1561, *1557*, **1558**, *1559–1561*
  exocrine pancreatic cancer 1294
  happiness 1560
  human–animal bond 1560–1561, 1563–1564, *1563*
  hunger 1559
  hydration 1559, *1559*
  hygiene 1559–1560
  male reproductive system tumors 1313
  mobility 1560, *1560*
  more good days than bad 1560–1561
  pain and pain management 1555–1556, 1558–1559, *1559*
  pericardial disease 284
  veterinary palliative care and hospice care 1555–1564
  see also euthanasia; palliative radiation therapy
endoscopic nephrolithotomy 1155
endoscopy
  biopsy 510–511, 526–527, *527*
  biopsy instruments and working channel use 510–511
  capsule endoscopy *531*, 532
  chronic enteropathies 635
  cleaning and maintenance 511–512, *511–512*
  colonoscopy 524–525, *525*
  double balloon enteroscopy 531–532
  duodenoscopy 520–522, *521–522*
  equipment options 507–508, *508*–509
  erosions 513, *514*, 521–522
  esophageal stricture management 530
  esophagoscopy 515–517, *516*
  foreign body removal 529–530, *530*
  friability 512–513, *513*, 521–522, 526
  future directions 530–532
  gallbladder and extrahepatic biliary ducts 724
  gastrointestinal tract 507–532
  gastroscopy 517–519, *519*
  general manipulations 510, *510*
  granularity 513, *513*, 521–522, 526
  hyperemia 515
  ileoscopy 525–526
  interventions 527–530
  large intestinal and distal small intestinal procedures 522–526
  lymphatic dilation 513–514, *514*
  mass effects 514–515, *514*
  patient preparation/positioning 515, 517, 520, 522–525
  PEG-J tube placement 529
  PEG tube placement 527–529
  protoscopy 523–524
  record keeping 508–510
  technique for endoscope handling 510–512
  terminology 512–515, **512**, *513–514*
  upper gastrointestinal procedures 515–522
endothelins 225
endotoxins 683
endotracheal intubation 399
endotracheal wash (ETW) 307, **309–310**
end-tidal CO_2 327, 370–371, 377
enteral nutrition (EN) 452–453, 679, 1097
enteric dialysis 1172
enterococci 1059–1060
enzyme-linked immunosorbent assay (ELISA)
  canine brucellosis 964
  canine influenza virus 866
  ehrlichiosis and anaplasmosis 909–910
  endocrinology 33
  feline immunodeficiency virus 884
  feline leukemia virus 879
  fungal infections 991–993, 996
  leptospirosis 947
  pancreatitis 594
  protozoal and protozoa-like infections 1004–1006, 1008–1009, 1011, 1014
  tetanus 969
  viral infections 843–844
enzyme markers of liver disease 646–649
  canine inflammatory liver disease 698
  cirrhosis 707
  feline inflammatory liver disease 688
  gallbladder and extrahepatic biliary ducts 723

hypoadrenocorticism 83
metabolic diseases 677, 680, 682–683
seizures and movement disorders 764
statistical interpretation for practitioners 8–10
venomous snake bites 461
EO *see* endochondrial ossification
eosinophilic dermatitis 1498–1500
diagnosis 1499
etiology/pathophysiology 1498–1499
history and clinical signs 1499, *1499*
prognosis 1499–1500
signalment 1499
treatment 1499
eosinophilic gastritis 487, *488*
eosinophilic granuloma complex 1503–1505
diagnosis 1504
etiology/pathophysiology 1503
history and clinical signs 1503–1504, *1503–1504*
oral cavity and salivary glands 541–542, *541*
prognosis 1505
signalment 1503
treatment 1504–1505
eosinophilic leukemia 1228–1229
eosinophilic plaques 1504, *1504*
EPC *see* exocrine pancreatic cancer
ependymomas 779
EPI *see* exocrine pancreatic insufficiency
epibulbar melanoma 1263–1264
epidemic curves 834–835, *835*
epidermal collarettes *1385*, *1463*
epidermal growth factor (EGF) 1209
epidermal growth factor receptor (EGFR) 52
epidermal growth factor receptor (EGFR) agonists 62
epidermolysis bullosa acquisita (EBA) 1427–1428, *1427*
epilepsy *see* seizures/epilepsy
epiphysial growth center 1509, **1510**, 1511–1512
epulides 1253, 1256
equine tetanus antitoxin 968
ERG *see* electroretinography
erosions
approach to the dermatologic patient *1385*
autoimmune and immune-mediated skin disease *1429*
endoscopy 513, *514*, 521–522
superficial necrolytic dermatitis *1492*
erythema
atopic dermatitis *1404–1406*
cutaneous adverse food reactions *1420*
superficial necrolytic dermatitis *1492*
venomous snake bites 461
erythema multiforme (EM) 543, *543*, 1423–1424
erythrocytosis 1214–1215
erythroderma *1499*
ESBL *see* extended-spectrum beta-lactamase
Escherichia coli 1059, 1194
esophageal and stomach cancers 1283–1286
diagnosis 1284
epidemiology 1283
etiology/pathophysiology 1283
history and clinical signs 1283–1284
prognosis 1285
signalment 1283
treatment 1284–1285
esophagitis/gastroesophageal reflux disease 560–562
endoscopy 516, *516*
gastrointestinal imaging 478
motility disorders 564–567
esophagoscopy 515–517, *516*, 558, 562
esophageal and stomach cancers 1284
motility disorders 565
esophagostomy 452, 691
esophagus
abnormalities of the gastroesophageal junction 479, *479*
diagnostic approach 558–562
disorders 557–562
diverticulae 516
dysphagia 474
endoscopy 515–517, *516*, 530
fistula 478
foreign bodies 476–477, *477–478*, 558, 560–562
gastrointestinal imaging 474–479, *475–478*
generalized esophageal dilation 475–476, *475–476*
megaesophagus 558–560, 564
motility disorders 563–565
normal anatomy and physiology 557
prognosis for animals with esophageal disorders 559–560
recognition of esophageal disorders 557–558
strictures 478, 530, 561, 1047
treatment of esophageal disorders 559–561
tumors of the esophagus 478–479
upper gastrointestinal tract radiography/esophagram 474–475
vascular ring anomalies 476, *477*, 562
essential fatty acids *see* polyunsaturated fatty acids
essential thrombocytopenia 1228–1229
essential tremor syndromes 769–770
estrogen therapy 1160, 1184
ESWL *see* extracorporeal shock wave lithotripsy
ethylene glycol 439–440, 1092–1094
ETW *see* endotracheal wash
European Advisory Board on Cat Disease 956–957
euthanasia
approach to the cancer patient 1204
critical care setting 352
end-of-life care 1555–1557, 1560–1564
mycobacteriosis 983–984
rabies 894
trauma and burns 455
Eutrombicula alfreddugesi 1459–1460, *1500*
excoriations *1385*, *1405*
exercise and activity modification 1533–1534
exercise intolerance 120–121, 264
exfoliative cutaneous lupus erythematosus (ECLE) 1425–1426, *1426*
exhaled breath condensate (EBC) 299
exocrine pancreatic cancer (EPC) 1293–1295
diagnosis 1293–1294
epidemiology 1293
etiology/pathophysiology 1293
history and clinical signs 1293

exocrine pancreatic cancer (EPC) (*cont'd*)
prognosis 1294–1295
signalment 1293
treatment 1294
exocrine pancreatic insufficiency (EPI) 583–589
antibacterials 587–589
clinical features 584–585
cobalamin deficiency/supplementation 583, 588–589
diabetes mellitus 94
diagnosis 585–587
dietary modification 589
dysbiosis 583, 588, 622
etiology 583–584
histamine-2 receptor agonists and proton pump inhibitors 589
histopathology 586–587
pancreatic enzyme supplementation 586–588
pancreatic fecal elastase 586
pancreatitis 608
pathogenesis 583
prognosis 589
routine clinical pathology 585
signalment 584
treatment 587–589, **587**
trypsin-like immunoreactivity 585–586
extended-spectrum beta-lactamase (ESBL) 1059
external ophthalmoplegia 824–825
external validity 7–8
extraaxial hematomas 757
extracellular fluid (ECF) 357–358, 1069–1070, 1073, 1079–1085
extracellular matrix (ECM) 182
extracorporeal shock wave lithotripsy (ESWL) 1119–1120, 1145–1146, **1146**, 1156–1157
extrahepatic biliary obstruction (EHBO) 593, 669, *669*
extrahepatic cholestasis 669, *669*
extramedullary plasmacytoma (EMP) 1241–1246, *1242*, 1283–1285
extranodal lymphoma 1235, 1236
exudative effusions 334, 337–338
eyes and eyelids 400, 441, 1261–1262
see also ocular

f

facial nerve 738–739, 826
FAD *see* flea allergy dermatitis
FAIDS *see* feline acquired immune deficiency syndrome
falcine herniation 750
false negatives 10, 24–25
false positives 10, 24
familial glomerulopathies 1101, **1102**
fasciculations 769
FAST *see* focused assessment with sonography for trauma
fat overload syndrome (FOS) 444
fatty acid oxidation 182–183
FCoV *see* feline coronavirus
FCV *see* feline calicivirus
fecal alpha-1-proteinase inhibitors 633
fecal examination
coccidia 1024, *1024*, 1026
protozoal and protozoa-like infections 1019, *1019*
salmon poisoning disease 914
FECV *see* feline enteric coronavirus
feeding tubes 452, 1097–1098
feline acquired immune deficiency syndrome (FAIDS) 884
feline acquired skin fragility syndrome 1482, *1482*
feline acromegaly 43–48
diagnosis 44–45
etiology/pathophysiology and epidemiology 43–44
history and clinical signs 44
medical treatment 45–46
radiation therapy 47
surgical treatment 46
treatment 45–47
feline bronchial asthma 297–303
diagnosis 298–300
epidemiology 297
etiology/pathophysiology 297
history and clinical signs 297–298
monitoring and response to therapy 303
prognosis 303
respiratory pattern-based approach to dyspnea 290
treatment 300–303
feline calicivirus (FCV) 887–889
diagnosis 888
epidemiology 887
etiology/pathophysiology 887
history and clinical signs 887–888
oral cavity and salivary glands 536–537
prevention 889
prognosis 888
public health significance 889
signalment 887
treatment 888
feline cardiomyopathies
cardiovascular disease 119, 123–124
electrocardiography 172, *172*
heart failure 178–179
feline coronavirus (FCoV) 873–876
diagnosis 874–875
epidemiology 873
etiology/pathophysiology 873
history and clinical signs 873–874
prevention 875
prognosis 875
public health implications 875
signalment 873
treatment 875
feline cytauxzoonosis 1014–1016
diagnosis 1015
epidemiology 1015
etiology/pathophysiology 1014–1015
history and clinical signs 1015
signalment 1015
treatment and prognosis 1015–1016
feline enteric coronavirus (FECV) 782, 873–875
feline gastrointestinal eosinophilic sclerosing fibroplasia (FGESF) 549
feline herpesvirus (FHV-1) 887–889
cutaneous manifestations of systemic disease 1484, *1484*
diagnosis 888
epidemiology 887
etiology/pathophysiology 887
history and clinical signs 887–888
oral cavity and salivary glands 536–537
prevention 889
prognosis 888
public health significance 889
signalment 887
treatment 888
feline hyperthyroidism 75–80
concurrent kidney disease 79
diagnosis 77
etiology/pathophysiology and epidemiology 75–76
history and clinical signs 76–77, **76**
prognosis 79

systemic hypertension 220, 223
treatment 77–79, **77**
feline idiopathic cystitis (FIC) 1109–1110
feline idiopathic vestibular syndrome 791
feline immunodeficiency virus (FIV) 883–885
atopic dermatitis 1410
cutaneous manifestations of systemic disease 1484
diabetes mellitus 97
diagnosis 884
epidemiology 884
etiology/pathophysiology 883–884
hemotropic *Mycoplasma* 927
history and clinical signs 884
laboratory diagnosis 843–844
lymphomas 1236–1238
oral cavity and salivary glands 534, 536–537
prognosis 885
public health implications 885
signalment 884
treatment and prevention 884–885
feline infectious peritonitis (FIP) 873–875
forebrain disorders 782–783
meningoencephalitis and meningomyelitis 795, 801
seizures and movement disorders 761
feline inflammatory liver disease 687–693
diagnosis 688–690, *690*
epidemiology 687–688
etiology/pathophysiology 687
history and clinical signs 688, *689*
lymphocytic cholangitis 687–690, 693
neutrophilic cholangitis 687–690, 693
prognosis 693
signalment 688
treatment 690–693, **691**, **692**
feline ischemic encephalopathy (FIE) 787–788
feline leukemia virus (FeLV) 877–881
atopic dermatitis 1410
central nervous system tumors 1247–1248
clinical decision making 18
cutaneous manifestations of systemic disease 1484
diabetes mellitus 97
diagnosis 879–880
epidemiology 878
etiology/pathophysiology 877
hemotropic *Mycoplasma* 927
history and clinical signs 878–879
intestinal cancers 1287–1288
laboratory diagnosis 843–844
lymphomas 1236–1238
oral cavity and salivary glands 536–537
prevention and control 880–881
prognosis 880
public health implications 881
signalment 878
soft tissue sarcomas 1333
treatment 880
feline pancreatic lipase (fPL) 603–604
feline pansteatitis 1487
feline parvovirus (FPV) 869–871
diagnosis 870
epidemiology 869
etiology/pathophysiology 869
history and clinical signs 869–870
prevention 870
prognosis 870
public health implications 870
signalment 869
treatment 870
feline sarcoma virus (FeSV) 1333
FeLV *see* feline leukemia virus
femoral head and neck ostectomy (FHNO) 1540
FeSV *see* feline sarcoma virus
fever 434–435
FGESF *see* feline gastrointestinal eosinophilic sclerosing fibroplasia
FGF23 *see* fibroblast growth factor 23
FHNO *see* femoral head and neck ostectomy
FHV-1 *see* feline herpesvirus
fibroblast growth factor 23 (FGF23) 1079–1081, 1521–1522, 1527
fibrocartilaginous embolic myelopathy 821
fibrosarcoma (FSA) 1327
feline leukemia virus 878
oral tumors 1253–1256
fibrosis
canine inflammatory liver disease 698, 700
cirrhosis 705, 708–709
feline inflammatory liver disease 687, 691, 693
fibrous osteodystrophy (FOD) 1522–1524
diagnosis 1523–1524, *1523*
etiology/pathophysiology 1522
history and clinical signs 1522–1523
signalment 1522
treatment and prognosis 1524
FIC *see* feline idiopathic cystitis
FIE *see* feline ischemic encephalopathy
fine needle aspiration (FNA)
airway and lung cancers 1279–1280
approach to the dermatologic patient 1392
hepatobiliary disease 675
hepatobiliary tumors 1305
intraocular tumors 1266
lymphomas 1232, 1236–1237
male reproductive system tumors 1313, *1315*
ocular adnexal tumors 1262
orbital and optic nerve tumors 1268
salmon poisoning disease 914
soft tissue sarcomas 1334
FIP *see* feline infectious peritonitis
first aid 462
FISH *see* fluorescence *in situ* hybridization
fissures *1385*
fistula 478
FIV *see* feline immunodeficiency virus
flail chest 294–295
Flavivirus spp. *see* West Nile virus
flea allergy dermatitis (FAD) 1415–1417, *1416*
fleas 951–954
flow cytometry 1232
fluid accumulation 122
fluid analysis 279
fluid overload 1177–1178
fluid resuscitation 360–361
fluid therapy 355–364
acute kidney injury 1095
acute respiratory failure 388–389
albumin 360, 363
body fluid compartments 356–358
body water distribution 356–357
canine inflammatory liver disease 703
canine parvovirus type 2 859
catheter-related complications 356
catheter types 355–356
chronic kidney disease 1170
coccidia 1026

fluid therapy (*cont'd*)
constant rate infusions 363
critical care setting 347–349
crystalloid fluids 358–359
dehydration 361–362, 364
ehrlichiosis and anaplasmosis 911
end-of-life care 1559
feline inflammatory liver disease 690
feline viral upper respiratory tract disease 888
fever 434–435
glomerular disease 1106
head trauma 755
heat stroke 435–436
hypothermia 432–433
indications for fluid therapy 360–363
intravenous fluid types 358–360
maintenance fluids 362
metabolic diseases 680
monitoring of fluid therapy 363–364
motility disorders 577–579
pancreatitis 597, 606
rapid volume expansion 360–361
septic shock 426
shock 409–410
spotted fever and typhus group *Rickettsia* 939–940
surgical approaches to thoracic disease 328–329
synthetic colloids 359–360
trauma and burns 450–451, 453
urethral obstruction 1111–1112
vascular access 355–356
water movement 357–358
fluorescence *in situ* hybridization (FISH) 960
fluoroquinolones 310, 924, 1045–1046
fluoroscopy
canine chronic bronchitis 306–307
congenital heart disease 243, *243*
hepatobiliary disease 672, *672*
motility disorders 566, 572
ureteral obstruction 1120–1121, *1121*
FMCP *see* fragmented medial coronoid process
FNA *see* fine needle aspiration
focal ischemic alopecia 1433
focal/localized intrathoracic airway narrowing/collapse 383
focal/multifocal parenchymal disease 666–667
focused assessment with sonography for trauma (FAST)
pleural effusion 336
shock 406
surgical, traumatic, and bite wound infections 1033
trauma and burns 449
FOD *see* fibrous osteodystrophy
follicle-stimulating hormone (FSH) 29, 36–38
follicular casts *1387*, *1496*
food-responsive diarrhea (FRD) 627–629, 634–637
foramenal herniation 750
forebrain disorders 773–788
anatomy/function 773
anomalous causes 775–776
cerebrovascular accidents 785–787
clinical signs **774**
degenerative and developmental causes 775
differential diagnosis **774**
electrolyte disturbances 777–778
etiology/pathophysiology 773, **774**
feline ischemic encephalopathy 787–788
hepatic and uremic encephalopathy 776–777
hydrocephalus 775–776, *776*
infectious diseases 781–784
inflammatory/idiopathic causes 780–784
L2-hydroxyglutaric aciduria 775, *775*
metabolic causes 776–778
neoplastic causes 778–780
nutritional causes 780
storage diseases 775
vascular causes 785–788
foreign bodies
endoscopy 516, 519, 529–530, *530*
esophagus 476–477, *477–478*, 558, 560–562
fluid therapy 356
large intestine 502–504, *503*
linear foreign bodies 494, *494*
motility disorders 571
oral cavity and salivary glands 542
rectoanal diseases 615–616
small intestine 493–494, *494*
stomach 486–487, *486–487*
FOS *see* fat overload syndrome
fPL *see* feline pancreatic lipase
FPV *see* feline parvovirus
fractures 1518–1519
fragmented medial coronoid process (FMCP) 1542–1544
Francisella tularensis see tularemia
Frank–Starling curves 181–183, *181*
FRD *see* food-responsive diarrhea
free water deficit 362
friability 512–513, *513*, 521–522, 526
FSA *see* fibrosarcoma
FSH *see* follicle-stimulating hormone
functional ileus 497
functional urethral obstruction 1186–1187
fungal infections 985–1001
antifungal therapy 1049–1053
approach to the dermatologic patient 1393
cutaneous manifestations of systemic disease 1485, *1485*
diagnosis 985–986
epidemiology and signalment 985
etiology/pathophysiology 985
history and clinical signs 985
laboratory diagnosis 845–847, *846*
miscellaneous fungus-like infections 999–1000
principles of therapy of dermatologic diseases 1401
public health implications 987
treatment and prognosis 986–987
see also individual agents/diseases
furunculitis/furunculosis *1451–1452*, 1452, 1465

g

gag reflex 739
gait and posture
myelopathy 817–818
neurologic assessment 731–732
osteoarthritis 1531
gallbladder 721–726
diagnosis 723–725
epidemiology 722
etiology/pathophysiology 721–722, *722*
hepatobiliary disease 669–670, *670*
history and clinical signs 722–723
liver disease 651–652
prognosis 726
signalment 722

treatment 725
gallops 255, 270–271, 273
gamma-glutamyl transferase (GGT) *see* enzyme markers of liver disease
gas exchange efficiency 378–379
gastric adenocarcinomas 1284
gastric dilation 483, *483*
gastric dilation-volvulus (GDV)
acute poisoning 442
gastritis and gastric ulceration 550
gastrointestinal imaging 483–485, *484*
motility disorders 567
pulmonary thromboembolism 318
gastric inhibitory polypeptide (GIP) 49–50
gastric lavage 442
gastrinoma 1215–1216, 1300
gastritis and gastric ulceration 547–555
ancillary diagnostic testing 553
cirrhosis 706, 710–711
clinicopathologic examination 552
diagnostic approach 552–553
endoscopy 513, 518–519, *519*
epidemiology 549–550
etiology/pathophysiology 547–549, **548**
gastrointestinal imaging 487, *488*
histopathology 552–553
history and clinical signs 550–551
imaging 552
normal gastric mucosal barrier function 547
prognosis 555
treatment 553–554, **554**
gastroduodenal ulceration 644
gastroenteritis 550–551
gastroesophageal intussusception 479
gastroesophageal junction 479, *479*
gastroesophageal reflux 478, 560–561
gastroesophageal sphincter (GES) 563–564
gastrography 480–483
gastrointestinal eosinophilic sclerosing fibroplasia 491
gastrointestinal (GI) bleeding
gastrointestinal imaging 489
hypoadrenocorticism 82, 85
paraneoplastic syndromes 1220
gastrointestinal (GI) tract
acute poisoning 437, 438, 441–443
canine distemper virus 851–852
chronic enteropathies 627–637
cirrhosis 706, 710–711
computed tomography 469, 471–472, *472*
dysbiosis 621–626
general imaging principles 469–473
imaging contrast agents and pharmacoradiology 469
intraluminal contrast agents 470–471, *470*
magnetic resonance imaging 469, 472
motility disorders 563–581
radiography 469–471, *470*
scintigraphy 472–473
septic shock 424
shock 405, 406
trauma and burns 453
ultrasonography 471
see also endoscopy; *individual anatomical components*
gastrointestinal motility and integrity 351
gastrointestinal perforation 486–487
gastrointestinal stromal tumors (GIST) 1283–1285, 1287–1290, 1291
gastroprotectants 693, 701, 1216
gastroscopy 517–519, *519*, 552–553, 1284
GCS *see* Glasgow Coma Scale
GDV *see* gastric dilation-volvulus
gelatins 360
gels 1398, 1469
generalizability *see* external validity
generalized deep pyoderma 1465, *1465*
generalized esophageal dilation 475–476, *475–476*
generalized hepatomegaly 661, *662*
generalized systemic tumors 686
general proprioceptive (GP) system 732–734, 816
general somatic afferent (GSA) neurons 735
general somatic efferent (GSE) neurons 735
general visceral efferent (GVE) neurons 737
genetics and genetic testing
activating invasion and metastasis 1210
avoiding immune destruction 1208
biology of cancer and cancer genetics 1205–1211
canine myocardial disease 259, 265
chronic enteropathies 627–628, 634–635
deregulating cellular energetics 1209–1210
enabling replicative immortality 1205–1206
evading growth suppressors 1206
genome instability and mutation 1207
inducing angiogenesis 1208–1209
liver disease 653
metabolic bone diseases 1526–1527
nonmelanoma skin cancers 1353
pituitary-dependent hyperadrenocorticism 50–51, **51**
resisting cell death 1206–1207
sustaining proliferative signaling 1209
tumor promoting inflammation 1207–1208
GERD *see* esophagitis/gastroesophageal reflux disease
GES *see* gastroesophageal sphincter
gestational diabetes 93
GFR *see* glomerular filtration rate
GH *see* growth hormone
GHRH *see* growth hormone-releasing hormone
GI *see* gastrointestinal
giant migrating contractions (GMC) 574
giardiasis 1018–1019
diagnosis 1018
epidemiology 1018
etiology/pathophysiology 1018
history and clinical signs 1018
signalment 1018
treatment and prognosis 1018–1019
gingival hyperplasia 534–535
gingivitis 533–536, *535*
GIP *see* gastric inhibitory polypeptide
GIST *see* gastrointestinal stromal tumors
Glasgow Coma Scale (GCS) 751–752, **752**, 758
see also Modified Glasgow Coma Scale
gliomas 1267

globulins 649–650
glomerular disease 1101–1107
  diagnosis 1102–1103
  etiology/pathophysiology 1101, **1102**
  history and clinical signs 1102
  prognosis 1107
  signalment 1101
  treatment 1103–1107, **1104**, **1105**
glomerular filtration rate (GFR)
  acute kidney injury 1089–1091, 1093, 1095
  feline hyperthyroidism 79
  hypothermia 432
  phosphorus homeostasis and disorders 1083–1084
  ureteral obstruction 1118
  urethral obstruction 1112
  urolithiasis 1149, 1151
glomerulonephropathy (GN) 1169–1170
glucagonoma 1299–1300, 1492
glucocorticoid receptors (GR) 50
glucocorticoids
  allergic skin diseases 1414–1415, 1417
  approach to the dermatologic patient 1395
  atopic dermatitis 1409–1410
  canine chronic bronchitis 308
  canine hypothyroidism 72
  cirrhosis 709
  cutaneous adverse food reactions 1422
  diabetes mellitus 93
  feline bronchial asthma 300–301, 303
  hypoadrenocorticism 81, 84–88
  hypoglycemia 107
  juvenile cellulitis 1446–1448
  meningoencephalitis and meningomyelitis 800–801
  metabolic bone diseases 1517
  metabolic diseases 677–678
  miscellaneous skin diseases 1499, 1504
  oral cavity and salivary glands 537, 543
  otitis externa/media 1475, **1477**, 1479
  paraneoplastic syndromes 1218
  pituitary-dependent hyperadrenocorticism 51–52
  urolithiasis 1126–1127
glucose metabolism 1209–1210
  see also hyperglycemia; hypoglycemia
glycated hemoglobin 96–97
glycogen storage disease (GSD) 105–106
glycoprotein hormones 36–38
glycosuria 66
GMC *see* giant migrating contractions
GME *see* granulomatous meningoencephalitis
GN *see* glomerulonephropathy
gonadotropin-releasing hormone (GnRH) 37–38, 1160
GP *see* general proprioceptive
G-protein 31, 75–76
GR *see* glucocorticoid receptors
granularity 513, *513*, 521–522, 526
granulomas 667
granulomatous meningoencephalitis (GME) 780, 797, 799, 801
gross deformities 449–450
growth hormone (GH) 38, 44–47
growth hormone-releasing hormone (GHRH) 38, 43
growth plates 1509–1511, **1510**
GSA *see* general somatic afferent
GSD *see* glycogen storage disease
GSE *see* general somatic efferent
gut microbiota *see* dysbiosis
GVE *see* general visceral efferent
gynecologic cancers 1317–1320
  diagnosis 1317–1320
  epidemiology 1317–1319
  etiology/pathophysiology 1317–1319
  history and clinical signs 1317–1319
  ovarian tumors 1319–1320
  prognosis 1318–1320
  signalment 1317–1319
  treatment 1318–1320
  uterine tumors 1317–1318
  vaginal tumors 1318–1319

h

H2RA *see* histamine-2 receptor antagonists
H3N2 virus 865–867, 1036
H3N8 virus 865–867, 1036
HA *see* hydroxyapatite
HAC *see* hyperadrenocorticism
HAI *see* nocosomial and multidrug-resistant infections
happiness 1560
hazard rates *see* incidence rates
HBT *see* heart-based tumors
HCC *see* hepatocellular carcinoma
HCM *see* hypertrophic cardiomyopathy
HDDS *see* high-dose dexamethasone suppression
HDO *see* high-definition oscillometry
HE *see* hepatic encephalopathy
head trauma 748–758
  clinical assessment 750–753, **751–752**, *752*
  confirmation of injury and diagnosis 753–755, *754*
  injury-related intracranial physiology 748
  monitoring parameters **751**
  pathophysiology of brain injury 748–750, *750*
  prognosis 758
  refractory head trauma 757–758
  treatment 755–757
hearing 739
heart-based tumors (HBT) 1271–1275
heart failure (HF)
  acute life-threatening heart failure 194–197, **195**
  additional therapies 197
  antithrombotics **188**, 191–192
  beta-adrenergic blockers **187**, 190–191
  calcium channel blockers **188**, 191, 193
  cardiogenic shock 415
  chronic heart failure 185–192, **187–188**
  classification 177–178
  compensatory phase 179–181
  components of the circulatory system 175
  cough suppression 194
  determinants of normal cardiac function 175–177
  determinants of ventricular systolic function 176–177
  dietary modifications **188**, 192
  diuretics 186, **187**, 192–196, **195**
  etiology **176**
  failing heart 177–183
  hemodynamics and development of pulmonary edema 183
  initial insult 178–179
  long-term adaptive responses 180–181

management 185–197
origin of ventricular contraction 175–176
pathophysiology 175–184
phases of heart failure 178–183
positive inotropes **187**, 189–190, 194, **195**, 196
refractory chronic heart failure 192–194
septic shock 423
short-term adaptive responses 179–180
therapeutic implications of pathophysiologic mechanisms 183
transition phase 181–183, *181*
vasodilators 186, **187**, 188–189, 193–194, **195**, 196–197
see also congestive heart failure
heart rate/rhythm 123, 169–170, *170*
see also electrocardiography
heart sounds 123–124, 448
heat stroke 435–436
etiology/pathophysiology 435
prognosis 436
treatment 435–436
Helicobacter spp. 549, 553–554
helminths 913–915
helper T lymphocytes (Th) 1403, 1568–1569
hemagglutination inhibition assay 866
hemangiosarcoma (HSA) 1339–1345
cardiac neoplasia 1271–1274
diagnosis/staging 1341–1342, **1342**
epidemiology 1340
etiology/pathophysiology 1327–1328, 1339–1340
feline 1340–1341
hepatobiliary disease 668
history and clinical signs 1340–1341
liver disease 685–686
nonmelanoma skin cancers 1355–1356
ocular adnexal tumors 1261–1262
pericardial disease 279
prognosis 1344–1345
signalment 1340
treatment 1342–1344, **1342**
hematology
acute poisoning 437
antimicrobials 1047
canine chronic bronchitis 306
chronic kidney disease 1165, **1167**, 1170–1171
cirrhosis 707
endocrine manifestations of cancer 1215
gallbladder and extrahepatic biliary ducts 723
glomerular disease 1102–1103
hemangiosarcoma 1341
hypoadrenocorticism 83, 89
hypoglycemia 107–108, 110
liver disease 652–653
Lyme borreliosis 942–943
lymphoid leukemias 1224
lymphomas 1233
meningoencephalitis and meningomyelitis 797
motility disorders 564
myelodysplastic syndromes 1230
myopathies 812
neuromuscular junction diseases 804
pancreatitis 602
plasma cell disorders 1243–1245
polyuria and polydipsia 66
prostatic diseases 1158
protozoal and protozoa-like infections 1013–1015, *1013*, 1018
pulmonary thromboembolism 317
spotted fever and typhus group *Rickettsia* 939
surgical, traumatic, and bite wound infections 1031
tularemia 957
urolithiasis 1133
valvular heart disease 251
hematomas 667
hematopoietic stem cell transplantation (HSCT) 1202, 1225
hemiwalking 733
hemodialysis 440, 443
hemodynamic compromise 400
hemodynamics 183, 200, 204
hemoglobin
critical care setting 350–351
shock 411–412
statistical interpretation for practitioners 9–10
hemoperfusion 443
hemorrhage
head trauma 749
pericardial disease 277
venomous snake bites 459
vestibular disease 793
hemorrhagic parenchymal contusions 757
hemorrhagic stroke 785–786
hemothorax 343
hemotropic *Mycoplasma* 927–930
diagnosis 928, *929*
epidemiology 927, **928**
etiology/pathophysiology 927
history and clinical signs 927
prognosis 929
public health implications 929
signalment 927
treatment 928–929
hepatic congestion 672
hepatic encephalopathy (HE)
cirrhosis 706, 710–711
feline inflammatory liver disease 691
forebrain disorders 776–777
metabolic diseases 679, 682
pathophysiology 643–644, *644*
hepatic lipidosis 678–680
hepatic portal vein (HPV) 671, *671*, 673, *673*
hepatitis
canine inflammatory liver disease 695–703
cirrhosis 705, 707, 709, 711
diagnosis 653
diagnostic imaging 666, *666*
feline inflammatory liver disease 687
metabolic diseases 681–683
signalment 645
toxic diseases of the liver 683
hepatobiliary disease
advanced imaging techniques 659, 673–675
anatomy and physiology 641
biliary system 659–660, 664, 668–670, *669–670*
classification 659
computed tomography 659, 674
diagnosis 658
diagnostic imaging 659–675
fluoroscopy 672, *672*
history and clinical signs 645
image-guided sampling 675
imaging features of hepatobiliary disease 664–673
lymphatic drainage 660
lymph nodes 664
magnetic resonance imaging 659, 675

hepatobiliary disease (*cont'd*)
neoplastic disease 667–668, *667–668*
normal hepatobiliary anatomy 659–660
parenchymal disease 664–667, *665–666*
parenchymal structure 664
radiography 659, 660–663, *661–662*
scintigraphy 659, 674
ultrasonography 659, 663–674, *663*, *665–671*, *673*
vasculature 660, 664, 670–673, *671–673*
hepatobiliary tumors 1303–1306
bile duct tumors 1303–1304, 1306
diagnosis 1305
epidemiology 1304
etiology/pathophysiology 1303–1304
hepatocellular tumors 1303, 1305–1306
history and clinical signs 1304–1305
mesenchymal tumors/sarcomas 1304, 1306
neuroendocrine tumors 1304, 1306
signalment 1304
treatment and prognosis 1305–1306
hepatocellular adenoma 1303
hepatocellular carcinoma (HCC) 684–685
diagnosis 1305
diagnostic imaging 667, *667*
etiology/pathophysiology 1303–1304
signalment 1304
treatment and prognosis 1305–1306
hepatocutaneous syndrome 666, *666*
hepatomegaly 95, 661, *662*
hepatotoxicity 1051
hepatozoonosis 1011–1014
diagnosis 1013–1014, *1013*
epidemiology 1012
etiology/pathophysiology 1011–1012
history and clinical signs 1013
signalment 1013
treatment and prognosis 1014
herbal remedies 580
hereditary nephritis 1101
HES *see* hydroxyethyl starches
HF *see* heart failure
hiatal hernia 479, *479*
HIF-1 *see* hypoxia inducible factor-1
high-definition oscillometry (HDO) 221–222
high-dose dexamethasone suppression (HDDS) **53–54**, 56
high-fiber diet 589
histamine-2 receptor antagonists (H2RA)
esophageal disorders 560
exocrine pancreatic insufficiency 588–589
gastritis and gastric ulceration 553
motility disorders **575**, 580
histamine receptors 1362
histiocytic sarcoma (HS) 1327, 1443–1444
histograms 11–12, *11*
histology/histopathology
acute kidney injury 1094
airway and lung cancers 1280
alopecia 1438
approach to the dermatologic patient 1394–1396
bacterial infections 844
canine distemper virus 852
canine histiocytic disorders 1442–1448
cardiac neoplasia 1273
central nervous system tumors 1248–1249
chronic enteropathies 636
cirrhosis 708–709
esophageal and stomach cancers 1284
exocrine pancreatic cancer 1293
exocrine pancreatic insufficiency 586
feline acromegaly 45
feline coronavirus 875
forebrain disorders 775, *775*
fungal infections 845, 985–987, 993, *993*, 998, 1000, *1000*
gastritis and gastric ulceration 552–553
hemangiosarcoma 1341
intestinal cancers 1288
liver disease 656–658
lymphomas 1232, 1237
mammary cancer 1322
mast cell tumors 1361–1362, 1365
miscellaneous skin diseases 1496–1497
myopathies 813
pancreatic endocrine tumors 1299
pancreatitis 596–597, 604
protozoal and arthropod-borne infections 839–841
rabies 894
soft tissue sarcomas 1335
superficial necrolytic dermatitis 1492
urinary tract tumors 1308
viral infections 843
histoplasmosis 990–992
antifungal therapy 1050, 1052
diagnosis 991–992, 991
epidemiology and signalment 991
etiology/pathophysiology 990–991
gastritis and gastric ulceration 550
history and clinical signs 991
public health implications 992
treatment and prognosis 992
HLA *see* human leukocyte antigen
Ho:YAG laser lithotripsy 1146–1147, *1146*
HO *see* hypertrophic osteopathy
HOAC *see* hypoadrenocorticism
HOD *see* hypertrophic osteodystrophy
Holter recording 213, 256
homeopathy 1344
hopping responses 733
hormone receptors 30–31
hormone replacement therapy (HRT) 1170
hormones and hormonal disorders
canine hypothyroidism 73
cutaneous manifestations of systemic disease 1481–1484
diabetes mellitus 93, **94**
endocrinology 29–33, *30*, *32*
neuroendocrinology 35–41, **37**
principles of therapy of dermatologic diseases 1402
Horner syndrome 737, 827, *827*
hospice care 1555–1564
hospital-acquired infections (HAI) *see* nocosomial and multidrug-resistant infections
hospital-based cohort studies 20–21
hospital-based cross-sectional studies 17–18
HPV *see* hepatic portal vein
HRIG *see* human anti-rabies immune globulin
HRT *see* hormone replacement therapy

HS *see* histiocytic sarcoma
HSA *see* hemangiosarcoma; human serum albumin
HSCT *see* hematopoietic stem cell transplantation
HT *see* systemic hypertension
human–animal bond
  behavioral problems 1572
  end-of-life care 1560–1561, 1563–1564, *1563*
human anti-rabies immune globulin (HRIG) 897
human-directed aggression 1574
human leukocyte antigen (HLA) 113
human melanoma immunotherapy 1351
human serum albumin (HSA) 363
humidification 399
hunger 1559
HVS *see* hyperviscosity syndrome
hydration and dehydration
  acute kidney injury 1092
  chronic kidney disease 1170
  end-of-life care 1559, *1559*
  fluid therapy 361–362, 364
  see also sodium and water homeostasis
hydrogen peroxide 442
hydroxyapatite (HA) 1129–1130, 1512
hydroxyethyl starches (HES) 359
hygiene 1559–1560
hypalgesia 735
hyperadrenocorticism (HAC)
  endocrine manifestations of cancer 1213
  endocrinology 30, 32
  hepatobiliary disease *662*
  pituitary-dependent hyperadrenocorticism 49–63
  polyuria and polydipsia 67
  systemic hypertension 220, 223
  urolithiasis 1126–1127
  see also Cushing disease
hyperaldosteronism 89–92, 220
hyperbilirubinemia 651, 874
hypercalcemia *see* calcium homeostasis and disorders
hypercapneic respiratory failure 381–383, 388–389
hypercapnia *see* hypoventilation
hypercholesterolemia 651
hypercoagulability 316–317, *317*
hypercorticolism 1481–1482
hyperemia 515
hypereosinophilic syndrome 549
hyperesthesia 818
hyperglobulinemia 649–650, 874
hyperglycemia
  critical care setting 350
  diabetes mellitus 93–94, 96–101
  metabolic diseases 679
hyperinflated lungs 298
hyperkalemia *see* potassium homeostasis and disorders
hyperkeratosis *1492*, *1502*
hyperkinetic movement disorders 768–769, **768**, *771*
hyperlipidemia 593, 599
hypermagnesemia *see* magnesium homeostasis and disorders
hypernatremia *see* sodium and water homeostasis
hyperoxaluria 1126
hyperparathyroidism 1082, 1522–1523
hyperphosphatemia *see* phosphorus homeostasis and disorders
hyperpigmentation/hypermelanosis
  approach to the dermatologic patient *1387*
  atopic dermatitis *1405*
  bacterial pyodermas *1463–1464*
  cutaneous adverse food reactions *1420*
hyperproteinemia 298
hypersensitivity reactions
  allergic skin diseases 1414–1415, *1415*
  antimicrobials 1045, 1047
  feline bronchial asthma 297
  venomous snake bites 461, 462–463
hypertension
  chronic kidney disease 1165, **1167**, 1168–1170
  critical care setting 349
  glomerular disease 1105–1106, **1105**
  head trauma 755, 757
  vestibular disease 792–793
  see also systemic hypertension
hyperthermia 433–434
  etiology/pathophysiology 433–434
  head trauma 750
  surgical approaches to thoracic disease 330
  treatment 434
hyperthyroidism
  metabolic bone diseases 1527–1528
  metabolic diseases 678
  statistical interpretation for practitioners 15
  see also feline hyperthyroidism
hypertonic saline 358–359, 360, 409, 755
hypertrophic cardiomyopathy (HCM)
  canine myocardial disease 265
  cardiogenic shock 415
  cardiovascular disease 123, *136*
  feline myocardial disease 267–273
  heart failure 178, 190
  myelopathy 821
hypertrophic osteodystrophy (HOD) 1549–1550
hypertrophic osteopathy (HO) 1220, 1279
hyperventilation 367, 757
hyperviscosity syndrome (HVS) 1241, 1244
hypoadrenocorticism (HOAC) 81–92
  atypical hypoadrenocorticism 87–88
  autoimmune polyglandular syndromes 113–115
  cats 88–92
  diagnosis 82–85, 88–91
  dogs 81–88
  epidemiology/signalment 82, 88, 90
  etiology/pathophysiology 81, 88–90
  history and clinical signs 82, 88, 90, *90*, **90**
  hyperaldosteronism in cats 89–92
  hypoglycemia 107
  motility disorders 564
  polyuria and polydipsia 67, 86, 88
  prognosis 87, 89, 92
  treatment 85–87, 89, 91
hypoalbuminemia
  feline coronavirus 874
  hypoadrenocorticism 83
  liver disease 649
  metabolic diseases 682
  septic shock 425
hypoalbuminuria 1102–1103
hypocalcemia *see* calcium homeostasis and disorders
hypocholesterolemia 83

hypoglycemia 103–111
acquired hepatic dysfunction 107–108
artifactual hypoglycemia 104–105
clinical signs 104, 109
congenital hepatic disease 103, 105
critical care setting 350
diabetes mellitus 99–101
diagnostic approach to associated disorders 106–107, 109, 110
etiology/pathophysiology 104–111, **104**
forebrain disorders 777
glycogen storage disease 105–106
heat stroke 436
history 105
hypoadrenocorticism 83, 85, 107
liver disease 650
maintenance of normal glucose concentrations 103–104
microvascular dysplasia 105
neonatal and juvenile hypoglycemia 106
nonislet tumor-induced hypoglycemia 106–107
pancreatic endocrine tumors 1297–1298
paraneoplastic syndromes 1218
persistent hyperinsulinemic hypoglycemic syndrome 108–109
portosystemic vascular anomalies 103, 105
renal failure 107
sepsis-induced hypoglycemia 108
signalment 105
treatment and prognosis 106–107, 109–110
virulent babesiosis 108
xylitol toxicity 109–110
hypokalemia *see* potassium homeostasis and disorders
hypomagnesemia *see* magnesium homeostasis and disorders
hyponatremia *see* sodium and water homeostasis
hypoparathyroidism 1084
hypophosphatemia *see* phosphorus homeostasis and disorders
hypophosphatemic rickets 1527
hypophysectomy 46
hypopigmentation/hypomelanosis
approach to the dermatologic patient *1387*
autoimmune and immune-mediated skin disease *1426*
bacterial pyodermas *1464*
hypotension
critical care setting 349
head trauma 755
pulmonary thromboembolism 319
septic shock 421, 426–427
surgical approaches to thoracic disease 326
hypotensive resuscitation 361
hypothalamus 35, *36*, 41, 50
hypothermia 431–433
cardiopulmonary resuscitation 371
etiology/pathophysiology 431–432
head trauma 750, 757
prognosis 433
respiratory pattern-based approach to dyspnea 292, 295
surgical approaches to thoracic disease 326, 329
treatment 432–433
hypothesis testing
clinical decision making 20–21
infectious disease 835–836
statistical interpretation for practitioners 8–10
hypothyroidism
antimicrobials 1047
autoimmune polyglandular syndromes 114–115
cutaneous manifestations of systemic disease 1482–1483
vestibular disease 792–793
see also canine hypothyroidism
hypoventilation
acute respiratory failure 382–384
mechanical ventilation 393
respiratory monitoring in critical care 378
surgical approaches to thoracic disease 325–326
hypovolemic shock
hypoadrenocorticism 82, 89
portosystemic shunts and microvascular dysplasia 715
septic shock 422
sodium and water homeostasis 1071
trauma and burns 453
hypoxemia
acute respiratory failure 383–386, **384**, *385*, 389–390, **390**, 397–398
canine chronic bronchitis 308
feline bronchial asthma 299
mechanical ventilation 393, 397–398
pulmonary thromboembolism 313, 319
respiratory monitoring in critical care 375–379
respiratory pattern-based approach to dyspnea 293
surgical approaches to thoracic disease 325–326
hypoxia
hypothermia 432
metabolic diseases 680
pulmonary hypertension 225
shock 403–404
hypoxia inducible factor-1 (HIF-1) 1209

i

IBD *see* inflammatory bowel disease
IBS *see* irritable bowel syndrome
ICD *see* implantable cardioverter defibrillators
ICF *see* intracellular fluid
ICGN *see* immune complex-mediated glomerulonephritis
ichthyosis 1500–1503
diagnosis 1503
etiology/pathophysiology 1500–1501
history and clinical signs 1501–1503, *1501–1502*
prognosis 1503
signalment 1501
treatment 1503
ICP *see* intracranial pressure
icterus 642, *642*, 721, 723
ICU *see* intensive care unit
idiopathic megaesophagus 559, 564
idioventricular rhythm 200, *203*
IE *see* infectious endocarditis
I:E *see* inspiratory:expiratory
IFA *see* immunofluorescence assay; immunofluorescent antibody
IFN *see* interferons
IGF *see* insulin-like growth factor
IHC *see* immunohistochemistry

IHD *see* intermittent hemodialysis
IL *see* interleukins; intermediate lobe
ILAE *see* International League Against Epilepsy
ileoscopy 525–526
image-guided sampling 675
IMHA *see* immune-mediated hemolytic anemia
immune complex-mediated glomerulonephritis (ICGN) 1101, 1103, 1106–1107
immune-mediated hemolytic anemia (IMHA)
  chronic enteropathies 634
  clinical decision making 19–23, *20*
  paraneoplastic syndromes 1219–1220
  pulmonary thromboembolism 319
immune-mediated thrombocytopenia (ITP) 23, 1220
immune system
  biology of cancer and cancer genetics 1208
  canine inflammatory liver disease 696
  chronic enteropathies 628
  critical care setting 351
  cutaneous manifestations of systemic disease 1487–1488
  ehrlichiosis and anaplasmosis 903–905
  neuromuscular junction diseases 804–806
  oral cavity and salivary glands 542–544, *543*
  rectoanal diseases 614, **615**
  tularemia 955
  see also autoimmune and immune-mediated skin disease; vaccination
immunization *see* vaccination
immunofluorescence assay (IFA)
  canine distemper virus 852
  ehrlichiosis and anaplasmosis 909–910
  protozoal and protozoa-like infections 1004, *1004*, 1006, 1008, 1011, 1014
immunoglobulins 1241–1242, 1428
immunohistochemistry (IHC)
  canine histiocytic disorders 1442–1444
  chronic enteropathies 634
  feline coronavirus 875
  intestinal cancers 1287–1292
  male reproductive system tumors 1314–1315
  mast cell tumors 1364
  melanoma 1347
  oral cavity and salivary glands 537, 542
  papillomaviruses 863
  plasma cell disorders 1245
  rabies 894
immunophenotyping 1224, 1233, 1237
immunosuppression/immunotherapy
  atopic dermatitis 1411–1412
  autoimmune and immune-mediated skin disease 1423–1431, **1425**
  bartonellosis 924
  bone and joint tumors 1331
  canine distemper virus 851–852
  canine herpesvirus 855–856
  canine histiocytic disorders 1442–1448
  chronic enteropathies 636
  chronic kidney disease 1170
  feline coronavirus 875
  feline inflammatory liver disease 693
  feline leukemia virus 878
  forebrain disorders 781
  fungal infections 986–988
  glomerular disease 1106–1107
  hemangiosarcoma 1343
  hemotropic *Mycoplasma* 927–928
  Lyme borreliosis 943
  melanoma 1349–1351, *1350*
  meningoencephalitis and meningomyelitis 800–801, **800**
  miscellaneous skin diseases 1498–1500
  mycobacteriosis 980
  nocardiosis 980
  nocosomial and multidrug-resistant infections 1058
  nonmelanoma skin cancers 1356, 1357
  oral tumors 1255
  papillomaviruses 863
  paraneoplastic syndromes 1220
  principles of therapy of dermatologic diseases 1400
  protozoal and protozoa-like infections 1019
  spotted fever and typhus group *Rickettsia* 939–940
impetigo 1463
implantable cardioverter defibrillators (ICD) 204
impression smears 1387–1391
IMRT *see* intensity-modulated radiation therapy
incidence odds/odds ratios 15–16
incidence rates 14–15, 21–22
incontinence 1184–1188
indolent ulcer 1504–1505, *1504*
inducible nitric oxide synthase (iNOS) 423
infectious disease
  advantages/disadvantages of diagnostic methods **840**
  approach to the dermatologic patient 1376
  bacterial infections 844–845
  canine inflammatory liver disease 695–696
  communicating findings 836
  confirming presence of disease outbreak 834
  cutaneous manifestations of systemic disease 1484–1486
  descriptive epidemiology 834–835, *835*
  disease monitoring and surveillance 833–834
  epidemiology 833–837
  esophageal and stomach cancers 1283–1284
  establishing a case definition 834
  establishing an investigation team 834
  fever 434
  fluid therapy 356
  forebrain disorders 781–784
  formulating and testing hypotheses 835–836
  fungal infections 845–847, *846*
  gallbladder and extrahepatic biliary ducts 721–722, 725
  gastritis and gastric ulceration 549–553
  implementing control and prevention measures 836
  kennels and multicat environments 1063–1066
  laboratory diagnosis 839–847

infectious disease (*cont'd*)
liver disease 653
male reproductive system tumors 1314–1315
meningoencephalitis and meningomyelitis 795–801
myelopathy 821
nonmelanoma skin cancers 1354–1355, 1357
One Health 3–5
oral cavity and salivary glands 533–538
outbreak investigations 834–836
pleural effusion 340–341
protozoal and arthropod-borne infections 839–843
sample collection, processing, and transport **841**
seizures and movement disorders 762, 768–769
septic shock 421–428
soft tissue sarcomas 1333
surgical approaches to thoracic disease 330
surgical, traumatic, and bite wound infections 1029–1034
trauma and burns 454–457
urolithiasis 1126–1128, 1137, 1139–1143
venomous snake bites 463
vestibular disease 791–792
viral infections 843–844
see also individual agents/diseases; *individual diseases/agents*
infectious endocarditis (IE)
diagnosis 251, *251*
epidemiology 250
etiology/pathophysiology 250
history and clinical signs 250–251
prognosis 251
treatment 251
valvular heart disease 250–251
infectious vaccines 1568–1569
infiltrates 315
infiltration 356
infiltrative neoplasia 668
inflammation and inflammatory disease
alopecia 1433, *1434*, **1434**
atopic dermatitis 1403
biology of cancer and cancer genetics 1207–1208
canine inflammatory liver disease 695–703
chronic enteropathies 627–628, 636
feline inflammatory liver disease 687–693
forebrain disorders 780–784
gastritis and gastric ulceration 547–555
glomerular disease 1101
large intestine 500, *501*
meningoencephalitis and meningomyelitis 798–799
myelopathy 821
myopathies 811–813
neuroophthalmology 823
oral cavity and salivary glands **534**, 536–537, 543–544
pancreatitis 592–593, 599–600, 608
rectoanal diseases 614, **615**
skeletal development and homeostasis 1516
small intestine 491–492, *492*
stomach and duodenum 487, *488*
trauma and burns 445–446
vestibular disease 791–794
see also individual disorders
inflammatory bowel disease (IBD)
chronic enteropathies 627–637
dysbiosis 621–622, *623*, 624–625
gallbladder and extrahepatic biliary ducts 722
gastritis and gastric ulceration 548, 551–552
metabolic bone diseases 1527
motility disorders 572
inflammatory carcinomas 1322–1323
influenza viruses
canine infectious respiratory disease complex 1035–1037
canine influenza virus 865–867
One Health 4–5
inguinal panniculitis *982*
innate immunity 421–422
iNOS *see* inducible nitric oxide synthase
inositol triphosphate (IP3) 179
inspiratory:expiratory (I:E) ratio 396
insulin
acute kidney injury 1096
diabetes mellitus 93, **94**, 97–101, **97–99**
feline acromegaly 45–46
hypoadrenocorticism 85
hypoglycemia 107
insulin resistance 93, 99–100, 679
pancreatic endocrine tumors 1298
insulin-like growth factor (IGF)
endocrinology 29
feline acromegaly 43–47
hypoglycemia 106
paraneoplastic syndromes 1218
insulinoma 32, 1297–1299
integument hemangiosarcoma 1340–1341, 1345
intensity-modulated radiation therapy (IMRT) 1203, 1257
intensive care unit (ICU) 347, 571–572
interdigital pyoderma 1466–1467, *1466*
interferons (IFN)
atopic dermatitis 1403
feline immunodeficiency virus 885
hemangiosarcoma 1344
oral cavity and salivary glands 537–538
interleukins (IL) 1403
intermediate lobe (IL) 35–36
intermittent common source epidemic curves 835, *835*
intermittent hemodialysis (IHD) 1149–1150, 1175–1176
intermittent positive pressure ventilation (IPPV)
acute respiratory failure 389, 398
complications 400–401
indications for mechanical ventilation 394
nursing care 402
settings 395–397
internal ophthalmoplegia 824–825, *825*
internal validity 8
International League Against Epilepsy (ILAE) 759–760
International Renal Interest Society (IRIS) **1091**, 1105–1106, **1105**, 1165, **1166**, 1178
interstitial cell tumors 1311
interstitial lung disease *229*
intertrigo 1462–1463, *1462–1463*
intervertebral disc disease (IVDD) 819
intestinal cancers 1287–1292
diagnosis 1289
epidemiology 1288
etiology/pathophysiology 1287–1288
history and clinical signs 1289

prognosis 1291–1292
signalment 1288–1289
treatment 1289–1291
intestinal herniation 496
intestinal intussusception 494–495, 495, 571
intestinal mucosal immune system 628
intestinal pseudoobstruction 571
intestinal volvulus/torsion 496–497
intraabdominal hypertension 295
intraaxial hematomas 757
intracardiac neoplasia 414–415
intracellular fluid (ICF) 357, 1069–1070
intracorporeal lithotripsy (EHL) 1146–1147
intracranial disease 295
intracranial neoplasia *see* central nervous system tumors
intracranial pressure (ICP)
critical care setting 347, 350
forebrain disorders 785
head trauma 748, 749–750, 754–757
vestibular disease 790
intradermal allergen testing 1407–1408, *1407*
intraluminal contrast agents 470–471, *470*
intramembranous ossification (IO) 1509
intraocular tumors 1264–1267
diagnosis 1266
history and clinical signs 1266
primary tumors 1264–1266, *1264–1266*
prognosis 1267
secondary uveal neoplasms 1267
treatment 1266–1267
intrapericardial cysts 275
intravascular contrast agents 471
intravenous catheters 355
intravenous lipid emulsions (IVLE) 443–444
intussusception
gastroesophageal 479
large intestine 504, *504*
motility disorders 571
small intestine 494–495, *495*, 571
invasion 1210
IO *see* intramembranous ossification
iodinated contrast agents 470–471, 482
iodine 78–79
IP3 *see* inositol triphosphate
IPPV *see* intermittent positive pressure ventilation
iridociliary epithelial tumors 1265–1266, *1266*
IRIS *see* International Renal Interest Society
irritable bowel syndrome (IBS) 576
ischemia 446
ischemic stroke 785
isolation/culture
approach to the dermatologic patient 1393–1394
bacterial infections 844–845
bacterial pyodermas 1468–1469
canine distemper virus 852
fungal infections 846–847, 985–986, 998
nonhemotropic *Mycoplasma*, *Ureaplasma*, and L-form bacteria 934, *934*
prostatic diseases 1159
protozoal and arthropod-borne infections 843
urolithiasis 1132–1133
viral infections 844
yersiniosis 953
isoxazolines 1452–1454
ITP *see* immune-mediated thrombocytopenia
IVDD *see* intervertebral disc disease
IVLE *see* intravenous lipid emulsions

j

Jarisch–Herxheimer reaction 924
jaundice 642, *642*, 721, 723
jejunal lymph nodes 492
jejunojejunal intussusception 494–495, *495*
J-tubes 529
junctionopathies 382
justice principle 1561–1563
juvenile cellulitis 1447–1448
clinical signs 1447
diagnosis 1447–1448
pathogenesis 1447
signalment 1447
treatment and prognosis 1448
juvenile hypoglycemia 106

k

Kaplan–Meier survival curves 20–21, *20*, 248, *248*
KCS *see* keratoconjunctivitis sicca
kennels and multicat environments 1063–1066
cleaning and disinfection 1064–1065
culture of compliance 1065
managing outbreaks 1065
modes of transmission 1063
prevention of disease transmission 1063–1064
protection from zoonotic pathogens 1065–1066
risks 1063
vaccination 1064
keratoconjunctivitis sicca (KCS) 1047
Key–Gaskell syndrome 828

l

L2-hydroxyglutaric aciduria 775, *775*
lactate 406, 411
lactulose 710, 717
LAD *see* linear IgA disease
lagenidiosis 1485–1486
lamellar bone 1513
laparoscopic-assisted cystoscopy 1149
laparoscopic biopsy 657–658
laparotomy and laparoscopy 725
large cell lymphoma 1238–1239
large intestine
cecal or colonic intussusception 504, *504*
colonic volvulus/torsion 504, *505*
computed tomography 500, *500*
congenital abnormalities of the colon 504–505
displacement of the colon 505
endoscopy 522–526
gastrointestinal imaging 498–505, *500–505*
inflammatory disorders 500, *501*
intestinal cancers 1287–1292
megacolon 500–504, *502–503*
pneumocolonography 499
radiography 498–500, *501–505*
tumors of the large intestine 500, *501*
ultrasonography 498–500, *501*, *503*
laser ablation 538
laser therapy 1267
latex agglutination assay 993

lavage 1032
see also bronchoalveolar lavage
laxatives 612–613, 616
LC *see* lymphocytic cholangitis
L-carnitine deficiency **188**, 192
LCP *see* Legg–Calvé–Perthes
LDDS *see* low-dose dexamethasone suppression
LDL *see* low-density lipoprotein
left atrial enlargement
cardiovascular disease 130, *134–137*
feline myocardial disease 271, 273
valvular heart disease 246–247
left bundle branch block (LBBB) 172–173, *174*
left-sided congestive heart failure 131–132, *134*, *136–137*
left ventricular eccentric hypertrophy 246
left ventricular enlargement 130, *134–135*, *137*
left ventricular hypertrophy 268
left ventricular outflow tract (LVOT) obstruction 265, 415
Legg–Calvé–Perthes (LCP) disease 1547–1548
leiomyoma/leiomyosarcoma
esophageal and stomach cancers 1283, 1285
intestinal cancers 1287, 1289, 1291–1292
leishmaniosis 1009–1011
cutaneous manifestations of systemic disease 1485, *1486*
diagnosis 1010–1011
epidemiology 1010
etiology/pathophysiology 1009–1010
history and clinical signs 1010
signalment 1010
treatment and prognosis 1011
LEM *see* leukoencephalomyelopathy
lens-induced uveitis 95
leprosy/leproid granuloma syndromes 980–983
leptospirosis 945–949
acute kidney injury 1091, 1093, 1098
canine inflammatory liver disease 696, 702
diagnosis 946–947
epidemiology 945–946
etiology/pathophysiology 945
history and clinical signs 946
prevention 948
prognosis 948
public health implications 948–949
signalment 946
treatment 947–948
leukemia *see* feline leukemia virus
leukemia inhibitory factor and receptor (LIF/LIFR) 51
leukoencephalomyelopathy (LEM) 782
leukopenia 870
leukopheresis 1370, 1371
leuteinizing hormone (LH) 36–38
level of consciousness (LOC) 448, 753
L-form bacteria 931–935
LH *see* luteinizing hormone
lice *see* pediculosis
lichenification
approach to the dermatologic patient *1386*
atopic dermatitis *1405*
cutaneous adverse food reactions *1420*
LIF/LIFR *see* leukemia inhibitory factor and receptor
limbal melanoma 1263–1264
limb function assessment 752, *752*
lincosamides 1046
linear foreign bodies 494, *494*
linear IgA disease (LAD) 1428
lingual hemangiosarcoma 1341
lipid metabolism 650–651
see also hepatic lipidosis
liver disease 641–658
acquired portosystemic shunts 643
anatomy and physiology 641
ascites 643
biochemical evaluation 645–652
canine inflammatory liver disease 695–703
cholestasis 641–642
coagulopathy 644
cytology 655–656
diagnosis 645–658
feline inflammatory liver disease 687–693
gastroduodenal ulceration 644
genetics and genetic testing 653
hematology 652–653
hepatic encephalopathy 643–644, *644*
histopathology 656–658
history and clinical signs 645, **646**
icterus 642, *642*
imaging 653
interpretation of clinical pathology 653, **654**
malignancies/neoplasia 684–686
metabolic diseases 677–683
newer tests 653
pathophysiology of important clinical presentations 641–644
portal hypertension 643
septic shock 423
serology 653
signalment 644–645
toxic diseases 683–684
urinalysis 653
urolithiasis 1129
see also hepatic; hepatobiliary disease
liver failure 1071
liver flukes 690
liver function tests 649–652, 707–708
liver lobe torsion 667
liver pseudofunction tests 707
livestock 4–5
LMN *see* lower motor neuron
LMWH *see* low molecular weight heparin
lobular orbital adenoma 1267
LOC *see* level of consciousness
localized hepatomegaly 661, *662*
longitudinal observational studies
case–control studies 21–23
clinical decision making 18–25
clinical trials 23–25
cohort studies 19–21, *20*
loop diuretics 417
loss of nociception 818
lotions 1398
low-density lipoprotein (LDL) 1370
low-dose dexamethasone suppression (LDDS) 31–32, *32*, **53–54**, 54, 56
lower airway 290–291
lower motor neuron (LMN) 731–735, 807, 1184–1186
lower urinary tract (LUT) 1124, 1127–1128, 1136–1149
low-fat diet 589
low molecular weight heparin (LMWH) 321–322
L-type calcium channels 175–176
lung cancers
diagnosis 1279–1280
epidemiology 1278–1279
etiology/pathophysiology 1278
history and clinical signs 1279

prognosis 1280, **1281**
signalment 1279
statistical interpretation for practitioners 7
treatment 1280
lung-digit syndrome 1489–1490
LUT *see* lower urinary tract
luteinizing hormone (LH) 29
LVOT *see* left ventricular outflow tract
Lyme borreliosis 941–944
diagnosis 942–943
epidemiology 941
etiology/pathophysiology 941
history and clinical signs 941–942
Lyme arthritis 941–943
Lyme nephritis 942, 943
One Health 4
prevention 942, 943
prognosis 943
public health implications 944
signalment 941
treatment 943
lymphadenitis 951
lymphadenomegaly 1348
lymphangiectasia 522, *522*
lymphatic dilation 513–514, *514*
lymphatic drainage 660
lymph nodes
biology of cancer and cancer genetics 1210
bone and joint tumors 1328–1329
hepatobiliary disease 664
mast cell tumors 1360
melanoma 1348
oral tumors 1254
rectoanal diseases 609–610
soft tissue sarcomas 1334
lymphocytic cholangitis (LC) 687–690, 693
lymphoid leukemias 1223–1225
diagnosis 1224–1225, *1224–1225*
epidemiology 1223–1224
etiology/pathophysiology 1223
feline leukemia virus 878
history and clinical signs 1224
prognosis 1225
signalment 1224
treatment 1225
lymphoma/lymphosarcoma 1231–1239
airway and lung cancers 1277–1278
canine lymphomas 1231–1236
cardiac neoplasia 1271–1274
diagnosis/clinical staging 1232–1233, **1232**, 1236–1238
epidemiology 1231, 1236
etiology/pathophysiology 1231, 1236
extranodal forms of lymphoma 1235–1237
feline leukemia virus 878
feline lymphomas 1236–1239
history and clinical signs 1231–1232, **1232**, 1236
intestinal cancers 1287–1292
prognosis 1235–1236, 1239
signalment 1231, 1236
treatment 1233–1235, **1234**, 1238–1239, **1238**
lymphopenia 859
Lynxacarus radovsky 1457–1458
diagnosis 1457–1458
etiology/pathophysiology 1457
history and clinical signs 1457, *1458*
treatment and prognosis 1458
Lyssavirus spp. *see* rabies

m

macrocirculation 405
macrocyclic lactones 1452
macrolides 1046
macronodular hyperplasia 56
macrophage colony-stimulating factors (M-CSF) 1514–1515, *1515*
macules
approach to the dermatologic patient *1383*
atopic dermatitis *1404*
miscellaneous skin diseases *1499*
magnesium homeostasis and disorders 1085–1088
biologic importance of magnesium 1085–1086
distribution in the body 1085
etiology/pathophysiology 1086–1087, **1087**
hypermagnesemia 1087–1088
hypomagnesemia 1086–1087
laboratory assessment 1086
regulation of magnesium 1086
treatment 1087
magnesium sulfate supplementation 203–204
magnetic resonance imaging (MRI)
airway and lung cancers 1278–1279
bone and joint tumors 1330
cardiac neoplasia 1272–1273
central nervous system tumors 1248–1249, *1249*
cirrhosis 708
esophageal and stomach cancers 1284
feline acromegaly 45
forebrain disorders 775–776, 781, 783–787
fungal infections 996
gallbladder and extrahepatic biliary ducts 724
gastrointestinal imaging 469, 472
head trauma *750*, 753–754, *754*
hepatobiliary disease 659, 675
meningoencephalitis and meningomyelitis 798
motility disorders 569
myelopathy 819
neuroophthalmology 823, 825, 827
oral tumors 1254
orbital and optic nerve tumors 1268
osteoarthritis 1531
pancreatitis 594
pericardial disease 280
pituitary-dependent hyperadrenocorticism 57
pulmonary thromboembolism 319
seizures and movement disorders 762
spinal cord injury 743–744, *744*
vestibular disease 792–794
maintenance fluids 362
major histocompatibility complex (MHC) 1567–1569
Malassezia spp. 988–989
approach to the dermatologic patient 1376, 1391
bacterial pyodermas 1462, 1466
diagnosis 988–989
epidemiology and signalment 988
etiology/pathophysiology 988
history and clinical signs 988
miscellaneous skin diseases 1495–1498, 1502, *1502*
otitis externa 1474, *1474*
public health implications 989
treatment and prognosis 989, 1052
male feminizing syndrome 1488
male reproductive system tumors 1311–1315
diagnosis 1311–1315, *1315*
epidemiology 1311–1314
etiology/pathophysiology 1311–1314

male reproductive system tumors (*cont'd*)
history and clinical signs 1311–1314
penis, prepuce, and scrotal tumors 1313–1314
prognosis 1312–1315
prostate tumors 1312–1313
signalment 1311–1314
testicular tumors 1311–1312
transmissible venereal tumor 1314–1315
treatment 1312–1315
malignancies and neoplasia
activating invasion and metastasis 1210
adjunctive therapies 1204
advanced diagnostics 1201
approach to the cancer patient 1199–1204
avoiding immune destruction 1208
biology of cancer and cancer genetics 1205–1211
chemotherapy 1202
clinical features and diagnostic testing 1200
concepts and definitions 1199
cutaneous manifestations of systemic disease 1488–1490
deregulating cellular energetics 1209–1210
diagnosis 1201
enabling replicative immortality 1205–1206
end-of-life management 1204
endoscopy 517, 518–519
esophagus 478, *479*
evading growth suppressors 1206
exocrine pancreatic insufficiency 584
feline immunodeficiency virus 884
feline leukemia virus 878
forebrain disorders 778–780
gallbladder and extrahepatic biliary ducts 721–722
gastritis and gastric ulceration 548, 550–551, 553
genome instability and mutation 1207
grading 1200–1201
hepatobiliary disease 667–668, *667–668*
history 1200
imaging 1201
inducing angiogenesis 1208–1209
initial assessment 1200
large intestine 500, *501*
liver disease 684–686
meningoencephalitis and meningomyelitis 798–799
metabolic bone diseases 1522, 1527
motility disorders 571
myelopathy 820–821
neurologic assessment 737
oral cavity and salivary glands 534, 538–541, *540*, 545
pain and pain management 1203
palliative care 1204
palliative radiation therapy 1203–1204
papillomaviruses 861–863
patient evaluation 1200
pericardial disease 284
prostatic diseases 1163
radiation therapy 1202–1203
recent treatment advances 1202
rectoanal diseases 609–610, 618–620, *619*
resisting cell death 1206–1207
small intestine 491–492, 495, *496*
staging 1200
stomach 487–489, *488*
surgical management 1202
sustaining proliferative signaling 1209
treatment 1201–1203
tumor promoting inflammation 1207–1208
ureteral obstruction 1117–1119, *1121*
urethral obstruction 1109–1111, 1115, 1117
vestibular disease 791, 793
see also individual types
malignant arrhythmias 461–462
malignant hyperthermia (MH) 376, 389, 433–434
malignant lymphoma 686
malignant melanoma (MM) 539, 1253–1256
MALT *see* mucosa-associated lymphoid tissue
mammary cancer 1321–1325
canine mammary cancer 1321–1323
diagnosis/staging 1322, **1322**, 1323–1324, **1324**
epidemiology 1321, 1323
etiology/pathophysiology 1321, 1323
feline mammary cancer 1323–1324
history and clinical signs 1321–1322, 1323
prognosis 1323–1324
signalment 1321, 1323
treatment 1322–1324
manometry 565, *566*
margination changes 663
mass effects 514–515, *514*
mass lesions
approach to the cancer patient 1199
endoscopy 519, 525
gastritis and gastric ulceration 548–549
vestibular disease 793
mast cell tumors (MCT) 1359–1367
biology of cancer and cancer genetics 1209
canine 1359–1365, *1360*, *1363–1364*
diagnosis/staging 1359–1362, *1360*, **1361**, 1365–1366
epidemiology 1359, 1365
esophageal and stomach cancers 1283, 1285
etiology/pathophysiology 1359
feline 1365–1366, *1363*
history and clinical signs 1359, *1360*, 1365, *1365*
intestinal cancers 1292
male reproductive system tumors 1313–1314
prognosis 1365–1366
signalment 1359, 1365
statistical interpretation for practitioners 7–8
treatment 1362–1366, *1363–1364*, **1363**
masticatory muscle myositis (MMM) 812
mastocytosis 552–553
MAT *see* microscopic agglutination test
matching controls 22
matrix metalloproteinases (MMP)
heart failure 182
hemangiosarcoma 1344
valvular heart disease 245
matrix-nucleation theory 1123
MCM-7 *see* minichromosome maintenance-7
M-CSF *see* macrophage colony-stimulating factors
MCT *see* mast cell tumors
MDR *see* multidrug-resistant
MDS *see* myelodysplastic syndromes
MEA *see* mean electrical axis

mean arterial pressure (MAP) 406
mean electrical axis (MEA) 170–173, *171–172*
mechanical ileus 492–493, *493*
mechanical load 382–383, 388–389
mechanical ventilation 393–402
  adjustments to improve $PaCO_2$ 398
  adjustments to improve PaO_2 398
  airway pressure settings 395
  airway suctioning 399
  anesthesia 397
  catheter care 400
  complications 400–401
  eye care 400
  general guidelines for initial ventilator settings 396–397
  goals 398
  hemodynamic compromise 400
  humidification 399
  hypoxemic respiratory failure 397–398
  indications for mechanical ventilation 393–394
  initial stabilization 397–398
  inspiratory:expiratory ratio and respiratory rate setting 396
  nursing care 398–400, 402
  oral care 400
  oxygen toxicity 401
  pneumothorax 401
  positive end-expiratory pressure settings 396
  recumbent patient care 400
  tidal volume settings 395
  tracheal tube management 399
  trigger settings 395–396
  ventilator-associated pneumonia 400
  ventilator breath types 394–395
  ventilator-induced lung injury 401
  ventilator settings 394–397
  weaning from mechanical ventilation 401–402
  see also individual techniques
mediastinal neoplasia 335, 1236–1237, 1239
mediastinitis *477*
medical wipes 1398
Mediterranean spotted fever 937
megacolon
  gastrointestinal imaging 500–502, *502–503*
  motility disorders 576, 579
  rectoanal diseases 612–613, *613*
megaesophagus 558–560
  acquired megaesophagus 558–559
  congenital megaesophagus 558
  gastrointestinal imaging 475–476, *475–476*
  idiopathic megaesophagus 559, 564
  motility disorders 564
  treatment 559
meibomian gland adenoma/epithelioma 1261
melamine urolithiasis 1132, *1132*
melanocytoma/melanoma 1347–1352
  anatomic site 1351–1352
  diagnosis/pathology/molecular biology 1347–1348
  etiology/pathophysiology/epidemiology 1347
  intraocular tumors 1264–1265, *1264–1265*
  male reproductive system tumors 1313–1314
  ocular adnexal tumors 1262
  prognosis 1351–1352
  signalment 1347
  staging 1348, 1352, **1352**
  treatment 1348–1351, *1350*
melanotroph cell marker 51
MEN *see* multiple endocrine neoplasia
menace response 736–737
meningioma 761, 779, 1267
meningitis 781–782
meningoencephalitis and meningomyelitis 795–801
  diagnosis 797–799
  epidemiology 796–797
  etiology/pathophysiology 795–796, **796**
  history and clinical signs 797
  prognosis 801
  signalment 797
  treatment 799–801
meningoencephalitis of unknown etiology (MUE) 799
meningoencephalitis of unknown origin (MUO) 780–781, 799
mentation *see* neurologic assessment
Merkel cell tumors 1355
mesenchymal tumors *see* sarcomas
mesenteric fat necrosis 492, *492*
mesenteric lymphangiography 342–343
mesenteric portovenography 672
mesothelial cells 334
mesothelioma *339*, 1272–1275
metabolic bone diseases 1521–1528
  calcium and phosphorus physiology 1521–1522
  fibrous osteodystrophy 1522–1524
  osteoporosis 1527–1528
  rickets and osteomalacia 1524–1527
metabolic diseases 677–683
  amyloidosis 680–681
  copper storage diseases 681–683
  cutaneous manifestations of systemic disease 1481–1484
  forebrain disorders 776–778
  hepatic lipidosis secondary to diabetes mellitus 678
  hepatic lipidosis/steatosis in cats 678–680
  liver changes due to anemia and shock 680
  liver in hyperthyroidism 678
  myelopathy 820
  oral cavity and salivary glands 544
  vacuolar hepatopathy and liver changes in Cushing disease 677–678
  vestibular disease 792
  see also individual disorders
metaphyseal vessels 1513–1514
metastases
  airway and lung cancers 1277, 1279
  approach to the cancer patient 1199
  biology of cancer and cancer genetics 1207, 1210
  bone and joint tumors 1328–1329, 1331
  exocrine pancreatic cancer 1294–1295
  gynecologic cancers 1320
  hemangiosarcoma 1340–1342
  hepatobiliary disease 668, *668*
  hepatobiliary tumors 1304
  intestinal cancers 1287, 1292
  liver disease 686
  male reproductive system tumors 1312–1314
  mammary cancer 1322–1324
  mast cell tumors 1360–1362
  melanoma 1347, 1351–1352
  oral tumors 1255
  pancreatic endocrine tumors 1298–1299
  paraneoplastic syndromes 1222
  soft tissue sarcomas 1338

methicillin-resistant (MR) staphylococci 1059, 1467–1468
methylxanthine bronchodilators 301
metronomic chemotherapy
  approach to the cancer patient 1203
  biology of cancer and cancer genetics 1209
  cardiac neoplasia 1274
  hemangiosarcoma 1344
  male reproductive system tumors 1312
  soft tissue sarcomas 1336–1337
MG *see* myesthenia gravis
MGCS *see* Modified Glasgow Coma Scale
MGUS *see* monoclonal gammopathy of unknown significance
MH *see* malignant hyperthermia
MHC *see* major histocompatibility complex; myosin heavy chain
MI *see* mitotic index
MIC *see* minimum inhibitory concentration
microarray-based technology, biology of cancer and cancer genetics 1207
Microbial Threats to Health: Emergence, Detection, and Response (IoM) 3
microcirculation 405
microhepatica 661, *662*
micrometastatic disease 1329, 1331
microscopic agglutination test (MAT) 946–948
microscopic examination *see* cytology; histology/histopathology
microspora 1026
microvascular dysplasia (MVD) 713–720
  classification and anatomy 713–714
  diagnosis 716
  etiology 713
  history and clinical signs 716
  hypoglycemia 105
  pathophysiology 714–715, **714**
  portal hypertension 715
  prognosis 719–720
  signalment 715
  therapeutic decision making 719
  treatment 717–720
micturition and associated disorders 1181–1188
  anatomy and physiology 1181, *1182*
  detrusor atony 1186
  detrusor hyperreflexia/overactive bladder 1186
  detrusor urethral dyssynergy 1186–1187
  dysautonomia 1188
  emptying disorders 1186–1188
  lower motor neuron bladder 1184–1186
  neurogenic functional urethral obstruction 1187
  storage disorders 1181–1186
  urethral sphincter mechanism incompetence 1182–1184, *1184*, **1185**
migrating motor complex (MMC) 565
mineralocorticoids 86
minichromosome maintenance-7 (MCM-7) 51
minimum dermatology database 1438
minimum inhibitory concentration (MIC) 845, 1192
Minnesota Urolith Center (MUC) 1127–1132
mirror-image artifacts 663, *663*
mites *see individual diseases*
mitotic index (MI) 7–8
mitral valve insufficiency 246, 251, 305
mitral valve regurgitation 147–148, *159*, 246
mitral valve stenosis (MVS) 234, 237
mixed/compound uroliths 1143–1144
mixed venous oxygen saturation 411–412
MLO *see* multilobular osteochondrosarcoma
MM *see* multiple myeloma
MMC *see* migrating motor complex
MMM *see* masticatory muscle myositis
MMP *see* matrix metalloproteinases; mucous membrane pemphigoid
MMVD *see* myxomatous mitral valve disease
mobility 352, 1560, *1560*
Modified Glasgow Coma Scale (MGCS) 455, **456**, 751–752, **752**, 758
modified live vaccines 1569
MODS *see* multiple organ dysfunction syndrome
molecular diagnostics
  actinomycosis 978
  bacterial infections 844–845
  fungal infections 846–847
  mycobacteriosis 982
  nocardiosis 979
  protozoal and arthropod-borne infections 843
  viral infections 844
  see also genetics and genetic testing; *individual techniques*
monoclonal gammopathy of unknown significance (MGUS) 1244–1245
monoclonal theory 50–51
Monro–Kellie hypothesis 749–750
morulae 909–910
motilin-like drugs **575**, 579
motility disorders 563–581
  associated diseases 570–572, 576
  causes 563–564, 567
  clinical signs 563, 565–567, 570, 574–576
  diagnostic tests 564–569, *566*, **568**, 572–574, **573**, 576–577
  dysautonomia and other neuromuscular diseases 570
  esophagus 563–565
  intestinal pseudoobstruction 571
  large intestine 574–579
  physiology 563, 565, 569, 574
  postoperative ileus and short bowel syndrome 570–571
  prokinetics 574, **575**, 579–580
  secondary small intestinal hypomobility 571–572
  small intestine 569–574
  stomach 565–569
  treatment 565, 569, 574, **575**, 577–579, **578**
mousses 1398
movement disorders 766–771
  diagnosis 770–771
  etiology/pathophysiology 766–770
  fasciculations and myokimia 769
  history 766
  hyperkinetic movement disorders 768–769, **768**, *771*
  treatment 771
  tremor syndromes 769–770
MPN *see* myeloproliferative neoplasms
MR *see* methicillin-resistant
MRI *see* magnetic resonance imaging
MUC *see* Minnesota Urolith Center
mucoceles 721, *722*, 724

mucocutaneous pyoderma 1464, *1464*
mucosa-associated lymphoid tissue (MALT) 1287
mucous membrane pemphigoid (MMP) 542, 1428
mucous membranes 121
MUE *see* meningoencephalitis of unknown etiology
multicat environments *see* kennels and multicat environments
multidrug-resistant (MDR) staphylococci 1467–1468
see also nocosomial and multidrug-resistant infections
multilobular osteochondrosarcoma (MLO) 1327, 1332
multiple endocrine neoplasia (MEN) 1297
multiple myeloma (MM) 1241–1246, **1243**
multiple organ dysfunction syndrome (MODS) 952
MUO *see* meningoencephalitis of unknown origin
mural masses 519
murmurs
canine myocardial disease 255
cardiovascular disease 120, 123–124, **124–125**
feline myocardial disease 270–271, 273
pleural effusion 335
respiratory pattern-based approach to dyspnea 292
valvular heart disease 247
muscle fasciculations 769
muscle size/tone 732–735
muscle weakness 82, 120–121
muscular contractions 574
muscular dystrophy 570
MVD *see* microvascular dysplasia
MVS *see* mitral valve stenosis
mycobacteriosis 980–984
diagnosis 982, *982*
epidemiology 980–981, **981**
etiology/pathophysiology 980
history and clinical signs 982, *982*
public health implications 983–984
signalment 981
treatment and prognosis 982–983, **983**
Mycoplasma spp. 1035, 1037
hemotropic *Mycoplasma* 927–930
nonhemotropic *Mycoplasma*, *Ureaplasma*, and L-form bacteria 931–935
mycotic meningoencephalitis 784
mycotoxin toxicity 441
mydriasis 824
myelodysplastic syndromes (MDS) 1229–1230
diagnosis 1230
epidemiology 1229
etiology/pathophysiology 1229
history and clinical signs 1230
signalment 1229
treatment and prognosis 1230
myelography 797–798, 819
myeloid neoplasia 1225–1229
acute myeloid leukemia 1225–1227
basophilic/eosinophilic leukemia and essential thrombocytopenia 1228–1229
chronic myelogenous leukemia 1227–1228
myeloproliferative neoplasms 1227–1229
polycythemia vera 1228
myelopathy 815–822
acute spinal cord dysfunction 818–819
anomalies 820
clinical signs 815–818, **816–817**
degenerative myelopathy 820
diagnostic approach 819–820
differential diagnosis **816**, 820–822
general proprioceptive ataxia 816
history 815
hyperesthesia 818
inflammatory disease 821
loss of nociception 818
metabolic disease 820
neoplasia 820–821
paresis/plegia 816–817, 821
pathophysiology 815
postural abnormalities 817–818
spinal reflex abnormalities 818
trauma 821
treatment 822
vascular occlusive disorders 821–822
myeloproliferative neoplasms (MPN) 1227–1229
myesthenia gravis (MG) 803–806
acquired myesthenia gravis 804–805
clinical presentation 803–804
congenital myesthenia gravis 805
esophageal disorders 558–560, 564
paraneoplastic syndromes 1220–1221
seronegative myesthenia gravis 805–806
treatment 806
myocardial disease
arrhythmogenic right ventricular cardiomyopathy 263–265, *263*, 267, 269–272
arterial thromboembolism 269
canine 253–265
diagnosis 255–259, *255–257*, **258**, 264–265, 270–272, *271–272*
dilated cardiomyopathy 253–262, *255–257*, **258**, **260**, 267, 269–271
epidemiology 254, 263–264, 269–270
etiology/pathophysiology 253–254, 263, *263*, 267–270, *268*
feline 267–274
history and clinical signs 254–255, 264, 270
hypertrophic cardiomyopathy 265, 267–273
prognosis 262, 265, 273
restrictive cardiomyopathy 267, 269–270
signalment 254, 264, 270
treatment 259–262, **260**, 265, 272–273
unclassified cardiomyopathy 267, 270
myocardial hemangiosarcoma 1340, 1344
myocarditis 414, 859
myoclonus 769
myocytes 181
myokymia 460, 769
myopathies 811–814
acute respiratory failure 382
diagnosis 812–813
epidemiology 811
etiology/pathophysiology 811
history and clinical signs 811–812
prognosis 813
signalment 811, **812**
treatment 813
myosin heavy chain (MHC) isoform 181
myotonia 768
myrdiasis 753

myxomatous mitral valve disease (MMVD) 245–250
cardiogenic shock 414
cardiovascular disease 119, 122–124
classification/staging **247**
diagnosis 247–248, *247*
epidemiology 246
etiology/pathophysiology 245–246
heart failure 189–190, 193–194
history and clinical signs 246–247
prognosis 248, *248*
treatment 248–250

n

nAChR *see* nicotinic acetylcholine receptors
nasal lymphoma 1237, 1239
nasal mycotic rhinitis 1485, *1485*
nasal tumors 1256–1258
diagnosis/staging 1257, **1257**
epidemiology 1257
etiology/pathophysiology 1256–1257
history and clinical signs 1257
prognosis 1258
signalment 1257
treatment 1257–1258
nasoesophageal/nasogastric feeding tubes 452, 1097–1098
nasopharyngeal polyps 791, *1477*
NC *see* neutrophilic cholangitis
N-cadherin 1210
NDI *see* nephrogenic diabetes insipidus
necrosis
esophageal disorders 562
oral cavity and salivary glands 544, *545*
pancreatitis 593
surgical, traumatic, and bite wound infections 1031
venomous snake bites 463
necrotizing leukoencephalitis (NLE) 780–781, 799–801
necrotizing meningoencephalitis (NME) 780–781, 795, 799–801
negative contrast agents 470, 481
neonatal hypoglycemia 106
neoplasia *see* malignancies and neoplasia
Neorickettsia helminthoeca see salmon poisoning disease
neosporosis 1005–1006
diagnosis 1006
epidemiology 1005
etiology/pathophysiology 1005
history and clinical signs 1005–1006, *1006*
signalment 1005
treatment and prognosis 1006
neostigmine bromide 806
Neotrombicula autumnalis 1459–1460
nephritic syndrome 1103
nephritis 942, 943
nephrogenic diabetes insipidus (NDI) 65–66, **66**, 68
nephroliths 1124, 1149–1156
nephrotoxicity
acute kidney injury **1090**
antifungal therapy 1049
antimicrobials 1041, 1044
neuroendocrine tumors 1304, 1306, 1355
neuroendocrinology 35–41
adenohypophysis and intermediate lobe 35–36
anatomy and physiology 35–40
glycoprotein hormones 36–38
hypothalamic-pituitary hormones and their primary functions **37**
hypothalamus 35, *36*, 41
oxytocin 40
pituitary gland 35–41, *36*
proopiomelanocortin-derived peptides 38–39
regulation of hormone secretion 41
regulation of the neuroendocrine system 40, *40*
somatomammotropic hormones 38
vascular supply 41
vasopressin, antidiuretic hormone, arginine vasopressin 39
neurogenic functional urethral obstruction 1187
neurogenic pulmonary edema 388–389
neurogenic shock 818
neurohypophysis 39–40
neurologic assessment 729–739
anatomic diagnosis 729–730
botulism 969
components of the neurologic examination 731–739
cranial nerves 735–739
critical care setting 347, 350
differential diagnosis 730
feline leukemia virus 879
fungal infections 992
gait and posture 731–732
gastritis and gastric ulceration 551
head trauma 751–752, **752**, 758
muscle size/tone and spinal reflexes 732–735
myelopathy 815–816, **817**, 818–819, 821
portosystemic shunts and microvascular dysplasia 714, 718
postural reactions 732–733
record keeping 730
sensorium/mental attitude 731
shock 406
trauma and burns 448
neurologic disease 883–884, 1488
neuromuscular disease 570, 770
neuromuscular junction (NMJ) diseases 803–809
anatomy and physiology 803
black widow spider envenomation 808
drug-induced neuromuscular blockade 808
myesthenia gravis 803–806
postsynaptic disorders 808
presynaptic disorders 807–808
snake envenomation 809
neuroophthalmology 823–828
amaurosis 823
anisocoria 824
cavernous sinus syndrome 827–828
dysautonomia 828
facial nerve paralysis 826
Horner syndrome 827, *827*
internal and external ophthalmoplegia 824–825, *825*
optic neuritis 823, *824*
trigeminal nerve deficit 825–826, *826*
neurotoxicity
antimicrobials 1046
botulism 968–970
neuromuscular junction diseases 807
neurotrophic/neuroparalytic keratitis 825–826, *826*
neutraceuticals 1344
neutrophilic cholangitis (NC) 687–690, 693
New York Heart Association (NYHA) 177–178

NFkappaB *see* nuclear factor kappa B
nicotinic acetylcholine receptors (nAChR) 803–807
NICTH *see* nonislet tumor-induced hypoglycemia
nitric oxide
  pulmonary hypertension 225
  pulmonary thromboembolism 320
  septic shock 423
nitrogen wash-out 325
NLE *see* necrotizing leukoencephalitis
NME *see* necrotizing meningoencephalitis
NMJ *see* neuromuscular junction diseases
nocardiosis 979–980
  diagnosis 979
  epidemiology 979
  etiology/pathophysiology 979
  history and clinical signs 979
  public health implications 980
  signalment 977, 979
  treatment and prognosis 979–980
nocosomial and multidrug-resistant infections 1057–1062
  antimicrobials 1045–1047, 1060
  cleaning and disinfection 1061
  colonization versus infection 1061
  concepts and definitions 1057
  hand hygiene and contact precautions 1061
  identification of hospital-acquired infections 1057
  management 1060–1062, **1060**
  pathogens of concern 1059–1060
  patient housing 1061
  presentations and risk factors 1058
  zoonotic infections 1061–1062
nodular dermatofibrosis 1489
nodules *1384*, *1466*
nonhemotropic *Mycoplasma*, *Ureaplasma*, and L-form bacteria 931–935
  abscesses and cellulitis in cats 934
  arthritis in cats/dogs caused by mycoplasmas 933
  CNS *Mycoplasma* infections in cats/dogs 933
  diagnosis 934, *934*
  epidemiology 931–932
  etiology 931, **932**
  history and clinical signs 932–934
  ocular *Mycoplasma* infections in cats 932–933
  public health implications 934
  respiratory *Mycoplasma* infections in cats/dogs 933
  signalment 932
  treatment 934
  urogenital *Mycoplasma* infections in dogs 933
non-immune complex-mediated glomerulonephritis (non-ICGN) 1101
noninfectious vaccines 1568
nonislet tumor-induced hypoglycemia (NICTH) 106–107
nonmaleficence principle 1561–1563
nonmelanoma skin cancers 1353–1357
  diagnosis 1355–1356
  epidemiology 1353–1355
  etiology/pathophysiology 1353
  history and clinical signs 1355
  prognosis 1357
  signalment 1355
  treatment 1356–1357
nonparametric analysis 10, **11**, 25
nonpyogenic hypothermia 295
nonregenerative normocytic normochromic anemia 1241–1242
nonsteroidal antiinflammatory drugs (NSAID)
  developmental orthopedic diseases 1540, 1542–1545, 1548–1550
  endoscopy 513, 518–519
  fever 435–436
  gastritis and gastric ulceration 549–550, 552–553
  intestinal cancers 1287, 1291
  nonmelanoma skin cancers 1356–1357
  osteoarthritis 1533
  septic shock 424–425
  skeletal development and homeostasis 1518
  toxic diseases of the liver 684
  trauma and burns 452
  venomous snake bites 464
NT-proBNP *see* B-type natriuretic peptide
nuclear factor kappa B (NFkappaB) 31
nuclear scintigraphy *see* scintigraphy
nucleoside analogs 875
nursing care
  critical care setting 352
  mechanical ventilation 398–400, 402
  surgical approaches to thoracic disease 329
  trauma and burns 454–455
nutrient artery 1513
nutrition *see* diet and nutrition
NYHA *see* New York Heart Association
nystagmus 738, 791

O

OA *see* osteoarthritis
OAB *see* overactive bladder
obesity
  cardiovascular disease *128*
  diabetes mellitus 93–94
  osteoarthritis 1532–1533
obstipation 612–613
obstructive uropathy *see* ureteral obstruction; urethral obstruction
OC *see* osteochondrosis
OCD *see* osteochondrosis dissecans
ocular adnexal tumors 1261–1264
  diagnosis 1262
  eyelids, third eyelid, conjunctiva, and cornea 1261–1262, *1262*
  history and clinical signs 1262
  limbal/epibulbar melanoma 1263–1264
  prognosis 1263, 1269
  secondary orbital tumors 1269
  treatment 1262–1263
ocular decontamination 441
ocular *Mycoplasma* infections 932–933
ocular posttraumatic sarcoma 1266
oculocephalic reflex 753
odds/odds ratios 15–16, 22
odontogenic tumors and cysts 538–539
ODS *see* osmotic demyelination syndrome
OER *see* oxygen extraction ratio
OG *see* osmole gap
ointments 1398, 1469
olfactory glial cell transplantation 746
oligodendrogliomas 779–780
oliguria 1177–1178
omega 3 fatty acids *see* polyunsaturated fatty acids

OMM *see* oral malignant melanoma
oncotic pull 349
One Health 3–5
  animal domain 4
  factors driving One Health 3
  human domain 3–4
  role for companion animal experts 4
open cardiac massage 370–371
OPG *see* osteoprotegerin
opioid analgesics 410, **410**
opossums 892
optic neuritis 823, *824*
oral cavity and salivary glands 533–546
  burns 544, *545*
  eosinophilic granuloma 541–542, *541*
  etiology/pathophysiology 533, **533**
  foreign bodies 542
  gingivitis and periodontitis 533–536, *535*
  healthy oral tissues and glands 533
  immune-mediated and autoimmune diseases 542–544, *543*
  malignant melanoma 539
  mechanical ventilation 400
  metabolic disease 544
  odontogenic tumors and cysts 538–539
  salivary gland disease 545–546
  squamous cell carcinoma 539–541, *540*
  stomatitis 536–538, *537–538*
oral malignant melanoma (OMM) 1347–1348
oral nitrates 193
oral rabies vaccines (ORV) 896
oral tumors 1253–126
  diagnosis/staging 1254, **1254**
  epidemiology 1253
  etiology/pathophysiology 1253
  history and clinical signs 1254
  prognosis 1255–1256
  signalment 1254
  treatment 1254–1255
orbital and optic nerve tumors 1267–1269
  diagnosis 1268, *1268*
  history and clinical signs 1267–1268
  primary orbital tumors 1267
  treatment 1268–1269
organophosphate toxicity 388, 808
oropharyngeal dysphagia 473–474, 557
Ortoloni sign 1539
ORV *see* oral rabies vaccines
OSA *see* osteosarcoma
oscillometry (OSC) 221–222
osmolality 65, 440, 1070–1076
osmolarity 65
osmole gap (OG) 440
osmotic demyelination syndrome (ODS) 1073
osteoarthritis (OA) 1529–1536
  developmental orthopedic diseases 1534–1544
  diagnosis 1531, *1532*
  epidemiology 1530
  etiology/pathophysiology 1529–1530, *1530*
  exercise and activity modification 1533–1534
  history and clinical signs 1531
  pharmacologic/nonpharmacologic agents 1534–1535
  prognosis 1536
  signalment 1530–1531
  treatment: multimodal management pyramid 1531–1536, *1533*
  weight control 1532–1533
osteoblasts 1512, 1521
osteocalcin 1512
osteochondrosis dissecans (OCD)
  elbow dysplasia 1542–1544
  hock joint 1544–1545
  shoulder joint 1542
  stifle joint 1544
osteochondrosis (OC) 1540–1542
  epidemiology 1542
  etiology/pathophysiology 1541–1542
  manifestations **1541**
osteoclasts 1512–1513, 1521
osteolytic bone lesions 1242
osteomalacia *see* rickets and osteomalacia
osteomyelitis 921, *923*
osteonectin 1512
osteopontin 1512
osteoporosis 1244, *1244*
osteoprotegerin (OPG) 1514–1515, *1515*, 1521–1522
osteosarcoma (OSA) 1327–1332
OT *see* oxytocin
otic cytology 1391–1392
otitis externa 1471–1476
  cutaneous adverse food reactions 1419, *1420*
  diagnosis 1473–1474, *1474–1475*, **1475**
  etiology/pathophysiology 1471, *1472*, **1472**
  history and clinical signs 1472–1473, **1472–1473**, *1473–1474*
  signalment 1471–1472
  treatment and prognosis 1474–1476, *1476*, **1476**
  vestibular disease 791, 792
otitis media 1477–1479
  diagnosis 1477–1478, *1478*
  etiology/pathophysiology 1477
  history and clinical signs 1477
  signalment 1477, *1477*
  treatment and prognosis **1477**, 1478–1479, **1479**
  vestibular disease 791, 792
Otobius megnini 1460
Otodectes cynotis 1471, 1474
ototoxicity 1041
ovarian tumors 1319–1320
ovariohysterectomy 1318, 1321–1324
overactive bladder (OAB) 1186
over-the-needle catheters 355
oxalate urolithiasis 1093, 1124–1127, *1126*, 1137–1139
Oxalobacter formigenes 1126
oxygen extraction ratio (OER) 411–412
oxygen supplementation
  acute respiratory failure 389–390, **390**
  cardiogenic shock 417
  critical care setting 350
  feline bronchial asthma 300
  head trauma 756
  heart failure 197
  hypothermia 433
  respiratory pattern-based approach to dyspnea 290–291, 294
  shock 408
  surgical approaches to thoracic disease 329
  trauma and burns 450
oxygen toxicity 401
oxytocin (OT) 40, 41

p

p53 75–76, 1206–1207
PAA *see* pancreatic acinar atrophy
PAC *see* plasma aldosterone concentration
pacemakers
  cardiogenic shock 419–420
  supraventricular arrhythmias 208, 210–212, *210*
pain and pain management
  approach to the cancer patient 1203
  critical care setting 351–352
  end-of-life care 1555–1556, 1558–1559, *1559*
  feline inflammatory liver disease 690
  gallbladder and extrahepatic biliary ducts 723
  myelopathy 818
  oral cavity and salivary glands 537–538, 544
  pancreatitis 597, 599, 606
  paraneoplastic syndromes 1220
  pleural effusion 335
  rectoanal diseases 613–614
  shock 406, 410, **410**
  spinal cord injury 745, **745**
  surgical approaches to thoracic disease 326, 328
  trauma and burns 450–452
  urethral obstruction 1114
  venomous snake bites 463–464
palliative care *see* end-of-life care
palliative radiation therapy (PRT)
  approach to the cancer patient 1203–1204
  bone and joint tumors 1331
  nasal tumors 1258
  soft tissue sarcomas 1336
palpation
  cardiovascular disease 122, *122*
  pleural effusion 335
  rectoanal diseases 609, 610, 615
  trauma and burns 448–449
palpebral fissure 737
pANCA *see* perinuclear antineutrophilic cytoplasmic antibodies
pancreatic acinar atrophy (PAA) 584, 608
pancreatic elastase (PE-1) 594
pancreatic endocrine tumors 1297–1301
  diagnosis 1298–1300
  epidemiology 1297, 1299–1300
  etiology/pathophysiology 1297, 1299–1300
  gastrinoma 1300
  glucagonoma 1299–1300
  history and clinical signs 1297, 1299–1300
  insulinoma 1297–1299
  prognosis 1298–1300
  signalment 1297, 1299–1300
  treatment 1298–1300
pancreatic enzyme supplementation 586–588
pancreatic fecal elastase 586
pancreatic lipase deficiency 584–586
pancreatic secretory trypsin inhibitor (PSTI) 591
pancreatitis
  acute pancreatitis 591–599, 601–602
  biopsy and histology 604
  canine 591–600
  characterization in cats 602
  chronic pancreatitis 584, 591–594, 599–602, 607–608
  complications 608
  cytology and histology 596–597
  diagnosis 593–597, *598*, 602–605
  epidemiology 592
  etiology/pathophysiology 591–592
  exocrine pancreatic insufficiency 584
  feline 601–608
  history and clinical signs 592–593, **593**, *594*, 601–602, **602**
  hospitalization 606
  imaging 594, *594*, *596*, 605
  interpretation of specialized tests 604–605
  motility disorders 572
  outpatient management 607–608
  pancreas-specific biochemistry 594, 604–605, 608
  physical examination 601–602
  prognosis 600
  routine laboratory tests 593, 602–603
  speciality diagnostic tests 603–605
  specific pancreatic lipase test 603–605, 608
  treatment 597–600, 606–608, **607**
pancytopenia 1219
panniculitis 1487
panosteitis 1549
papillary squamous cell carcinoma 540
papillomas 1261
papillomaviruses (PV) 861–863
  clinical signs 862, **862**
  diagnosis 862–863
  epidemiology 861
  etiology/pathophysiology 861
  nonmelanoma skin cancers 1354, 1357
  prevention 863
  public health implications 863
  signalment 862
  treatment and prognosis 863
papules
  approach to the dermatologic patient *1383*
  atopic dermatitis *1404*, *1406*
  miscellaneous skin diseases *1499*
paradoxical breathing 335
paralytic ileus 497
parametric analysis 10, **11**, 25
paraneoplastic syndromes 1217–1222
  anemia/thrombocytopenia 1219–1220
  cutaneous manifestations of systemic disease 1488–1490
  hypercalcemia 1217–1218
  hypertrophic osteopathy 1220
  hypoglycemia 1218
  myasthenia gravis 1220–1221
  paraneoplastic alopecia 1221–1222, 1293, 1433, 1489, *1489*
  paraneoplastic exfoliative dermatitis 1488–1489
  paraneoplastic pemphigus 1490
  superficial necrolytic dermatitis 1221
paraprostatic cysts 1160–1161, *1161*
parasitic infections
  endoscopy 519
  feline bronchial asthma 298
  forebrain disorders 783–784
  gallbladder and extrahepatic biliary ducts 721, 722, 725
  gastritis and gastric ulceration 550

parasitic infections (*cont'd*)
otitis externa 1471, 1473–1474
principles of therapy of dermatologic diseases 1401–1402
rectoanal diseases 615
parasitic skin diseases 1449–1460
cheyletiellosis 1456–1457
demodicosis 1449–1454
Dermanyssus gallinae 1458–1459
Lynxacarus radovsky 1457–1458
pediculosis 1459
scabies 1454–1456
ticks 1460
trombiculosis 1459–1460
parathyroid hormone (PTH)
endocrinology 31–32
metabolic bone diseases 1521–1523
paraneoplastic syndromes 1217
phosphorus homeostasis and disorders 1079–1084
skeletal development and homeostasis 1515
parathyroid hormone-related peptide (PTH-rp) 1217, 1522
parenchymal disease 664–667, *665–666*
parenchymal structure 664
parenteral nutrition (PN) 453
paresis/plegia
myelopathy 816–817, 821
neurologic assessment 731–734
protozoal and protozoa-like infections 1006, *1006*
rabies 893
seizures and movement disorders 770–771
paroxysmal ventricular tachycardia 413–414
PARR *see* polymerase chain reaction for antigen receptor rearrangement
parvoviral enteritis 571
Pasteurella spp. 340
patella luxation (PL) 1546–1547
patent ductus arteriosus (PDA)
cardiovascular disease 123, *135*, 149–151, *160*
congenital heart disease 231, 235–237, 241–244
pulmonary hypertension *228*
pathologic bone resorption 1517–1518
patient preparation/positioning 515, 517, 520, 522–525
Patnaik grading system 1361
patterned alopecia 1436, *1436*
pattern recognition 731
pattern recognition receptors (PRR) 422
PCCL *see* percutaneous cystolithotomy
PCD *see* plasma cell disorders
PCNL *see* percutaneous nephrolithotomy
PCR *see* polymerase chain reaction
PDA *see* patent ductus arteriosus
PDH *see* pituitary-dependent hyperadrenocorticism
PDK4 mutation 253, 259
PE-1 *see* pancreatic elastase
PE *see* pemphigus erythematosus
pediculosis 1459
PEEP *see* positive end-expiratory pressure
PEG *see* percutaneous endoscopic gastrostomy
peliosis hepatis 673
PEM *see* polioencephalomyelopathy
pemphigus complex 1428–1430, *1429*
pemphigus erythematosus (PE) 1430
pemphigus foliaceus (PF) 1429–1430, *1429*
pemphigus vegetans (PV) 1430
pemphigus vulgaris (PV) 542, 1430
penetrating trauma
epidemiology 447–449, 454
oral cavity and salivary glands 542
respiratory pattern-based approach to dyspnea 294
penicillins 1045
penis 1313–1314
percutaneous cystolithotomy (PCCL) 1147–1149, *1148*
percutaneous endoscopic gastrostomy (PEG) tubes 527–529, 560
percutaneous nephrolithotomy (PCNL) 1155
percutaneous thrombogenic coil embolization (PTCE) 718, 720
perforation
esophageal disorders 562
large intestine *501*
small intestine *494*, 497
perfusion
acute respiratory failure 384–385
cardiogenic shock 413
fluid therapy 360–361, 363–364
shock 406
perianal fistulae 613–614, *614*, **615**
pericardial disease 275–285
congenital 275–277, *276*
constrictive pericarditis 284–285
intrapericardial cysts 275
pericardial effusion 277–284, *282–283*
pericardiocentesis 280–284, *283*
peritoneopericardial diaphragmatic hernia 275–277, *276*
pericardial effusion 277–284
cardiac neoplasia 1273
cardiogenic shock 414, 416
diagnosis 278–280, *279–282*
etiology/pathophysiology 277–278
history and clinical signs 278
signalment 278
treatment and prognosis 280–284, *283*
pericardial tamponade 413, 416, 418–419
pericardiocentesis 280–284, *283*
pericarditis 343
perineal reflex 735
perinuclear antineutrophilic cytoplasmic antibodies (pANCA) 634
periodontitis 533–536, *535*
period prevalence 18
periosteal capillaries 1514
periosteal trauma 1517
peripheral arterial pulsations 121–122
peripheral nervous system (PNS) 789–792
peritoneal dialysis 1175–1176
peritoneal-pericardial diaphragmatic hernia *139*
peritoneopericardial diaphragmatic hernia (PPDH) 275–277
diagnosis 275, *276*
epidemiology 275
etiology/pathophysiology 275
history and clinical signs 275
signalment 275
treatment and prognosis 275–277
peritonitis 424–426
persistent atrial standstill 208–211
diagnosis 210, *210*
epidemiology/signalment 209
etiology/pathophysiology 208–209
history and clinical signs 209
treatment and prognosis 210–211
persistent hyperinsulinemic hypoglycemic syndrome 108–109

persistent right aortic arch (PRAA) 562
personal protective equipment (PPE)
fungal infections 988
kennels and multicat environments 1064–1066
leptospirosis 948–949
mycobacteriosis 984
nocosomial and multidrug-resistant infections 1061
yersiniosis 954
PET *see* positron emission tomography
PF *see* pemphigus foliaceus
P:F ratio 379
P-glycoprotein 634
PH *see* portal hypertension; pulmonary hypertension
pharmacocardiology 469
pharyngeal phase dysphagia 474
pharyngeal tumors 1258
pharynx
assessment of pharyngeal function 473–474
gastrointestinal imaging 473–474
normal anatomy and examination technique 473
ultrasonography 473
phlebotomy 1215
phosphate urolithiasis 1129–1130, 1142–1143
phosphaturic mesenchymal tumor, mixed connective tissue variant (PMT-MCT) 1527
phosphorus homeostasis and disorders 1079–1085
acute kidney injury 1097
anatomy and physiology 1079, *1080*
chronic kidney disease 1171, **1171**
clinical signs 1082–1083
epidemiology of hyperphosphatemia 1084
etiology/pathophysiology **1082**, 1084–1085, **1084**
hyperphosphatemia 1083–1085, 1097, 1171, **1171**
hypophosphatemia 1082–1083
laboratory assessment 1081–1082
metabolic bone diseases 1521–1527
regulation of phosphorus 1079–1081, *1080*, **1081**
treatment 1083, 1085
photodynamic therapy 1356
photopheresis 1370
PHPTH *see* primary hyperparathyroidism
physiologic shunting 384–385
pilomatricoma 1355
pituitary–adrenal axis 55
pituitary-dependent hyperadrenocorticism (PDH) 49–63
adrenal-directed therapies 57–61, **58**
baseline diagnostics 53
classification 49, **50**
diagnosis 53–57, **53–54**
diagnosis and treatment 1213–1214
differential diagnosis 55, 56
etiology/pathophysiology 1213
etiology/pathophysiology and epidemiology 49–52
feline acromegaly 45
history and clinical signs 52–53, **52**
metabolic diseases 677–678
pathogenesis 50–52
pituitary-directed therapies **58**, 61–63
prevalence 49–50
prognosis 63
surgical treatment 57, 62–63
treatment 57–63, **58**
pituitary gland 35–41, *36*, 51
pituitary macroadenomas 779
PL *see* patella luxation
plague *see* yersiniosis
plantigrade stance 96, *96*
plaques *1406*, 1504, *1504*
plasma aldosterone concentration (PAC) 91
plasma-based coagulation assays 317
plasma cell disorders (PCD) 1241–1246
diagnosis 1243–1245, *1243–1244*, **1243**
epidemiology 1242
etiology/pathophysiology 1241–1242, *1242*
history and clinical signs 1243
prognosis 1246
signalment 1242–1243
treatment 1245–1246
plasma cell leukemia 1241–1246
plasmapheresis 1370–1371
plasma proteins 649–650
plasma renin activity (PRA) 91
plateletpheresis 1369, 1372
Platynosomum spp. 721
PLE *see* protein-losing enteropathy
pleocytosis 798
pleural effusion 333–344
airway and lung cancers 1279
anatomy and physiology 333–334, **334**
bilothorax 343
canine myocardial disease 255
cardiovascular disease 125
chylothorax 338, 341–343, *342*
clinical signs and physical examination 335, **336**
diagnosis 336–338
evaluation of pleural fluid 337–339, **337**
hemothorax 343
imaging techniques 336–337, 340
monitoring pleural pressure 335, 338–339
pathophysiology of pleural fluid accumulation 334–335, **335**
pulmonary thromboembolism 313
pyothorax **337**, 339–341, *340*
respiratory pattern-based approach to dyspnea 291
specific pleural fluid tests 338
surgical approaches to thoracic disease 326–327, 328, 330
thoracoscopy 339, *339*
transudative and exudative effusions 334, 337–338
pleural filling disorders 382, 387
pleural space 291–292
PLN *see* protein-losing nephropathy
PLR *see* pupillary light reflex
PMI *see* point of maximum intensity
PMT-MCT *see* phosphaturic mesenchymal tumor, mixed connective tissue variant
PN *see* parenteral nutrition
pneumatosis 484, *484*
pneumocolonography 499
pneumocytosis 1020
pneumonia
mechanical ventilation 393, 400
nocosomial and multidrug-resistant infections 1058
respiratory pattern-based approach to dyspnea 292
pneumothorax
head trauma 750–751
mechanical ventilation 401
pleural effusion 338
pulmonary thromboembolism 314
respiratory pattern-based approach to dyspnea 291–292

pneumothorax (*cont'd*)
surgical approaches to thoracic disease 326–327, 330
point-of-care (POC) tests 316, 417, 947
point of maximum intensity (PMI) 124
point source epidemic curves 834, *835*
poisoning *see* acute poisoning
polioencephalomyelopathy (PEM) 782
polycythemia 1214–1215
polycythemia vera (PV) 1228
polymerase chain reaction for antigen receptor rearrangement (PARR) 633, 1232
polymerase chain reaction (PCR/RT-PCR)
actinomycosis 978
acute kidney injury 1093
bacterial infections 845
bartonellosis 920, 923
canine brucellosis 964
canine infectious respiratory disease complex 1036
canine influenza virus 866
canine parvovirus type 2 859
ehrlichiosis and anaplasmosis 910–911
feline coronavirus 874–875
feline immunodeficiency virus 884
feline inflammatory liver disease 690
feline leukemia virus 877, 879–880
feline viral upper respiratory tract disease 888
fungal infections 847
hemotropic *Mycoplasma* 928
leptospirosis 947
Lyme borreliosis 941–942
meningoencephalitis and meningomyelitis 799
nonhemotropic *Mycoplasma*, *Ureaplasma*, and L-form bacteria 934
papillomaviruses 863
protozoal and arthropod-borne infections 843
protozoal and protozoa-like infections 1004, 1006, 1011, 1014–1015, 1017, 1019–1020
Q fever 960
rabies 894
salmon poisoning disease 914
spotted fever and typhus group *Rickettsia* 939
tetanus 968–969
tularemia 957
viral infections 844
Wolbachia pipientis infection 918
polyphagia 94
polyps 616–617, *616*
polyunsaturated fatty acids (PUFA)
atopic dermatitis 1409–1410
chronic kidney disease 1169, 1172
cutaneous manifestations of systemic disease 1487
feline bronchial asthma 303
miscellaneous skin diseases 1497, 1503, 1505
osteoarthritis 1535
polyuria and polydipsia (PU/PD) 65–68
diabetes mellitus 94, 96
diagnosis 66–68
etiology/pathophysiology 65–66, **66**
first-tier diagnostic tests 66–67
gastritis and gastric ulceration 551
history and clinical signs 66
hypoadrenocorticism 67, 86, 88
liver disease 645
physiology of water metabolism 65
portosystemic shunts and microvascular dysplasia 714
rectoanal diseases 609
second-tier diagnostic tests 67
signalment 66
treatment 68, **68**
water deprivation test 67–68
POMC *see* proopiomelanocortin
portal hypertension (PH)
cirrhosis 705, 711
hepatobiliary disease 672–673
pathophysiology 643
portosystemic shunts and microvascular dysplasia 715
portal thrombosis 673
portal venous hypoplasia/microvascular dysplasia (PVH-MVD) 713, 715–717
portosystemic shunts *see* acquired portosystemic shunts; congenital portosystemic shunts
portosystemic vascular anomalies (PSVA) 103, 105
positive end-expiratory pressure (PEEP)
acute respiratory failure 385–386, 388–389, 398
complications 401
fluid therapy 364
head trauma 756
respiratory pattern-based approach to dyspnea 292
settings 396
surgical approaches to thoracic disease 326
positive inotropes
heart failure **187**, 189–190, 194, **195**, 196
septic shock 427
shock 410
positive pressure ventilation (PPV) 320
positron emission tomography (PET) 1210
postclipping hair follicle arrest 1436–1437, *1437*
postoperative ileus 570–571
postural reactions 732–733, 818
see also gait and posture
potassium citrate supplementation 1138
potassium homeostasis and disorders
acute kidney injury 1096–1098
acute respiratory failure 382
chronic kidney disease 1171
dialysis 1177–1178
feline inflammatory liver disease 690
glomerular disease 1104–1105
hyperkalemia 85, 88, 209, *210*, 1096–1098, 1104–1105, 1109–1112, **1112**, 1177–1178
hypoadrenocorticism 85, 88, 90
hypokalemia 90, 382, 690, 1171
supraventricular arrhythmias 209, *210*
urethral obstruction 1109–1112, **1112**
potassium magnesium pyrophosphate urolithiasis 1132
potentiated sulfonamides 1046–1047
power 10, 24
PPDH *see* peritoneopericardial diaphragmatic hernia
PPE *see* personal protective equipment
PPI *see* proton pump inhibitors
PPV *see* positive pressure ventilation
PRA *see* plasma renin activity

PRAA *see* persistent right aortic arch
prebiotics 623–624
precipitation-crystallization theory 1123
precision 8
precordial thump 204
preload 176
prepuce 1313–1314
pressure support ventilation (PSV) 395
prevalence 12–13, 18
preventive nursing care 454–455
primary focal neoplasia 667, *667*
primary hyperparathyroidism (PHPTH) 1082
primary visceral mastocytosis 1359
primitive neuroectodermal tumors (PTEN) 779
PRL *see* prolactin
probiotics 623–626, 637
proctoscopy 616
proinflammatory cytokines 445–446
prokinetics 574, **575**, 579–580, 612
prolactin (PRL) 38, 41
prolapse 617–618, *617*
proliferation markers 51
proliferative signaling 1209
proopiomelanocortin (POMC) 38–39, 52
propagating epidemic curves 835, *835*
prophylactic antimicrobial protocols 1194
prosenchephalon *see* forebrain disorders
prostacyclins 225
prostate tumors 502, *503*, 1312–1313
prostatic cysts 1157–1160
prostatic diseases 1157–1163
  anatomy and physiology 1157, *1158*
  benign prostatic hyperplasia and prostatic cysts 1157–1160, *1159*, **1160**
  paraprostatic cysts 1160–1161, *1161*
  prostatitis and prostatic abscesses 1161–1163, *1162*, **1162**
  squamous metaplasia of prostatic epithelial cells 1163
prostatitis 1161–1163
  diagnosis 1161–1162, *1162*
  etiology 1161
  history and clinical signs 1161
  prognosis 1162–1163
  treatment 1162, **1162**
protein catabolism 650
protein-losing enteropathy (PLE) 627, 630, 632–633, 636–637
protein-losing nephropathy (PLN) 627, 942–943
protein/polypeptide hormones 29
proteinuria
  chronic kidney disease 1165, **1166**, 1168–1170, *1169*
  glomerular disease 1102–1103
  polyuria and polydipsia 66
proton pump inhibitors (PPI)
  esophageal disorders 560–561
  exocrine pancreatic insufficiency 589
  gastritis and gastric ulceration 553
  pancreatitis 599
protoscopy 523–524
protozoal and protozoa-like infections 1003–1021
  cutaneous manifestations of systemic disease 1485, *1486*
  forebrain disorders 783–784
  laboratory diagnosis 839–843
  see also individual agents/diseases
PRR *see* pattern recognition receptors
PRT *see* palliative radiation therapy
pruritus
  allergic skin diseases 1416–1417
  alopecia 1437–1438
  approach to the dermatologic patient 1376
  atopic dermatitis 1403–1412
  bacterial pyodermas 1466
  parasitic skin diseases 1450, 1453–1454, 1457
PS *see* pulmonary valve stenosis
pseudocoprostasis 614–615
pseudohyperparathyroidism 1522
Pseudomonas spp.
  bacterial pyodermas 1465, *1465*
  nocosomial and multidrug-resistant infections 1060
  otitis externa 1472
PSTI *see* pancreatic secretory trypsin inhibitor
PSV *see* pressure support ventilation
PSVA *see* portosystemic vascular anomalies
psychological etiologies 1574
PTCE *see* percutaneous thrombogenic coil embolization
PTE *see* pulmonary thromboembolism
PTEN *see* primitive neuroectodermal tumors
PTH *see* parathyroid hormone
PTH-rp *see* parathyroid hormone-related peptide
ptosis 827, *827*
public health
  actinomycosis 979
  anthrax 974
  bartonellosis 924
  botulism 970
  canine brucellosis 965
  canine distemper virus 853
  canine herpesvirus 856
  canine infectious respiratory disease complex 1037–1038
  canine influenza virus 867
  canine parvovirus type 2 859
  coccidia 1025, 1026
  Ebola virus 902
  ehrlichiosis and anaplasmosis 911–912
  feline coronavirus 875
  feline immunodeficiency virus 885
  feline leukemia virus 881
  feline parvovirus 870
  feline viral upper respiratory tract disease 889
  fungal infections 987–990, 992, 994–995, 997–1000
  hemotropic *Mycoplasma* 929
  infectious disease 833–834, 836
  kennels and multicat environments 1065
  leptospirosis 948–949
  Lyme borreliosis 944
  mycobacteriosis 983–984
  nocardiosis 980
  nonhemotropic *Mycoplasma*, *Ureaplasma*, and L-form bacteria 934
  One Health 3–5
  papillomaviruses 863
  Q fever 960
  rabies 891, 895–897
  salmon poisoning disease 914
  surgical, traumatic, and bite wound infections 1032, 1034
  tetanus 968
  tularemia 957

public health (*cont'd*)
West Nile virus 900
Wolbachia pipientis infection 918
yersiniosis 954
PUFA *see* polyunsaturated fatty acids
pulmonary edema
acute respiratory failure 382, 388–389
canine myocardial disease 254–255, 261
cardiogenic shock 416
feline myocardial disease 268
gastrointestinal imaging 475
heart failure 183
mechanical ventilation 393
pericardial disease 277
pulmonary thromboembolism 313
respiratory pattern-based approach to dyspnea 289, 292–293
valvular heart disease 246
pulmonary function testing 307–308
pulmonary hypertension (PH) *138*, *154*, 225–230
congenital heart disease 241–242
diagnosis 226–227
echocardiography 227, *228–229*
electrocardiography 227, *228*
epidemiology 225
etiology/pathophysiology 225, *226*
heart failure 193–194
history and clinical signs 226
physical examination 226
prognosis 229
pulmonary thromboembolism 313, 319–320
right heart catheterization 227
signalment 226
thoracic radiography 227, *227*
treatment 228–229
pulmonary infarction 313, 316
pulmonary neoplasia *229*
pulmonary parenchyma 292–293, **293**
pulmonary regurgitation 144, 147, *154–155*
pulmonary thromboembolism (PTE) 313–323
acute respiratory failure 386
antithrombic strategies 321–323
cardiac function testing 318–319, *318*
clinical signs 314
computed tomography pulmonary angiography 319, *319*
definitive diagnostic imaging 319–320
diagnosis 314–320
etiology/pathophysiology 313, **314**
heart failure 191–192
initial diagnostics 315–316, *316*
magnetic resonance imaging and clot-labeling techniques 319
management 320–323
mechanical ventilation 393
respiratory pattern-based approach to dyspnea 293–294
risk profiling 316–317, *317*
selective pulmonary angiography 319–320
suggested diagnostic approach/algorithm 314–315, *315*
supportive therapy 320
thrombolysis 320–321
pulmonary valve stenosis (PS) 231, 233–235, *238*, *241*, 243–244
pulmonary vascular resistance (PVR) 227
pulse 405–406, 448
pulse oximetry 327
PU/PD *see* polyuria and polydipsia
pupillary light reflex (PLR) 823–824
pupils 736–737
purine urolithiasis 1128–1129, *1128*
pustules *1384*, *1429*
PV *see* papillomaviruses; pemphigus vegetans; pemphigus vulgaris; polycythemia vera
P-values 8–10, 25
PVH-MVD *see* portal venous hypoplasia/microvascular dysplasia
PVR *see* pulmonary vascular resistance
pyelography 1093
pyloric obstruction 485, *485–486*
pyoderma 1461–1470
classifications and presentations 1461–1467
deep pyodermas 1465–1467, *1465–1467*
etiology/pathophysiology 1461
methicillin-resistant and multidrug-resistant staphylococci 1467–1468
Staphylococcus aureus phage lysate therapy 1470
superficial pyodermas 1463–1465, *1463–1464*
surface pyodermas 1461–1463, *1462–1463*
systemic therapy 1468–1469
topical therapy 1469
treatment 1468–1470
pyogenic granuloma 536, *537*
pyogranulomatous disease 921, *922*
pyothorax **337**, 339–341, *340*, 427
pyrexia
feline inflammatory liver disease 688
gallbladder and extrahepatic biliary ducts 722
respiratory pattern-based approach to dyspnea 292
surgical approaches to thoracic disease 330
pythiosis 999–1000
diagnosis 1000
epidemiology and signalment 1000
etiology/pathophysiology 999–1000
history and clinical signs 1000
public health implications 1000
treatment and prognosis 1000
Pythium spp. 550

q

Q fever 959–961
diagnosis 960
epidemiology 959
etiology/pathophysiology 959
history and clinical signs 960
prognosis 960
public health implications 960
signalment 960
treatment 960
quality of life 1557–1561, *1557*, **1558**, *1559–1561*

r

RAAS *see* renin-angiotensin-aldosterone system
rabies 891–897
clinical signs 893–894
diagnosis 894
epidemiology 891–892
etiology/pathophysiology 891
history 892–893
preexposure/postexposure prophylaxis 896–897
prevention 892–897

prognosis 894
public health implications 891, 895–897
signalment 892
soft tissue sarcomas 1333
surgical, traumatic, and bite wound infections 1034
treatment 894
vaccination-induced vasculitis 1433, *1434*
raccoons 892
radiation therapy (RT)
airway and lung cancers 1278, 1280
approach to the cancer patient 1202–1203
bone and joint tumors 1331
cardiac neoplasia 1274
central nervous system tumors 1250–1252
exocrine pancreatic cancer 1294
feline acromegaly 47
gynecologic cancers 1318–1319
male reproductive system tumors 1312–1313, 1315
mast cell tumors 1362–1363
melanoma 1348
nasal tumors 1257–1258
oral tumors 1254–1256
orbital and optic nerve tumors 1269
plasma cell disorders 1245
soft tissue sarcomas 1335–1337
urinary tract tumors 1308
radioactive iodine therapy 77–78
radiofrequency catheter ablation 217–218
radiography
acute kidney injury 1093
airway and lung cancers 1277–1278
bartonellosis *923*
bone and joint tumors 1328, *1329*, 1331
canine chronic bronchitis 306, *307*
canine inflammatory liver disease 698, 703
canine myocardial disease 256–257, *256*
cardiogenic shock 416
cardiovascular disease 127–134
central nervous system tumors 1248–1249
cirrhosis 708
common abnormal cardiac radiographic patterns 130–132, **133**, *134–139*
congenital heart disease 237, 238, *239*
contrast agents and pharmacoradiology 469–471, *470*, 480–483, *481*, 490–491, *491*, 499
developmental orthopedic diseases 1539–1540, 1543–1548, 1550–1551
dorsoventral view 128–129, *132*
esophageal and stomach cancers 1284
esophageal disorders 558, 561–562
esophagus 474–479, *475–479*
exocrine pancreatic cancer 1293–1294
feline acromegaly 44–45
feline bronchial asthma 298
feline hyperthyroidism 76–77
feline inflammatory liver disease 688
feline myocardial disease 270
fungal infections 993–994, 996
gallbladder and extrahepatic biliary ducts 724
gynecologic cancers 1317–1318
head trauma 750–751, 753, *754*
hepatobiliary disease 659, 660–663, *661–662*
hepatobiliary tumors 1305
hypoadrenocorticism 83–84, 89
large intestine 498–500, *501–505*
lateral views 127–128, *128–130*
leptospirosis 946
lymphomas 1233
male reproductive system tumors 1312–1313
metabolic bone diseases 1523–1524, *1523*, 1526, *1526*
motility disorders 564–565, 568, 572, **573**, 576–577
myelopathy 819
normal thoracic radiography 127–130, *128–130*, **128**, **131**, *132*
osteoarthritis 1531, *1532*
pancreatitis 594, *596*, 605
paraneoplastic syndromes 1218
pericardial disease 275, *276*, 278
pharynx 473
pituitary-dependent hyperadrenocorticism 56
plasma cell disorders 1244, *1244*
pleural effusion 336, 340
prostatic diseases 1161
protozoal and protozoa-like infections 1020
pulmonary hypertension 227, *227*
pulmonary thromboembolism 315–316, *316*
rectoanal diseases 609
respiratory pattern-based approach to dyspnea 292–293, **293**
septic shock 425
small intestine 489–498, *491–493*
spinal cord injury *742–743*, 743
stomach 480–486, *481*, *483–486*, *488*, 497–498
ureteral obstruction 1119, *1120*
urethral obstruction 1110–1111, *1111*, *1114*, *1116*
urinary tract tumors 1308
urolithiasis 1134, *1134–1135*, *1153*, *1156*
valvular heart disease 248
vertebral heart score 128–130, *130*, **131**
radioimmunoassay (RIA) 32–33
radiopharmaceuticals 1203
radioscintigraphy 568–569
randomized masked clinical trials 23–24
RANK-RANKL 1514–1515, *1515*, 1521–1522
rapid slide agglutination test (RSAT) 964
rapid volume expansion 360–361
RBC *see* red blood cells
RCM *see* restrictive cardiomyopathy
reactive oxygen species (ROS) 446
real-time polymerase chain reaction *see* polymerase chain reaction
receptor tyrosine kinase (RTK) 1209
recombinant vector vaccines 1569
record keeping
critical care setting 348
endoscopy 508–510
neurologic assessment 730
rectal examination
micturition and associated disorders 1183
prostatic diseases 1158
urinary tract tumors 1307
rectal prolapse 617–618, *617*
rectal temperature 448

rectoanal diseases 609–620
anal sac adenocarcinoma 609–610
anal sac impaction 610–611
atresia ani and rectoanal strictures 611–612, *611*
constipation, obstipation, and megacolon 612–613, *613*
foreign bodies 615–616
perianal fistulae 613–614, *614*, **615**
polyps 616–617, *616*
pseudocoprostasis 614–615
rectal prolapse 617–618, *617*
rectal tumors 618–620, *619*
tears and trauma 618
recumbent patient care 400
recurrent urinary tract infections 1191–1192
red blood cells (RBC) 350–351
reference ranges 9–10
referral
behavioral problems 1574–1577, *1575*, **1576**
critical care setting 348–349
motility disorders 568–569
reflexes
head trauma 752–753
myelopathy 818
neurologic assessment 732–733, 734–735
refractory head trauma 757–758
refractory heart failure 250
regulatory T cells (Treg) 1208
rehabilitation 455
reinduction chemotherapy 1234
renal disease 1242
renal failure 107
renal function 351
renal hemangiosarcoma 1341
renal lymphoma 1237–1239
renin-angiotensin-aldosterone system (RAAS)
canine myocardial disease 260–261
feline myocardial disease 273
glomerular disease 1103–1105
heart failure 179–180, 186, 188–189, 196–197
shock 404–405
sodium and water homeostasis 1070
systemic hypertension 219, 222
valvular heart disease 245–246
reperfusion 446
RER *see* resting energy requirement
RES *see* reticuloendothelial system
rescue chemotherapy 1234–1235
respiratory auscultation 124–125
respiratory disease
canine distemper virus 851–852
canine infectious respiratory disease complex 1035–1038
feline viral upper respiratory tract disease 887–889
nonhemotropic *Mycoplasma*, *Ureaplasma*, and L-form bacteria 933
respiratory monitoring in critical care 373–380
assessment of the adequacy of alveolar ventilation 376–377, **376**
assessment of the adequacy of oxygenation 377–378
clinical signs of dyspnea 375–376
clinical signs of respiratory distress 373–375, **374**
determination of response to specific or empiric therapies 376
evaluation of gas exchange efficiency 378–379
identifying respiratory distress and dyspnea 373–376
purpose 373
use of pulmonary mechanics to categorize disease 380
resting energy requirement (RER) 453, 599
restrictive cardiomyopathy (RCM)
cardiogenic shock 415
cardiovascular disease 124
feline myocardial disease 267, 269–270
heart failure 190
retained cartilaginous core 1545–1546
reticuloendothelial system (RES) 1049–1050
retinal toxicity 1046
retinoid therapy 1356
retrograde contrast urethrocystography 1158
retrograde transit 567
retroperitoneal hemangiosarcoma 1341
return of spontaneous circulation (ROSC) 365, 368–371
reverberation 664
rhabdomyosarcoma 1272
rhinosporidiosis 999–1000
diagnosis 1000, *1000*
epidemiology and signalment 1000
etiology/pathophysiology 999–1000
history and clinical signs 1000
public health implications 1000
treatment and prognosis 1000
RIA *see* radioimmunoassay
rickets and osteomalacia 1524–1527
diagnosis 1525–1526, *1526*
etiology/pathophysiology 1524
history and clinical signs 1525
inherited rickets 1526–1527
signalment 1525
treatment and prognosis 1526
Rickettsia spp. 250, 937–940
RIFLE *see* Risk Injury Failure End Stage Kidney Disease
right bundle branch block (RBBB) 172–173, *173*
right heart catheterization 227
right-sided congestive heart failure 132
right-to-left shunting 384, 389
right ventricular hypertrophy 132, *134*, *138*, 172, *173*
rinses 1397–1398
Risk Injury Failure End Stage Kidney Disease (RIFLE) 1091
risk ratios 20
RIT *see* rush immunotherapy
Rocky Mountain spotted fever 937–940
ROS *see* reactive oxygen species
ROSC *see* return of spontaneous circulation
ROTEM *see* thromboelastometry
RSAT *see* rapid slide agglutination test
RT *see* radiation therapy
RTK *see* receptor tyrosine kinase
RT-PCR *see* polymerase chain reaction
Rule of 20, 349–352
rush immunotherapy (RIT) 302–303

S

SA *see* sebaceous adenitis
salivary glands *see* oral cavity and salivary glands
salivary staining 1404, *1405*
Salmonella spp. 1060

salmon poisoning disease (SPD) 913–915
diagnosis 914
epidemiology 913
etiology/pathophysiology 913, *914*
history and clinical signs 913–914
prognosis 914
public health implications 914
signalment 913
treatment 914
SAM *see* systolic anterior motion of the mitral valve
sampling and sample size 7, 10, 24
SAPE *see* sentinel acute pancreatitis event
saprophytic mycobacteriosis 980–984
sarcomas
hepatobiliary tumors 1304, 1306
mammary cancer 1323
orbital and optic nerve tumors 1267
soft tissue sarcomas 1333–1338
sarcoplasmic reticulum 175–176, 182
SARS *see* severe acute respiratory syndrome
SAS *see* subaortic stenosis
SBA *see* serum bile acid
scabies 1454–1456
canine 1454–1455
diagnosis 1455–1456
etiology/pathophysiology 1454, *1454*, 1456
feline 1456
history and clinical signs 1454–1456, *1455–1456*
treatment and prognosis 1455–1456
scales
approach to the dermatologic patient *1386*
autoimmune and immune-mediated skin disease *1426*
miscellaneous skin diseases *1496*, 1500–1503, *1501–1502*
scatterplots 12, *13*
SCC *see* squamous cell carcinoma
SCFE *see* slipped capital femoral epiphysis
Schiff–Sherrington posture 818
schistocytes 1219
schistocytosis 317
Schmidt syndrome 113–114
SCI *see* spinal cord injury
scintigraphy
biology of cancer and cancer genetics 1210
bone and joint tumors 1329
cirrhosis 708
gastrointestinal imaging 472–473
hepatobiliary disease 659, 674
motility disorders 568–569
portosystemic shunts and microvascular dysplasia 716, 719
screening tests 10, 1385–1394
scrotal tumors 1313–1314
SD *see* sudden death
sebaceous adenitis (SA) 1495–1498
diagnosis 1496–1497
etiology/pathophysiology 1495
history and clinical signs 1495–1496, *1496*
prognosis 1498
signalment 1495
treatment 1497–1498
sebaceous benign tumors 1354
secondary orbital tumors 1269
secondary uveal neoplasms 1267
sedation
heart failure 197
rectoanal diseases 616
respiratory pattern-based approach to dyspnea 290–291
spinal cord injury 743
surgical, traumatic, and bite wound infections 1031, 1034
trauma and burns 451–452
seizures/epilepsy 759–766
axis 1: seizure phenomenology 759–760
axis 2: seizure type 761
axis 3: etiology 761
axis 4: syndrome 761
axis 5: impairment from epilepsy 761
cardiogenic shock 415
diagnosis 762
head trauma 756–757
history and clinical signs 759–761, **760**
hyperthermia 434
meningoencephalitis and meningomyelitis 801
pathophysiology 759, *760*
portosystemic shunts and microvascular dysplasia 718
treatment 762–766, **767**
see also movement disorders
selection bias 23–24
selective pulmonary angiography 319–320
seminomas 1311–1312
senile osteoporosis 1527
SENL *see* surgically assisted endoscopic nephrolithotomy
sensory neuropathies 1488
sentinel acute pancreatitis event (SAPE) hypothesis 592
sentinel lymph node (SNL) 1210
sepsis/septic shock 421–429
antimicrobial therapy 427–428
diagnosis 425–426
dysregulated immunity 422
epidemiology 424
etiology/pathophysiology 421–424, **422**
feline inflammatory liver disease 690
history and clinical signs 424–425
hypoglycemia 108
innate immunity 421–422
motility disorders 571–572
physiologic consequences 422–424
prognosis 428
response to infection or injury 421–424
resuscitation 426–427
signalment 424
source control 427
supportive care 428
trauma and burns 454
treatment 426–428
septal defects 151, *160*
septal flattening *229*
serology *see* blood chemistry/serology
serotonergic 5-HT_4 agonists **575**, 579
serotonin receptor agonists 302
Sertoli cell tumors 1311
Sertoli-Leydig cell tumors 1319
serum albumin concentration 630–632
serum bile acid (SBA) 652
serum cobalamin concentration 632
serum protein electrophoresis (SPE) 1243–1244, *1243*
severe acidemia 1178
severe acute respiratory syndrome (SARS) 4–5, 1037–1038
severe fibrosing pleuritis 343
severe pulmonic stenosis *138*
sex hormone dermatoses 1483
SGPS *see* sterile granuloma/pyogranuloma syndrome
SH *see* systemic histiocytosis

shampoos
  atopic dermatitis 1408–1409
  bacterial pyodermas 1469
  miscellaneous skin diseases 1497, 1503
  principles of therapy of dermatologic diseases 1397
Shapiro–Wilk test 10
shock 403–412
  blood pressure 405–406, 411
  cellular effects of hypoxia 404
  classification 403, 406–407
  compensatory mechanisms 404–405
  diagnosis 405–406
  etiology 403–404
  lactate 406, 411
  macro- and microcirculation 405
  metabolic diseases 680
  mixed venous or central venous oxygen saturation 411–412
  oxygen delivery 403–405, 407–408
  pathophysiology and effect on organ systems 404–405
  reevaluation and endpoints of resuscitation 410–412
  sensors of cardiovascular homeostasis 404
  sodium and water homeostasis 1076
  trauma and burns 448, 450, 453–454
  treatment 409–410, **410**
  see also cardiogenic shock; septic shock
short bowel syndrome 570–571
short-chain fatty acids (SCFA) 621–623
SIADH *see* syndrome of inappropriate antidiuretic hormone secretion
sialadenosis 545
sialoceles 546
SIBO *see* small intestinal dysbiosis and/or bacterial overgrowth
sick sinus syndrome 207–208
  diagnosis 207, *208*
  epidemiology/signalment 207
  etiology/pathophysiology 207
  history and clinical signs 207
  treatment and prognosis 208, **209**
silicate urolithiasis 1131, 1143
SIMV *see* synchronized intermittent mandatory ventilation
single nucleotide polymorphism (SNP) 43–44
sinonasal aspergillosis 995–997, *996*
sinus bradycardia 205–207
  diagnosis 205, *207*
  etiology/pathophysiology 205
  history and clinical signs 205
  signalment 205
  treatment and prognosis 205–207
SIRS *see* systemic inflammatory response syndrome
six-minute walk test (6MWT) 308
skeletal development and homeostasis 1509–1519
  bone healing after fracture 1518
  bone morphology 1512–1514
  bone pathophysiology 1516–1518
  bone physiology 1514–1516
  complications with fracture healing 1518–1519
  composition of bone 1512–1513
  epiphysis-associated growth 1509, **1510**, 1511–1512
  growth plate-associated growth 1509–1511, **1510**
  inflammation/repair/remodeling response to injury 1516
  intramembranous and endochondrial ossification 1509–1511
  modeling and remodeling of bone 1514–1515, *1515*
  pathologic bone resorption 1517–1518
  periosteal trauma 1517
  reactive new bone formation 1517
  skeletal development 1509, **1510**
  structure of bone 1513
  thermal injury to bone 1516
  vascular injury to bone 1516–1517
  vascular supply to bone 1513–1514
skin scrapes 1391–1393, 1451, 1455, 1457, 1459–1460
skin turgor 361
skull fractures 749, 757–758
SLC2A9 gene mutations 1129
SLC3A1 gene mutations 1130–1131
SLC7A9 gene mutations 1131
SLE *see* systemic lupus erythematosus
sliding hiatal hernia 479, *479*
slipped capital femoral epiphysis (SCFE) 1550–1551
SLO *see* symmetric lupoid onychitis/onychodystrophy
small cell lymphoma 1238
small intestinal dysbiosis and/or bacterial overgrowth (SIBO) 583, 588
small intestine
  adhesions 495–496, *496*
  endoscopy 522–526
  foreign bodies and linear foreign bodies 493–494, *494*
  gastrointestinal imaging 489–498, *490–496*, **492–493**
  herniation 496
  inflammatory disorders 491–492, **492**
  intestinal cancers 1287–1292
  intussusception 494–495, *495*, 571
  motility disorders 569–574
  obstruction/mechanical ileus 492–493, *492–496*, **493**
  paralytic/functional ileus 497
  postoperative appearance 497–498
  radiography 489–498, *491–496*
  tumors of the small intestine 491–492, 495, *496*
  ulceration/perforation 497
  ultrasonography 489–498, *490*, **492**, *495–496*
  volvulus and/or torsion 496–497
small-volume resuscitation 361
SMRA *see* steroid-responsive meningitis-arteritis
snake bites *see* venomous snake bites
SNARE proteins 803
SND *see* superficial necrolytic dermatitis
SNP *see* single nucleotide polymorphism; sterile nodular panniculitis
SNS *see* sympathetic nervous system
sodium and water homeostasis 1069–1077
  acute kidney injury 1092, 1097–1098
  anatomy and physiology 1069–1070, *1070*
  causes/classification of hypernatremia 1074, **1075**
  causes/classification of hyponatremia 1071–1072, **1071**, **1072**
  cirrhosis 710

clinical manifestations of hypernatremia 1074–1075
clinical manifestations of hyponatremia 1072–1073
concepts and definitions 1069
consequences of chronic hypernatremia 1075
consequences of chronic hyponatremia 1073
endocrine manifestations of cancer 1214
fluid therapy 362
forebrain disorders 777–778
heart failure 193
hypernatremia 777–778, 1069, 1074–1076
hypoadrenocorticism 82, 85
hyponatremia 193, 778, 1069, 1071–1074, 1097–1098
management of hypernatremia 1075–1076
management of hyponatremia 1073–1074
osmoregulation and volume regulation 1070–1071
polyuria and polydipsia 65–68
syndrome of inappropriate ADH secretion 1072–1073, **1072**
see also dehydration
sodium bicarbonate infusion 1096
sodium–calcium exchanger 177
sodium–potassium exchanger 179–180
soft tissue sarcomas (STS) 1333–1338
canine 1334–1337
diagnosis 1334
epidemiology 1333
etiology/pathophysiology 1333
feline 1337–1338
history and clinical signs 1334
prognosis 1337–1338
signalment 1334
treatment 1334–1337
solid tumors 1207–1208
solitary osseous plasmacytoma (SOP) 1241–1246
somatomammotropic hormones 38
SOP *see* solitary osseous plasmacytoma
source control 427
SPD *see* salmon poisoning disease
Spec-fPL assay 603–605, 608
speckle tracking echocardiography (STE) **152**, *162*
spinal cord dysfunction 818–819
spinal cord injury (SCI) 741–748
clinical assessment 742–744, *743–744*
instability of the vertebral column 742, *742*
myelopathy 815–822
pathophysiology 741–742, *742*
prognosis 748
trauma and burns 446
treatment 744–747, *745*, **745–746**, *747*
spinal cord neoplasia *see* central nervous system tumors
spinal reflexes 732–733, 818
spinal shock 818
spinning-disc interferometry 910
spirocercosis 319, 1283–1284, 1333
splenectomy 1366
splenomegaly 707
splints 747
sporotrichosis 998–999
diagnosis 999
epidemiology and signalment 998
etiology/pathophysiology 998
history and clinical signs 999
public health implications 999
treatment and prognosis 999
spot-on lotions 1398
spotted fever and typhus group *Rickettsia* 937–940
clinical signs 938–939
diagnosis 938–939
epidemiology 938
etiology/pathophysiology 937–938
laboratory testing 939
signalment 938
sprays 1398, 1469
squamous cell carcinoma (SCC)
esophageal and stomach cancers 1283
male reproductive system tumors 1313–1314
nonmelanoma skin cancers 1354–1356
ocular adnexal tumors 1261–1263, *1262*
oral cavity and salivary glands 539–541, *540*
oral tumors 1253–1256
papillomaviruses 861–863
squamous metaplasia of prostatic epithelial cells 1163
SRD *see* steroid-responsive diarrhea
SRS *see* stereotactic radiosurgery
SRT *see* stereotactic radiation therapy
SSI *see* surgical site infections
stabilization techniques 744–745, *745*, 746–747, **746**, *747*
Staphylococcus spp. 1059
bacterial pyodermas 1461–1465, *1462*, *1465*, 1467–1470
urolithiasis 1136
valvular heart disease 250
S. aureus phage lysate therapy 1470
Starling's law 176, 333–334, **334**, 357, 413
statins 599
statistical analysis 7–16
clinical decision making 25
cumulative incidence 13–14
describing data distributions 10–12, *11–13*
external validity 7–8
hypothesis testing 8–10
incidence odds and incidence odds ratios 15–16
incidence rates 14–15
internal validity 8
measures of association and effect 12–15
parametric versus nonparametric tests 10, **11**
prevalence 12–13
STE *see* speckle tracking echocardiography
stents
ureteral obstruction 1120–1121, *1120*
urethral obstruction 1115–1117, *1116*
urolithiasis 1153–1155, *1153*, **1154**
stereotactic radiation therapy (SRT) 47
stereotactic radiosurgery (SRS)
approach to the cancer patient 1203
bone and joint tumors 1331
central nervous system tumors 1250
sterile granuloma/pyogranuloma syndrome (SGPS) 1446–1447
clinical signs 1446, *1446*
diagnosis 1446–1447
pathogenesis 1446

sterile granuloma/pyogranuloma syndrome (SGPS) (*cont'd*)
signalment 1446
treatment and prognosis 1447
sterile neutrophilic dermatosis 1500
sterile nodular panniculitis (SNP) 1444–1446
clinical signs 1445, *1445*
diagnosis 1445
pathogenesis 1444
signalment 1444
treatment and prognosis 1445–1446
sterilization (reproductive) 964–965
see also cleaning and disinfection
steroid-responsive diarrhea (SRD) 627, 629, 634
steroid-responsive meningitis-arteritis (SMRA) 797–798, 800–801
stomach
chronic gastric outlet/pyloric obstruction 485, *485–486*
computed tomography 488–489
foreign bodies 486–487, *486–487*
gastric dilation 483, *483*
gastric dilation volvulus 483–485, *484*
gastric ulcers 487
gastrography 480–483
gastrointestinal bleeding 489
gastrointestinal imaging 479–489, *481–488*
inflammatory conditions of the stomach and duodenum 487, *488*
motility disorders 565–569
postoperative appearance 497–498
radiography 480–486, *481*, *483–486*, *488*, 497–498
tumors of the stomach 487–489, *488*
ultrasonography 480, *482*, 485–488, *486–488*, 498
stomatitis 536–538, *537–538*
feline immunodeficiency virus 884–885
feline leukemia virus 879
storage disorders
detrusor hyperreflexia/overactive bladder 1186
lower motor neuron bladder 1184–1186
micturition and associated disorders 1181–1186
urethral sphincter mechanism incompetence 1182–1184, *1184*, **1185**
see also copper storage diseases
strabismus 737–738
strain and strain rate imaging **152**, *161*
Streptococcus spp. 250, 1035–1038, 1065–1066
stress 96, 549
strictures
esophageal disorders 478, 530, 561
gastrointestinal imaging 478, 530
rectoanal diseases 611–612
stroke volume 413
struvite urolithiasis 1127–1128, *1127*, *1136*, 1139–1141
STS *see* soft tissue sarcomas
Student's t-test 8–10
SUB *see* subcutaneous ureteral bypass
subaortic stenosis (SAS) 231, 233, 237, 243
subcutaneous fluids 1559, *1559*
subcutaneous ureteral bypass (SUB) 1155–1156, *1156*
subepidermal blistering diseases 1427–1428, *1427*
sublumbar lymphadenopathy 502–503, *503*
subtotal colectomy 613
sudden death (SD)
canine myocardial disease 254
cardiogenic shock 414
leptospirosis 946
sulfonamides
canine hypothyroidism 72–73
coccidia 1024–1025
side-effects and drug–drug interactions 1046–1047
toxic diseases of the liver 684
superficial bacterial folliculitis 1463–1464, *1463–1464*
superficial necrolytic dermatitis (SND) 1491–1493
clinical signs 1491–1492, *1492*
cutaneous manifestations of systemic disease 1483
diagnosis 1492
etiology/pathophysiology 1491
paraneoplastic syndromes 1221
signalment 1491
treatment and prognosis 1492–1493
supraventricular arrhythmias 205–218
anatomy and physiology 205, *206*
atrial fibrillation 212–215, *214*
atrioventricular block 211–212, *212*
differential diagnosis **206**
other forms of supraventricular tachyarrhythmia 215–218, *215*
pacemaker therapy 208, 210–212, *210*
persistent atrial standstill 208–211, *210*
sick sinus syndrome 207–208, *208*, **209**
sinus bradycardia 205–207, *207*
supraventricular tachycardias (SVT) 215–218
canine myocardial disease 263
cardiogenic shock 419
diagnosis 216
epidemiology/signalment 216
etiology/pathophysiology 215–216, *215*
history and clinical signs 216
treatment and prognosis 216–218
surgical biopsy 657
surgically assisted endoscopic nephrolithotomy (SENL) 1155
surgical management
airway and lung cancers 1278, 1280
approach to the cancer patient 1202
bone and joint tumors 1330–1331
cardiac neoplasia 1273
central nervous system tumors 1250
congenital heart disease 243, *243*
developmental orthopedic diseases 1540, 1543, 1545–1548
esophageal and stomach cancers 1285
exocrine pancreatic cancer 1294
feline acromegaly 46
feline inflammatory liver disease 691
fungal infections 1000
gallbladder and extrahepatic biliary ducts 725
gynecologic cancers 1318
head trauma 757–758
hemangiosarcoma 1342–1343
hepatobiliary tumors 1306
hypoadrenocorticism 91

intestinal cancers 1289–1290
male reproductive system tumors 1312, 1314–1315
mammary cancer 1322–1324
mast cell tumors 1362, 1366
melanoma 1348
micturition and associated disorders 1184
nonmelanoma skin cancers 1356
ocular adnexal tumors 1263–1264
oral tumors 1254, 1256
orbital and optic nerve tumors 1268
osteoarthritis 1535
pancreatic endocrine tumors 1298, 1300
papillomaviruses 863
pericardial disease 280–285, *283*
pharyngeal tumors 1258
pituitary-dependent hyperadrenocorticism 57, 62–63
plasma cell disorders 1245–1246
pleural effusion 342–343
portosystemic shunts and microvascular dysplasia 718
prostatic diseases 1162
rectoanal diseases 609–611, 613–614, 616–620
respiratory pattern-based approach to dyspnea 291–292
soft tissue sarcomas 1334–1337
spinal cord injury 746–747, **746**, *747*
thoracotomy 325–330
ureteral obstruction 1120–1121, *1120–1121*
urethral obstruction 1115–1117, *1116*
urinary tract tumors 1309–1310
urolithiasis 1144, 1150–1151
surgical site infections (SSI) 1029–1032
diagnosis 1030–1031, **1030–1031**
epidemiology 1029–1030
etiology/pathophysiology 1029
history and clinical signs 1030
nocosomial and multidrug-resistant infections 1058, 1060
public health implications 1032
signalment 1030
treatment and prognosis 1031–1032
suture-induced urolithiasis 1131, *1131–1132*, 1144
SVT *see* supraventricular tachycardias
swelling 461
symmetric lupoid onychitis/onychodystrophy (SLO) 1505–1506, *1505*
sympathetic nervous system (SNS)
heart failure 179
systemic hypertension 219
valvular heart disease 245–246
synbiotics 623–624
synchronized intermittent mandatory ventilation (SIMV) 394, 396, 401
syncope
canine myocardial disease 255, 264
cardiogenic shock 415
cardiovascular disease 120–121
congenital heart disease 240
valvular heart disease 246
syndrome of inappropriate antidiuretic hormone secretion (SIADH) 1072–1073, **1072**, 1214
synovial cell sarcoma 1327
synoviocentesis 1531
synthetic colloids 359–360, 409
acute kidney injury 1095
glomerular disease 1106
head trauma 755
septic shock 426
systemic histiocytosis (SH) 1442–1443
systemic hypertension (HT) 219–224
classifications 219
diagnosis 221–222
epidemiology 220
etiology/pathophysiology 219–220, **220**
history and clinical signs 221
patient selection and set-up 221
prognosis 223–224
signalment 220–221
target organ damage 219–221, **220**, 223–224
treatment and monitoring 222–223
systemic inflammatory response syndrome (SIRS)
Ebola virus 901
fluid therapy 358
septic shock 421–422, **422**, 425
trauma and burns 445
systemic lupus erythematosus (SLE) 542, 1487
systemic therapy
bacterial pyodermas 1468–1469
miscellaneous skin diseases 1497–1498, 1503
principles of therapy of dermatologic diseases 1399
systemic medications for hormonal disorders 1402
systemic veins 121
systolic anterior motion of the mitral valve (SAM) 265, 268–269

t

T3/T4 *see* thyroid hormones
tachycardia 405, 410, 448
see also supraventricular tachycardias; ventricular tachycardia
tachypnea
cardiogenic shock 416
cardiovascular disease 120
feline bronchial asthma 297
feline myocardial disease 270, *271*
pleural effusion 338
respiratory pattern-based approach to dyspnea 293, 295
target organ damage (TOD) 219–221, **220**, 223–224
TAT *see* tube agglutination test
taurine deficiency
canine myocardial disease 259
heart failure **188**, 192
metabolic diseases 678–679
TB *see* tuberculosis
T-box transcription factor (Tpit) 51
TBSA *see* total body surface area
TBW *see* total body water
TDI *see* tissue Doppler imaging
TEG *see* thromboelastography
telogen defluxion 1437
TEN *see* toxic epidermal necrolysis
tender loving care 352
teratogenicity 1051
testicular tumors 1311–1312, 1488
tetanus/tetany 967–968
diagnosis 968
epidemiology 967
etiology/pathophysiology 967
history and clinical signs 967–968
hyperkinetic movement disorders 768–769
public health implications 968
signalment 967
treatment and prognosis 968

tetracyclines
hemotropic *Mycoplasma* 929
salmon poisoning disease 914
side-effects and drug–drug interactions 1047–1048
tetralogy of Fallot (ToF) 234, 243
tFAST[3] *see* trauma, triage, and tracking
TFAST *see* thoracic focused assessment with sonography for trauma
Th *see* helper T lymphocytes
therapeutic plan 1396
therapeutic plasma exchange (TPE) 1179–1180, 1370–1371
thermoregulation
fever 434–435
heat stroke 435–436
normal thermoregulation 431
see also hyperthermia; hypothermia
thiamine deficiency 780
thiazide diuretics 1138–1139
third eyelid 737, 1261–1262, *1262*
thoracic focused assessment with sonography for trauma (TFAST) 336, 406
thoracocentesis
acute respiratory failure 389
monitoring pleural pressure 335, 339, 343
respiratory pattern-based approach to dyspnea 291–292
thoracoscopy 339, *339*
thoracotomy 325–330
arrhythmias 326, 329
arterial blood gas analysis 328
arterial blood pressure 327
complications 329–330
continual effusion and pneumothorax 326–327, 330, 335, 343
dyspnea 329
electrocardiography 327
fluid therapy 328–329
hypotension 326
hypothermia 326, 329
hypoxemia and hypoventilation 325–326
nursing care 329
oxygen supplementation 329
pain and pain management 326, 328
pathophysiology of thoracotomy 325–327
postoperative management 328–330
postoperative monitoring 327–328
pulse oximetry and end-tidal CO_2 327
thoracotomy tubes and pleural drainage 327, 328, 330, 335, 343
THR *see* total hip replacement
three-dimensional echocardiography **152**
thrombocytopenia
cirrhosis 706
ehrlichiosis and anaplasmosis 903–905, 911
essential thrombocytopenia 1228–1229
paraneoplastic syndromes 1219–1220
plasma cell disorders 1241
pulmonary thromboembolism 317
thromboelastography (TEG) 315, 316–317, *317*
thromboelastometry (ROTEM) 316–317, *317*
thrombolysis 320–321
thrombophlebitis 356
through-the-needle catheters 355
thymoma 559
thyroid hormones (T3/T4)
autoimmune polyglandular syndromes 114
canine hypothyroidism 71–73
diabetes mellitus 97
endocrinology 30–31, *30*, 33
feline hyperthyroidism 78–79
neuroendocrinology 36
thyroid-stimulating hormone (TSH)
autoimmune polyglandular syndromes 114
canine hypothyroidism 71–73
endocrinology 29, 32–33
neuroendocrinology 36, 40, *40*
thyrotropin receptor (TSHR) 76
thyrotropin-releasing hormone (TRH) 40, *40*, 71
thyroxine *see* thyroid hormones
tick-borne diseases
ehrlichiosis and anaplasmosis 903–912
Lyme borreliosis 941–944
neuromuscular junction diseases 807
parasitic skin diseases 1460
protozoal and protozoa-like infections 1011–1018
spotted fever and typhus group *Rickettsia* 937–940
TIMP *see* tissue inhibitors of matrix metalloproteinases
TIO *see* tumor-induced osteomalacia
tissue Doppler imaging (TDI) **152**, *161*
tissue inhibitors of matrix metalloproteinases (TIMP) 182, 245
tissue plasminogen activator (t-PA) 320–321
TKI *see* tyrosine kinase inhibitors
TLI *see* trypsin-like immunoreactivity
TLR *see* toll-like receptors
TMT *see* transient myocardial thickening
TNM *see* tumor-node-metastasis
tobacco smoking 7
ToF *see* tetralogy of Fallot
toll-like receptors (TLR) 422
tooth resorption 14–15
topical decontamination 441
topical therapy
antifungal therapy 1052
atopic dermatitis 1408–1409
bacterial pyodermas 1469
common formulations of topical agents 1397–1399
miscellaneous skin diseases 1497, 1503
principles of therapy of dermatologic diseases 1397–1399
total body surface area (TBSA) 446, 449
total body water (TBW) 1069–1070, *1070*
total hip replacement (THR) 1540
tourniquets 462
toxic diseases
liver 683–684
nonspecific reactive hepatitis due to endotoxins 683
vestibular disease 792–794
see also drug toxicity
toxic epidermal necrolysis (TEN) 1424
toxoplasmosis 1003–1005
diagnosis 1004–1005, *1004*
epidemiology 1003
etiology/pathophysiology 1003
history and clinical signs 1004
signalment 1003
treatment and prognosis 1005
t-PA *see* tissue plasminogen activator

TPE *see* therapeutic plasma exchange
Tpit *see* T-box transcription factor
tracheobronchomalacia 290–291
traction injury 819
transesophageal echocardiography **152**
transient myocardial thickening (TMT) 273
transmissible venereal tumor (TVT) 1314–1315
transsphenoidal hypophysectomy (TSH) 62–63
transtentorial herniation 750, *750*
transtracheal wash (TTW) 307, **309**
transudative effusions 334, 337–338
trauma and burns 445–457
  acute phase response 446
  alopecia 1433
  burns 446–447, 449, 455–457, 544, *545*
  central nervous system trauma 741–758
  coagulation and inflammation 445
  developmental orthopedic diseases 1541
  diagnosis 448–449
  epidemiology 447
  etiology/pathophysiology 445–447
  history and clinical signs 447–448
  intraocular tumors 1266
  ischemia and reperfusion 446
  myelopathy 821
  oral cavity and salivary glands 544, *545*
  primary phase 449–450
  prognosis 455–457, **456**
  rectoanal diseases 618
  respiratory pattern-based approach to dyspnea 294
  secondary phase 450–455
  septic shock 424
  signalment 447
  skeletal development and homeostasis 1516–1519
  surgical, traumatic, and bite wound infections 1029–1034
  systemic inflammatory response 445
  traumatic brain injury/spinal cord injury 446, 455
  treatment 449–455
  vestibular disease 792
  see also wound care
traumatic brain injury 446, 455
traumatic diaphragmatic herniation/avulsion 382
trauma, triage, and tracking (tFAST^3) 291–293, **293**
treatment trials 1394
Treg *see* regulatory T cells
tremor syndromes 769–770
Treppe effect 177
triage
  Animal Trauma Triage Score 455, **456**
  behavioral problems 1572–1574, *1573*
  critical care setting 347
  trauma, triage, and tracking 291–293, **293**
triceps reflex 735
trichoblastoma 1354
trichoepithelioma 1355
trichography 1392, 1438
trichomoniasis 1019–1020, *1019*
Trichophyton mentagrophytes 1428, 1430
trichoscopy 1451, 1457–1458, *1458*
tricuspid regurgitation 227, *228*
tricuspid valve dysplasia (TVD) 231, 234, 237
trigeminal nerve 738–739, 825–826, *826*
triglycerides
  liver disease 650–651
  metabolic diseases 678–679
  pleural effusion 342
  urolithiasis 1127
triiodothyronine *see* thyroid hormones
trombiculosis 1459–1460
  diagnosis 1460
  history and clinical signs 1459–1460, *1460*
  treatment and prognosis 1460
troponin 239–240
trypanosomiasis 1006–1009
  African trypanosomiasis and *T. evansi* 1008–1009
  American trypanosomiasis 1007–1008
  diagnosis 1008–1009, *1009*
  epidemiology 1007–1008
  etiology/pathophysiology 1007
  history and clinical signs 1007–1008
  signalment 1007–1008
  treatment and prognosis 1008–1009
trypsin-like immunoreactivity (TLI) 585–586, 603, 608
TSH *see* thyroid-stimulating hormone; transsphenoidal hypophysectomy
TSHR *see* thyrotropin receptor
TTW *see* transtracheal wash
tube agglutination test (TAT) 964
tuberculosis (TB) 980–984
tularemia 955–957
  diagnosis 956–957
  epidemiology 955–956, *956*
  etiology/pathophysiology 955
  history and clinical signs 956
  public health implications 957
  signalment 956
  treatment and prognosis 957
tumor-induced osteomalacia (TIO) 1527
tumor-node-metastasis (TNM) staging 1200
  hemangiosarcoma 1341–1342, **1342**
  mammary cancer 1322, **1322**, 1324, **1324**
  mast cell tumors **1361**
  melanoma 1352, **1352**
TVD *see* tricuspid valve dysplasia
TVT *see* transmissible venereal tumor
type 1 errors *see* false positives
type 2 errors *see* false negatives
typhlitis 500, *501*
typhus group *Rickettsia see* spotted fever and typhus group *Rickettsia*
tyrosine kinase inhibitors (TKI)
  atopic dermatitis 1411
  biology of cancer and cancer genetics 1209
  cardiac neoplasia 1274
  hemangiosarcoma 1344
  mast cell tumors 1364, 1366

u

UACR *see* urine aldosterone to creatinine ratio
UAP *see* ununited anconeal process
UCCR *see* urine cortisol to creatinine ratio
UCM *see* unclassified cardiomyopathy
UES *see* upper esophageal sphincter
UFH *see* unfractionated heparin
ulceration
  allergic skin diseases *1416*
  approach to the dermatologic patient *1385*
  atopic dermatitis *1406*

ulceration (*cont'd*)
autoimmune and immune-mediated skin disease *1426*
cirrhosis 706, 710–711
cutaneous adverse food reactions *1420*
endoscopy 518–519, *519*
gastritis and gastric ulceration 547–555
liver disease 644
miscellaneous skin diseases 1504–1505, *1504*
oral cavity and salivary glands 536, 541–542
small intestine 497
ultrasonography
acute kidney injury 1093
acute respiratory failure 389
bone and joint tumors 1328–1329
canine hypothyroidism 73
canine inflammatory liver disease 698, 703
cardiogenic shock 419
central nervous system tumors 1248–1249
chronic enteropathies 635
cirrhosis 708, *708*
endocrine manifestations of cancer 1213–1216
esophageal and stomach cancers 1284
esophagus 478
exocrine pancreatic cancer 1294
feline inflammatory liver disease 688–689, *690*
fungal infections 991
gallbladder and extrahepatic biliary ducts 724
gastritis and gastric ulceration 552
gastrointestinal tract 471
glomerular disease 1102–1103
gynecologic cancers 1319
head trauma 751
hepatobiliary disease 659, 663–674, *663*, *665–671*, 673–674, *673*
hepatobiliary tumors 1305
hypoadrenocorticism 83–84, 91
intestinal cancers 1289
large intestine 498–500, *501*, *503*
liver disease 653, 656–657
lymphomas 1233
male reproductive system tumors 1313
mast cell tumors 1360–1361, 1366
motility disorders 568, 572–574
orbital and optic nerve tumors 1268
pancreatic endocrine tumors 1300
pancreatitis 594, *594*, *596*, 605
paraneoplastic syndromes 1218
pericardial disease 275
pharynx 473
pituitary-dependent hyperadrenocorticism 56–57
pleural effusion 336, 340
polyuria and polydipsia 67
portosystemic shunts and microvascular dysplasia 719
prostatic diseases 1158–1161, *1158–1159*, *1161–1162*
rectoanal diseases 619
respiratory pattern-based approach to dyspnea 292–293, **293**
septic shock 425
shock 406
small intestine 489–498, *490*, **492**, *495–496*
spinal cord injury 744
stomach 480, *482*, 485–488, *486–488*, 498
superficial necrolytic dermatitis 1492
ureteral obstruction 1117–1118, *1118*
urethral obstruction 1111
urinary tract tumors 1308–1309
urolithiasis 1135
see also echocardiography; focused assessment with sonography for trauma
ultrasound-guided biopsy 656–657
ultraviolet/sunlight exposure 1354, 1424–1425, 1427
UMN *see* upper motor neuron
unclassified cardiomyopathy (UCM) 267, 270
uncomplicated urinary tract infections 1191, 1193–1194
unfractionated heparin (UFH) 321
United States Department of Agriculture (USDA) 896
ununited anconeal process (UAP) 1543–1544
UO *see* urethral obstruction
UPC *see* urine protein:creatinine ratio
upper airway 289–290, **290**
upper esophageal sphincter (UES) 563–564
upper motor neuron (UMN) 731–735, 816
upper urinary tract (UUT) 1124, 1149–1156, **1152**, *1153*, **1154**, *1156*
urate urolithiasis 1128–1129, *1128*, 1141–1142
Ureaplasma spp. 931–935
uremia
dialysis 1176–1177
oral cavity and salivary glands 544
urethral obstruction 1109
uremic encephalopathy 776–777
ureteral obstruction 1117–1122
diagnosis 1119
epidemiology and signalment 1118
etiology/pathophysiology 1117–1118, *1118*
history and clinical signs 1118
prognosis 1122
treatment 1119–1121, *1120–1121*
urolithiasis 1137, 1149–1156, **1152**
ureteroscopy 1155
urethral obstruction (UO) 1109–1117
diagnosis 1110–1111, *1110–1111*
epidemiology and signalment 1109–1110
etiology/pathophysiology 1109
history and clinical signs 1110
micturition and associated disorders 1186–1187
prognosis 1117
treatment 1111–1117, **1112**, *1113*, *1116*
urinary tract tumors 1309
urolithiasis 1137
urethral sphincter mechanism incompetence (USMI) 1182–1184, *1184*, **1185**
urethral tumors 1309
urinalysis
acute kidney injury 1092–1093
acute poisoning 438
cirrhosis 707
feline inflammatory liver disease 688
gallbladder and extrahepatic biliary ducts 723
glomerular disease 1102–1105
leptospirosis 946
liver disease 653
lymphomas 1233
plasma cell disorders 1243–1244
prostatic diseases 1159
spotted fever and typhus group *Rickettsia* 939

surgical, traumatic, and bite wound infections 1031
urinary tract infections 1190, **1192**
urolithiasis 1132
urinary antiseptics 1194
urinary incompetence 1182–1184, *1184*, **1185**
urinary tract 744
urinary tract infections (UTI) 1189–1195
ancillary therapies 1194
asymptomatic bacteriuria 1191
classifications of UTI 1191–1192
complicated UTIs 1194
diagnosis 1190
epidemiology/signalment 1189
etiology/pathophysiology 1189, **1191**
fungal infections 997–998
history and clinical signs 1189–1190
micturition and associated disorders 1187
nocosomial and multidrug-resistant infections 1058–1060
prognosis 1195, **1195**
recurrent UTIs or reinfections 1191–1192
spinal cord injury 747
treatment 1192–1195
uncomplicated UTIs 1191, 1193–1194
urethral obstruction 1114
urolithiasis 1124, 1128, 1133, 1136, 1149–1150
urinary tract tumors 1307–1310
bladder tumors 1307–1308, **1309**
diagnosis/staging 1307–1309, **1309**
epidemiology 1307, 1309
etiology/pathophysiology 1307, 1309
history and clinical signs 1307, 1309
renal tumors 1309–1310
signalment 1307, 1309
treatment and prognosis 1308–1309
urethral tumors 1309
urine aldosterone to creatinine ratio (UACR) 91
urine cortisol to creatinine ratio (UCCR) **53–54**, 54–56
urine protein:creatinine ratio (UPC) 1102–1105, 1165, **1166**
urine sediment 1132, 1190
urine specific gravity (USG) 66–68
urinology 351
urogenital *Mycoplasma* infections 933
urolithiasis 1123–1156
acute kidney injury 1093
bloodwork 1133
calcium phosphate urolithiasis 1129–1130, 1142–1143
concepts and definitions 1123
cystine urolithiasis 1130–1131, 1134, *1136*, 1143
diagnosis 1132–1136
educated guesses 1135–1136, *1136*
history and physical examination 1123–1124
imaging of the urinary tract 1134–1135, *1134–1135*
mechanisms of urolith formation 1123, *1124*
medical management of lower urinary tract stones 1136–1144, **1140**
medical management of upper urinary tract stones 1149–1150
mixed/compound uroliths 1143–1144
other types of urolithiasis 1131–1132, *1131–1132*, 1143–1144
oxalate urolithiasis 1093, 1124–1127, *1126*, 1137–1139
purine urolithiasis 1128–1129, *1128*
recurrence prevention strategies 1138–1144, **1140**
removal of lower urinary tract uroliths 1144–1149, *1145–1146*, **1146**, *1148*
removal of upper urinary tract uroliths 1149–1156, **1152**, *1153*, **1154**, *1156*
signalment by stone type 1124–1132, **1125**, **1126**
silicate urolithiasis 1131, 1143
specific tests to detect cystinuric dogs 1134
stone analysis 1133–1134, *1133*
struvite urolithiasis 1127–1128, *1127*, *1136*, 1139–1141
ureteral obstruction 1117–1119, 1121–1122
urethral obstruction 1109–1110, 1115
urinalysis 1132
urine culture 1132–1133
urticaria 1413–1414, *1414*, **1414**
USDA *see* United States Department of Agriculture
USG *see* urine specific gravity
USMI *see* urethral sphincter mechanism incompetence
uterine tumors 1317–1318
UTI *see* urinary tract infections
UUT *see* upper urinary tract
uveal melanocytoma/melanoma 1264, *1264*
uveitis *909*
uveodermatologic syndrome 1430–1431, 1487–1488

V

VA *see* ventricular arrhythmias
vaccination 1567–1570
anthrax 974–975
antigen delivery systems 1568–1569
canine distemper virus 853
canine herpesvirus 856
canine infectious respiratory disease complex 1037
canine parvovirus type 2 859
clinical decision making 21–23
feline coronavirus 875
feline immunodeficiency virus 884
feline leukemia virus 880–881
feline parvovirus 870
feline viral upper respiratory tract disease 889
immune system response to disease 1567–1568
infectious vaccines 1568–1569
kennels and multicat environments 1064
leptospirosis 948
Lyme borreliosis 942, 943
melanoma 1349–1350, *1350*
modified live vaccines 1569
noninfectious vaccines 1568
oral cavity and salivary glands 539
oral tumors 1255
papillomaviruses 863
protozoal and protozoa-like infections 1011
rabies 892–897
reasons for failures 1569–1570
recombinant vector vaccines 1569
soft tissue sarcomas 1333, 1337–1338
West Nile virus 900
yersiniosis 953–954

vacuolar hepatology 665, *665*
vacuolar hepatopathy 677–678
vaginal tumors 1318–1319
VAKI *see* Veterinary Acute Kidney Injury
validity *see* external validity; internal validity
valvular heart disease 245–252
  canine degenerative myxomatous mitral valve disease 245–250, *247–248*, **247**
  classification/staging of MMVD **247**
  diagnosis 247–248, *247*, 251, *251*
  epidemiology 246, 250
  etiology/pathophysiology 245–246, 250
  history and clinical signs 246–247, 250–251
  infectious endocarditis 250–251
  prognosis 248, *248*, 251
  treatment 248–250, 251
valvular interstitial cells (VIC) 245
vancomycin-resistant enterococci (VRE) 1059–1060
VAP *see* ventilator-associated pneumonia
vascular endothelial growth factor (VEGF) 539, 1208–1209
vascular occlusive disorders 821–822
vascular ring anomalies (VRA)
  congenital heart disease 234
  esophageal disorders 562
  gastrointestinal imaging 476, *477*
vasculature
  cutaneous manifestations of systemic disease 1487
  forebrain disorders 785–788
  hepatobiliary disease 660, 664, 670–673, *671–673*
  neuroendocrinology 41
  skeletal development and homeostasis 1513–1514, 1516–1517
  vestibular disease 792–793
vasculitis 1433, *1434*, 1487
vasodilation
  cardiogenic shock 418
  heart failure 186, **187**, 188–189, 193–194, **195**, 196–197
  hypothermia 433
  pulmonary thromboembolism 320
  septic shock 423
  valvular heart disease 250
vasopressin (VP) *see* antidiuretic hormone
vasopressors 410, 427
VCLE *see* vesicular cutaneous lupus erythematosus
VEGF *see* vascular endothelial growth factor
venomous snake bites 459–465
  antivenin therapy 462–464
  diagnosis 461–462
  epidemiology 460–461
  etiology/pathophysiology 459–460
  first aid 462
  history and clinical signs 461
  neuromuscular junction diseases 808
  prognosis 464, **465**
  signalment 461
  snake bite severity score 464, **465**
  treatment 462–464
venous admixture 383–384, 389
ventilation
  cardiopulmonary resuscitation 367, 371
  critical care setting 350
  head trauma 756
  respiratory monitoring in critical care 376–377, **376**
  see also mechanical ventilation
ventilation–perfusion (V–Q) mismatch
  acute respiratory failure 385–386, *385*, 389
  pulmonary thromboembolism 320
  respiratory monitoring in critical care 377–378
  surgical approaches to thoracic disease 325–326
ventilator-associated pneumonia (VAP) 400
ventilator-induced lung injury (VILI) 390, 401
ventricular arrhythmias (VA) 199–204
  acute therapy 203–204
  canine myocardial disease 255–256, 260–265
  chronic therapy 204
  diagnosis 200, *201–203*
  etiology/pathophysiology 199
  feline myocardial disease 270–271, 273
  history and clinical signs 199–200
  idioventricular rhythm 200, *203*
  signalment 199
  surgical approaches to thoracic disease 326, 329
  treatment 200–204, **203**
  ventricular fibrillation 200, 202–204, *202*, 204
  ventricular premature depolarizations/contractions 199–200, *202*
ventricular fibrillation 200, 202–204, *202*
ventricular premature depolarizations/contractions (VPC) 199–200, *202*
ventricular septal defect (VSD) 231, 232, 237, 241–243
ventricular synchrony 177
ventricular tachycardia (VT) 200, *202*, 204, 413–414, 419
vertebral heart score (VHS) 128–130, *130*, **131**
vesicles *1384*
vesicular cutaneous lupus erythematosus (VCLE) 1426–1427, *1426*
vestibular ataxia 732
vestibular disease 789–794
  anatomy/physiology 789
  anomalous/congenital causes 790, 792
  central vestibular disease 789–790, 792–794
  differentiating peripheral from central disease 789–790
  etiology 790–794
  idiopathic causes 791
  infectious causes 791
  inflammatory causes 791–794
  peripheral vestibular disease 790–792
  vascular causes 792–793
Veterinary Acute Kidney Injury (VAKI) staging scheme **1091**
veterinary bedside lung ultrasound examination (VetBLUE) 292–293, **293**
VHS *see* vertebral heart score
VIC *see* valvular interstitial cells
videotoscopy 1473, *1473*, 1478, *1478*
VILI *see* ventilator-induced lung injury
viral infections
  cutaneous manifestations of systemic disease 1484–1485, *1484*
  laboratory diagnosis 843–844

see also individual agents/diseases
viral papillomas 1261
viremia 878–880
virtual endoscopy 500, *500*
virulent babesiosis 108
visceral hemangiosarcoma 1340, 1344
visceral myopathy 570
viscoelastic coagulation testing 315, 316–317, *317*
vision 736–738
vitamin D deficiency 1524–1527
vitamin D-dependent rickets type I/II 1527
vitamin K1 antagonists 438–439
vitamin K agonists 322
vitamin supplementation 693, 702, 1487
vocalization 893
Vogt–Koyanagi–Harada-like syndrome 1430–1431
voiding urohydropropulsion (VUH) 1144–1145, *1146*
volvulus/torsion 496–497, 504, *505*
see also gastric dilation-volvulus
vomiting
acute kidney injury 1097–1098
acute poisoning 441–442
chronic kidney disease 1167–1168
endocrine manifestations of cancer 1215–1216
feline inflammatory liver disease 688, 693
feline parvovirus 870
gallbladder and extrahepatic biliary ducts 723
metabolic diseases 679–680
motility disorders 565–567, 570–572, 580
von Willebrand factor (vWF) 460
VPC *see* ventricular premature depolarizations/contractions
V–Q *see* ventilation–perfusion
VRA *see* vascular ring anomalies
VRE *see* vancomycin-resistant enterococci
VSD *see* ventricular septal defect
VT *see* ventricular tachycardia
VUH *see* voiding urohydropropulsion
vWF *see* von Willebrand factor

W

Walchia americana 1459–1460
Waldenström macroglobulinemia (WM) 1241–1246
wash-out 24
water balance *see* sodium and water homeostasis
water deprivation test (WDT) 67–68
weight change/management
cardiovascular disease 120–121
diabetes mellitus 94
osteoarthritis 1532–1533
Westermark sign 316, *316*
western immunoblotting 910
West Nile virus (WNV) 899–900
diagnosis 900
epidemiology 899
etiology/pathophysiology 899
prognosis 900
public health implications 900
signalment 899
treatment 900
wheals *1384*, *1407*
wheezes 125
WHO *see* World Health Organization
wild mammals
leptospirosis 945–946
rabies 891–895
yersiniosis 951–952
wipes 1398, 1469
withdrawal-flexor reflex 734–735
WM *see* Waldenström macroglobulinemia
WNV *see* West Nile virus
Wolbachia pipientis infection 917–918
diagnosis 918
epidemiology 918
etiology/pathophysiology 917
history and clinical signs 918
prognosis 918
public health implications 918
signalment 918
treatment 918
Wolff–Parkinson–White syndrome 414
Wood's lamp examination 439–440, 987
World Health Organization (WHO)
approach to the cancer patient 1200
hemangiosarcoma 1341–1342, **1342**
kennels and multicat environments 1064
lymphomas 1231–1232, **1232**
mammary cancer 1322, **1322**, 1324, **1324**
mast cell tumors **1361**
melanoma 1352, **1352**
oral tumors **1254**
World Small Animal Veterinary Association (WSAVA)
canine inflammatory liver disease 695
chronic enteropathies 635
endoscopy 508
feline inflammatory liver disease 687
hepatobiliary disease 659, 667
kennels and multicat environments 1064
wounds and wound management
bandaging 1032
critical care setting 352
exploration and initial debridement 1031
lavage 1032
nocosomial and multidrug-resistant infections 1058
surgical and traumatic wound infections 1029–1032, **1030–1031**
surgical, traumatic, and bite wound infections 1032
trauma and burns 450, 455
venomous snake bites 462, 463
wound closure 1032
wound preparation 1031
see also bite wounds
WSAVA *see* World Small Animal Veterinary Association

X

xanthine urolithiasis 1128–1129, *1128*
xanthomas 1483
xenogeneic DNA vaccination 1349–1350, *1350*
xylitol toxicity 109–110

Y

yersiniosis 951–954
diagnosis 953
epidemiology 952
etiology/pathophysiology 951
history and clinical signs 952–953
prevention 953–954
prognosis 953
public health implications 954
signalment 952
treatment 953

Z

zinc-responsive dermatosis 1486–1487, *1486*
Zollinger–Ellison syndrome 1215–1216
zoonotic infections
  approach to the dermatologic patient 1381
  canine brucellosis 965
  canine infectious respiratory disease complex 1037–1038
  kennels and multicat environments 1065–1066
  leptospirosis 945–949
  mycobacteriosis 980–984
  nocosomial and multidrug-resistant infections 1061–1062
  nonhemotropic *Mycoplasma*, *Ureaplasma*, and L-form bacteria 934
  One Health 3–5
  rabies 891–897
  tularemia 955–957
  West Nile virus 899–900

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